The Cognitive Impact of Chronic Low-level Carbon Monoxide Exposure in Older Adults

A thesis submitted for the degree of Doctor of Philosophy in Health Research

By

Beth Louise Cheshire

Faculty of Health and Medicine

Department of Health Research

Lancaster University

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Abstract

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Evidence of cognitive effects associated with low-level carbon monoxide (CO) is limited, but indicates neuropsychological impairments may follow exposure. Home exposure to low-level CO may be an unidentified cause of cognitive impairment that improved awareness could prevent. This thesis consists of a systematic literature review of acute low-level exposure, the development of data analysis methods and the cross-sectional and longitudinal study of the cognitive effects associated with chronic low-level exposure in older adults, a group identified as particularly vulnerable. Effects at a range of extremely low concentrations were analysed to determine thresholds of harm.

Results indicated that the cognitive effects follow a trajectory that can be represented on a continuum, from extremely low-level exposure and positive effects through higher concentrations and negative impacts. The proposed continuum can account for reported negative effects, absence of effects, and trends towards positive impacts in different cognitive functions, by small variations in exposure concentration and duration, providing an explanation for inconsistent findings within the literature. This model increases theoretical understanding, bridging the knowledge gap between beneficial effects and CO toxicity. Findings indicate that particular areas of cognition are more vulnerable, and others more resilient, to CO.

Analyses also revealed that the relationship between advancing age and specific cognitive functions was moderated by CO exposure, with greater exposure related to increased performance in younger older adults (59-74yrs) and decreased performance in old older adults (75-97yrs), suggesting that measures of frailty, rather than age alone, may be better indicators of CO vulnerability.

The research makes a significant contribution to knowledge, proposing a theory that explains the cognitive effects of low-level CO exposure, which could

ultimately be used in clinical settings to improve diagnosis and determine thresholds of harm. The analysis method presented provides an approach for future research that, in turn, may produce new evidence to underpin and inform exposure guidelines, policy, legislation and safety technology in order to keep those most vulnerable safe.

Contents

List of Tables

List of Figures

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This thesis has been completed by myself, Beth Cheshire, and has not been submitted for the award of a higher degree elsewhere.

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Chapter 1: Main Introduction

Carbon monoxide (CO) is a colourless, odourless, tasteless, and non-irritable gas that is formed by the partial combustion of fuel such as wood, coal, and gas. Common sources of CO include motor vehicle exhausts, industrial processes and natural sources such as wildfires. CO concentrations can accumulate indoors from cigarette smoke and from malfunctioning, inadequately ventilated, and poorly maintained heating and cooking appliances (Raub & Benignus, 2002). When exposed to high concentrations CO is poisonous. CO poisoning is one of the most common causes of accidental and intentional poisoning worldwide (Sykes & Walker, 2016), and in the UK causes an estimated 4000 visits to hospital emergency departments annually, of which 200 people are hospitalised and 30 die (Department of Health (DOH), 2011). However, evidence from epidemiological studies suggest that these statistics are likely to be a significant underestimate with CO poisoning often being undetected due to its unnoticeable properties and non-specific symptoms leading to misdiagnosis (Sykes & Walker, 2016). In addition to the morbidity and mortality associated with CO exposure, it is estimated that CO poisoning may cost the UK up to £178m each year in healthcare costs (The All-Party Parliamentary Carbon Monoxide Group (APPCOG; 2011). Carbon monoxide exposure therefore not only presents significant public health concern but also places a huge economic burden on health services.

A large proportion of poisonings and deaths worldwide are caused by accidental exposure (Raub, Mathieu-Nolf, Hampson, & Thom, 2000; Hampson, 2016). It is commonly agreed that accidental CO poisoning is mostly preventable through the correct installation and maintenance of domestic appliances and CO alarms (Hampson, 2016; Jones et al., 2016). It is alarming that accidental CO poisoning still occurs with many incidents unrecognised in the community, largely due to malfunctioning appliances and insufficient ventilation (Wilson, Saunders, & Smith 1998; De Juniac, Kreis, Ibison, & Murray, 2012). The problem does not appear to be related to hospital treatment, with the majority of patients surviving CO poisoning (98.6%), but with lack of public education and awareness of the risks associated with CO and the use of poorly installed or malfunctioning gas cooking and heating appliances (Wilson et al., 1998).

The effects associated with severe acute CO poisoning are well described. However, whether lower level exposures can result in short or long-term neuropsychological impacts is less clear, particularly under chronic exposure conditions. The focus of the thesis is to examine the effects of chronic low-level CO exposure in an older adult sample, a group identified as particularly vulnerable. The thesis consists of four studies: a systematic literature review of experimental studies on acute low-level exposure; the development of a CO data analysis method; and cross-sectional and longitudinal study of the neuropsychological effects associated with chronic low-level exposure in older adults. This introduction is divided into two core sections. The majority of evidence within the CO literature studies acutely poisoned patients; the first section therefore provides a background to severe exposure including mechanisms of toxicology, neuroimaging findings and subsequent neuropsychological sequelae (NS). Mortality and hospital admission rates, alongside factors that increase the risk of NS and poorer prognosis are also discussed in order to highlight groups most susceptible to CO. The second section focuses on lower-level CO including environmental concentrations and endogenous CO production, air quality and exposure guidelines, ambient CO levels within the home, the associated health and neuropsychological effects of low-level acute and chronic exposure and susceptible groups, particularly older adults.

Section 1.1 Severe Acute CO Poisoning

1.1.1 Epidemiology, Mortality and Hospital Admission Statistics

In the UK, the number of unintentional CO-related poisonings and deaths has decreased since the replacement of town gas with natural gas and the fitting of catalytic converters on cars (Wilson, Saunders, & Smith, 1998). However, natural gas requires double the amount of oxygen for combustion and when partial combustion occurs CO can be produced (Crawford, Campbell, & Ross, 1990). Accidental CO poisoning still occurs with many incidents unrecognised in the community, largely due to malfunctioning appliances and insufficient ventilation (Wilson et al., 1998; De Juniac et al., 2012). In the European Union (EU), a substantial number of deaths are caused by CO, with 140,490 CO-related deaths reported between 1980 and 2008. Additionally, further information from 11 states

revealed that unintentional poisoning accounted for the highest amount of deaths (54.7%) (Braubach et al., 2013). In England and Wales, data from the Office for National Statistics (ONS) between 1979 and 2012 revealed a total of 28,944 CO-related deaths, of which 2208 were due to unintentional non-fire-related CO poisoning (Fisher, Leonardi, & Flanagan, 2014). Annual mortality rates have gradually declined from 166 in 1979 to an average of 44 between 1996 and 2010 (Fisher et al., 2014) and are highest in individuals aged 25-64 years, accounting for 63.2% of cases. However, older adults (≥65 years) are most affected, accounting for 22.3% of all CO-related deaths (Braubach et al., 2013), a proportion higher than the proportion of this age group in the general population (14.1%), with survival rates decreasing with increasing age (Fisher Bowskill, Saliba, & Flanagan, 2013). Data sourced from the Carbon Monoxide and Gas Safety Society (COGSS) between 1996 and 2007, also revealed a high prevalence of non-fire related CO deaths in older adults aged over 65 years (39%).

The prevalence of accidental poisoning is further supported by CO-related hospital admissions figures. For example, Hospital Episode Statistics (HES) inpatient data between 2001 and 2010, revealed a total of 5,062 non-fire related CO poisoning National Health Service (NHS) hospital admissions, of which 48.7% were related to accidental exposure (Ghosh et al., 2015). These studies also highlight those most vulnerable, with higher admission rates observed in older adults (≥80 years) followed by the young (<10 years) (Ghosh et al., 2015). Additionally, mortality and hospital admission rates are higher in the winter months, potentially reflecting increased use of heating appliances and decreased ventilation to conserve heat (Ghosh et al., 2015; Wilson et al., 1998; De Juniac et al., 2012; Fisher et al., 2013; Braubach et al., 2013).

In relation to socioeconomic status, higher admission rates for accidental poisoning have been reported in areas of deprivation, with the exception of extremely deprived areas (Ghosh et al., 2015). Other studies however, have found no relationship between non-intentional CO-related poisonings and socioeconomic deprivation (Wilson et al., 1998). These findings may reflect a higher use of social housing and rented accommodation in extremely deprived

areas where previous health promotion work has mainly focused and legislation (such as legal requirements of gas safety checks) are in place to protect from CO poisoning (Wilson et al, 1998; Ghosh et al., 2015). De Juniac et al., (2012) found CO-related deaths to be most prevalent in owner occupied homes (58%). In support of this, figures from the EU Injury database (IDB) indicated that 87% of CO-related injuries occur in private residential areas (EuroSafe, 2008), with domestic fuel reported to be the most common source accounting for 52% of all non-intentional CO-related incidents (Wilson et al., 1998). The majority of non-fire related CO deaths have been associated with domestic appliances including heaters (28.4%), boilers (28.1%) and cookers (12.6%) (De Juniac et al., 2012). Moreover, data from the UK National Poisons Information service (NPIS) between 2014 and 2015 revealed that of 479 CO enquiries, 84% were home exposures with 62% due to a faulty appliance (NPIS, 2015). Malfunctioning or poorly ventilated domestic appliances appear to be the most common source of both non-fatal and fatal accidental CO poisoning incidents (Wilson et al., 1998; De Juniac et al., 2012; NPIS; 2015). The Carbon Monoxide and Gas Safety Society (COGSS; 1997) warned that all households are at risk of CO poisoning regardless of social class and type of residence.

Similar figures have been reported in the UK West Midlands region, the focus area of the studies within this thesis, with unintentional poisoning accounting for 43.2% of all CO-related hospital admissions between 1988 and 1994 (Wilson et al., 1998). This data, combined with figures from the Health and Safety Executive (HSE), revealed that of all CO-related incidents, 25.2% were non-intentional, and domestic fuel was the most common source accounting for 52.3% of cases. The West Midlands has also been found to have a higher prevalence of incidents than any other region in England (Fisher et al., 2013). Incidents were highly correlated with the winter months and high risk groups included older adults (>85 years) and the very young (0-4 years). Moreover, older adults had the greatest risk with an incident rate twice that of the very young group (Wilson et al., 1998).

The data indicate that approximately 45% of all CO-related hospital admissions in England are due to accidental poisoning (Ghosh et al., 2015; Wilson et al., 1998). Mortality rates have significantly declined nationally, however,

unintentional poisoning still accounts for the highest proportion of all CO-related deaths in Europe (Fischer et al., 2014; De Juniac et al., 2012; Braubach et al., 2013). Annual hospital admission rates for accidental exposure are much higher than the associated mortality rate (Ghosh et al., 2015; Fischer et al., 2014; De Juniac et al., 2012). The burden of accidental non-fatal CO poisoning is therefore greater than the burden from mortality (Ghosh et al., 2015). The figures reported in the majority of studies reviewed above however, are based on relatively old data and therefore are unlikely to reflect the current situation. Nevertheless, they indicate that accidental exposure incidents may be more prevalent in the West Midlands region and therefore the studies in the current thesis were based in the West Midlands, specifically Coventry. Importantly, these studies highlight vulnerable groups within the population that are at greater risk of accidental CO exposure with data revealing higher mortality and hospital admission rates amongst older adults (>65 years) (Fisher et al., 2013; De Juniac et al., 2012; Braubach et al., 2013), particularly those aged ≥80 years (Ghosh et al., 2015; Wilson et al., 1998). Older adults as a group were therefore the population of study in the current thesis.

1.1.2 Mechanisms of Toxicology

Prior to examining the effects associated with CO exposure, particularly the potential neuropsychological impacts, it is important to understand the underlying mechanisms of CO toxicity. This section summarises some of these pathways. The toxic effects of CO are primary mediated via hypoxic pathways through the binding of CO to haemoglobin (Hb), forming carboxyhaemoglobin (COHb). Carbon monoxide has an affinity for Hb around 240 times that of oxygen (O_2). The formation of COHb decreases the amount of Hb available for O_2 transport reducing the O_2 carrying capacity of the blood, leading to decreased O_2 supply to the tissues and organs (Haldane, 1895a; Raub & Benignus, 2002). Furthermore, COHb formation causes structural changes to Hb molecules leading to more stable binding to O_2 on the other haem groups (Harper & Croft-Baker, 2004). This increase in strength of O_2 dissociation from Hb inhibits the release of O_2 until very low partial pressures of O_2 within the tissues are reached. This causes the remaining oxyhaemoglobin dissociation curve to shift to the left, further decreasing O_2 delivery to the tissues (Haldane, 1895b; Raub & Benignus, 2002).

In response to reduced O_2 availability, compensatory mechanisms such as tachycardia and tachypnea are triggered in order to maintain O_2 supply leading to increased oxygen uptake, coronary and cerebral blood flow (CBF) and O_2 consumption in muscle. These increases in cardiac output and respiratory rate also lead to greater CO uptake. At a certain time point the amount of COHb in the blood will reach levels at which the heart can no longer produce an output that is large enough to compensate for the decrease in O_2 (Prockop & Chichkova, 2007; Raub & Benignus, 2002; Chiew & Buckley, 2014). Cardiac hypoxia and decreased cardiac output follows, resulting in the development of severe tissue hypoxia (Haldane, 1895a, 1895b; Chiew & Buckley, 2014). At this point death will occur unless intervention is initiated (Chiew & Buckley, 2014). The brain and the heart are most susceptible to CO toxicity and hypoxic injury due to their high O_2 demand. Increased cranial pressure and cerebral oedema result as a consequence of hypoxia resulting in reduced levels of consciousness, seizures, coma, and death (Prockop & Chichkova, 2007). Brain hypoxia also results in oxidative stress, inflammation, necrosis, and apoptosis causing injury to the cerebral cortex (Piantadosi, Zhang, Levin, Folz, & Schmechel 1997).

Other pathophysiological mechanisms have been suggested to account for the toxic effects of CO poisoning. CO is known to bind to intracellular haem proteins such as myoglobin and neuroglobin causing detrimental changes in cell function (Raub & Benignus, 2002). For example, CO binds to intracellular myoglobin in the heart and skeletal muscles forming carboxymyoglobin (COMb). The formation of COMb impairs oxygen supply to the mitochondria by inhibiting ATP production, leading to cellular respiratory dysfunction. This reduction of O_2 in the tissues impairs heart function (Prockop & Chichkova, 2007; Harper & Croft-Baker, 2005) and results in ischaemia, oxidative stress and the formation of O_2 free radicals promoting cell death (Hardy & Thom, 1994; Zhang & Piantadosi, 1992). Structural alterations to myelin basic protein can also occur triggering immunologic responses resulting in progressive demyelination of the cerebral white matter (CWM) and inflammation (Weaver, 2009).

1.1.3 Neuropsychological Effects

Carbon monoxide poisoning can be classified according to the exposure duration. Acute exposure includes durations up to 24 hours; chronic describes longer exposures lasting more than 24 hours (including intermittent exposure); and acute-on-chronic includes a combination of both exposures (Sykes & Walker, 2016). Poisoning severity is dependent upon the exposure duration and other environmental factors such as the concentration of CO in the air and ambient ventilation (Prockop & Chichkova, 2007). The majority of research on CO exposure has studied severe acute poisoning and the effects are well described. Initial symptoms are non-specific and include headache, fatigue, nausea and vomiting. As the ambient CO concentration and exposure duration increase, symptoms such as confusion and dizziness develop which are progressively followed by loss of consciousness, seizures and ultimately death (Raub & Benignus, 2002). Neuropsychological sequelae (NS) following acute CO poisoning can also present, including a wide range of neurological deficits, cognitive impairments, and affective changes. Symptoms can arise immediately after exposure and persist for an undetermined amount of time (persistent neuropsychological sequelae; PNS), or can be delayed in onset following apparent recovery of clinical symptoms, with an average latency of around three weeks (delayed neuropsychological sequelae; DNS) (Reynolds, Hopkins, & Bigler, 1999; Choi, 1983; 2002; Min, 1986; Weaver et al., 2002).

Symptoms can range from subtle changes in personality and mild cognitive impairment, detectable only through neuropsychological assessment, to severe deficits in cognitive functioning (Min, 1986; Choi, 1983; Hu, Pan, Wan, Zhang, & Liang, 2011). Commonly reported sequelae include impairments in memory, attention, concentration, executive function, verbal fluency, processing speed and visuospatial skills (Parkinson et al., 2002; Dunham & Johnstone, 1999; Reynolds et al., 1999; Porter, Hopkins, Weaver, Bigler, & Blatter, 2002; Weaver et al., 2002; Gale et al., 1999; Min, 1986; Pepe et al., 2011; Katirci, Kandis, Aslan, & Kirpinar, 2010; Yang et al., 2015; Chen et al., 2013; Chen et al., 2015; Chang et al., 2010). Memory impairments are most commonly observed, followed by deficits in attention, motor skill, processing speed, executive function, and visuospatial ability (Hopkins & Woon, 2006). Movement disorders such as

Parkinsonism symptoms are also frequently reported including gait abnormalities (shuffling gait), increased muscle tone (rigidity), tremor and bradykinesia (slowed movement) (Choi, 1983; Choi & Cheon, 1999; Choi, 2002; Min, 1986; Pepe et al., 2011; Chen et al., 2015). Affective sequelae often include personality changes, irritability, aggressiveness, apathy, depression, anxiety, obsessive-compulsive behaviour, elated mood, delusions and hallucinations (Jasper, Hopkins, Duker, & Weaver, 2005; Katirci et al., 2010; Reynolds et al., 1999; Gale et al., 1999; Smith & Brandon, 1973; Dunham & Johnstone, 1999; Min, 1986).

A key limitation of many studies examining the neuropsychological effects associated with CO poisoning is the lack of a control group (Weaver et al., 2002; Porter et al., 2002; Choi, 1983, 1999, 2002; Pepe et al., 2011; Min, 1986; Gale et al., 1999). However, results of more recent studies that included healthy controls indicate the presence of cognitive and affective sequelae following accidental poisoning (Katirci et al., 2010; Chang et al., 2010; Yang et al., 2015; Chen et al., 2013; Chen et al., 2015). Chang et al., (2010) reported impairments in visual and verbal memory, verbal fluency, executive function, and visuospatial ability which did not significantly improve by 10 months. Higher depression scores were also observed in patients at three months but were not present at 10 months. However, the sample size was small, with only 9 patients studied, limiting the generalisability of the results.

Two slightly larger studies by Chen et al., (2013; 2015) compared 22 and 20 patients respectively, and reported lower levels of cognitive functioning in CO poisoned patients initially that gradually improved over time. However, the majority of patients with delayed encephalopathy (DE) still presented with neuropsychiatric disorders at follow up. Yang et al., (2015) reported impaired attention, visual and verbal memory, and executive function in 21 patients with significant performance improvements observed at six months, except for in executive function (problem solving and concept formation). Katirci et al., (2010) studied 30 patients and observed significantly impaired immediate memory, spontaneous recall, attention, learning and visual and logical memory in patients that remained at six months. The results of these studies indicate a range of cognitive sequelae following CO poisoning and that impairments can persist for

at least six to 10 months (Chang et al., 2010; Katirci et al., 2010), with executive function deficits potentially particularly persistent (Yang et al., 2015). Results from a meta-analysis on the short and longer-term neuropsychological effects of CO poisoning, indicated significantly worse performance on measures of divided and sustained attention and processing speed in patients when compared to controls (Watt, Prado, & Crowe, 2017). When patient performance over time was examined, significant improvements were observed from the initial testing to follow-up (range: 6 weeks to 10 months) on measures of sustained attention, visuospatial ability, short-term and working memory. The authors concluded that CO poisoning can lead to a range of neuropsychological impairments that generally improve over time and therefore may in part, be reversible (Watt et al., 2017).

Longitudinal studies of neurological and cognitive sequelae following acute CO poisoning are limited. The majority of studies have typically included follow up of patients for one year durations or less (Jasper et al., 2005; Yang et al., 2015; Chang et al., 2010; Porter et al., 2002; Kesler et al., 2001; Katirci et al., 2010), therefore information on sequelae and long-term outcomes beyond the first year of poisoning is limited (Weaver, 2009). The incidence rate of DNS in CO poisoned patients is extremely variable with estimates from around 3% up to 40% (Choi, 1983; Parkinson et al., 2002; Pepe et al., 2011). Prognosis is also extremely variable with studies reporting persistent impairments in memory, attention, and executive function at six months in 52% of patients (Porter et al., 2002) and others reporting generally good outcomes with 60-80% of patients recovering within one year (Choi, 1983; 2002; Min, 1986). However, in some of these patients, mild memory deficits and Parkinsonism persisted and in around 25% of cases symptoms do not improve, indicating that sequelae can persist and may be permanent (Choi, 1983; Min, 1986).

Two studies with longer follow-up times (6-51 months, average 25 months) observed gradual improvements in cognitive functioning. However, the majority of patients with DE continued to present with neuropsychiatric disorders evidencing that symptoms can persist over one year post-exposure (Chen et al., 2013; Chen et al., 2015). Furthermore, case reports of severely poisoned patients

also document long-term cognitive effects, with gradual improvements in neuropsychological sequelae observed over three years except for in memory function which continued to decline over the time course (Reynolds et al., 1999). Cognitive deficits in areas of memory, attention, and executive function have been observed in 19% of patients and neurological abnormalities in 37% of patients six years after poisoning, indicating that significant long-term neuropsychological effects may follow (Hopkin & Weaver, 2008; Weaver, Hopkins, Churchill, & Deru, 2008).

Prevalence rates of depression and anxiety in CO poisoned patients are high initially, with studies reporting symptoms in 30-95% of patients (Gale et al., 1999; Smith & Brandon, 1973; Jasper et al., 2005; Porter et al., 2002; Katirci et al., 2010). These symptoms appear to be short, lasting a few months' post-exposure and therefore may be a reaction to the sudden and unexpected trauma related to the accident (Chang et al., 2010; Katirci et al., 2010). However, in attempted suicide cases where high percentages of pre-morbid psychiatric conditions are present, differentiation between pre-existing psychiatric disorders and affective disorders following CO poisoning is difficult (Quinn et al., 2009). For example, Jasper et al., (2005) found higher prevalence rates of pre-existing psychiatric disorders in a group of CO poisoned patients resulting from a suicide attempt (77%), compared to accidentally poisoned patients (11%). However, patients in the unintentional exposure group were just as likely to have anxiety and depression at six and 12 months post exposure. Moreover, Porter and colleagues (2002) found no significant differences in levels of depression between attempted suicide and accidentally poisoned patients at six months. Thus, affective disorders may arise secondary to CO poisoning and may not be fully explained by prior psychiatric disease (Jasper et al., 2005).

A further problem with associating neuropsychological impairments following CO poisoning is the complex relationship between cognitive impairment and mood disorders. For example, the manifestation of cognitive deficits following CO poisoning such as impaired memory and attention may contribute to mood deterioration. Likewise cognitive impairments may arise as symptoms of depression and be mistaken for cognitive decline (Quinn et al., 2009). However,

cognitive impairments have been reported in CO poisoned patients who have co-morbid anxiety and depression (Jasper et al., 2005), and depression following poisoning has been reported in patients who do not exhibit cognitive deficits (Smith & Brandon, 1973). This indicates that depression and anxiety may be associated with CO poisoning irrespective of cognitive outcome (Jasper et al., 2005). In summary, there is an extensive amount of evidence indicating the presence of neuropsychological effects following acute poisoning. However, prognosis is extremely variable with some patients making a full recovery, some improving significantly and others experiencing severe symptoms that persist for years post-exposure. It is likely that variations across studies in poisoning severity, population studied, patient selection methods, study designs, assessments, criteria used to quantify poisoning severity and follow-up durations account for the variation in reported incidence and prognosis rates of NS in patients following CO poisoning (Jasper et al., 2005).

1.1.4 Poisoning Severity, Risk Factors and Predictors of Delayed Neuropsychological Sequelae

CO poisoning is variable in its clinical presentation. Symptoms roughly correlate with COHb levels, in that symptom severity generally increases with rising COHb levels (Quinn et al., 2009; Varon, Marik, Fromm, & Gueler, 1999). Individuals with COHb levels below 10% may present with headache but are usually asymptomatic; levels around 20% are associated with headache, dizziness, confusion, and nausea; at 40% individuals commonly experience seizures, loss of consciousness, and coma; and at around 60% and above, death is likely (Varon et al., 1999). However, numerous studies have reported that blood COHb levels do not correlate with poisoning severity based on clinical symptoms (Sokal & Kralkowska, 1985; Dunham & Johnstone, 1999; Yeh et al., 2014). COHb has an average elimination half-life of around 320 minutes in young healthy adults breathing room air (Peterson & Stewart, 1970). Levels of blood COHb therefore fall quickly once an individual is removed from the CO source. The time elapsed between exposure and COHb measurement is therefore unlikely to accurately represent poisoning severity, with levels likely to have dropped significantly from the time of exposure (Sykes & Walker, 2016). Furthermore, COHb levels are not strongly associated with the occurrence of persistent symptoms or the

development of DNS and therefore prognosis (Chambers et al., 2008; Hampson and Hauff, 2008; Ku et al., 2010). Additionally, COHb reflects levels of CO in the blood only, not accounting for CO concentrations within tissue, which may further explain the reported inconsistencies between symptom severity and COHb levels (Messier & Myers, 1991).

COHb levels are therefore useful in the diagnosis of CO poisoning, but the absence of raised COHb concentrations does not exclude the possibility of poisoning (Sykes & Walker, 2016). The absence of a linear relationship between COHb levels and severity of symptoms also indicates the presence of additional underlying mechanisms in CO-toxicity, other than tissue and organ hypoxia due to hypoxaemia. That is, the well-established COHb hypoxia theory does not completely explain the pathophysiology of DNS that typically develop days to weeks post exposure after COHb levels have fallen (Roderique, Josef, Feldman, & Spiess, 2015; Yeh et al., 2014).

Studies have examined alternative indicators of poisoning severity such as loss of consciousness (LOC) (Hampson & Hauff, 2008; Pepe et al., 2011; Ku et al., 2010; Zou et al., 2015; Weaver et al., 2008; Weaver et al., 2007). Hampson and Hauff (2008) found that patients presenting with LOC had significantly higher average COHb levels. However, a high number of patients who experienced LOC had COHb levels below 10%, and some patients without LOC had COHb levels greater than 50%, indicating that LOC is not a reliable marker of poisoning severity (Hampson & Hauff, 2008). Other studies have reported that seizures, decreased systolic blood pressure (<90 mmHg) (Pepe et al., 2011), and reduced levels of consciousness (Pepe et al., 2011: Ku et al., 2010; Zou et al., 2015) are associated with the development of DNS.

Longer exposure duration and older age have been identified as potential risk factors in the development of DNS and prognosis. Patients aged ≥36 years or that had exposure durations of ≥24 hours and COHb levels ≥25% have been reported to be at increased risk of developing cognitive sequelae at six weeks than patients without these characteristics (Weaver et al., 2007). Pepe et al., (2011) also identified longer exposure duration (>6 hours) as a potential risk

factor in DNS development. Hu et al., (2011) explored potential risk factors that impact prognosis of CO poisoned patients with DE and found older age, shorter lucid interval, complications and lower activities of daily living (ADL) scores during hospital admission were potential risk factors leading to poorer prognosis. Older adults may therefore be at higher risk of developing DE and subsequent DNS following CO poisoning and are likely to have poorer prognosis (Hu et al., 2011; Weaver et al., 2007).

1.1.5 Neuroimaging Findings

Neuroimaging plays an important role in both diagnosis and treatment in the acute phase and in the assessment of possible NS in the chronic phase. The majority of brain imaging evidence comes from the study of severely poisoned patients. In the acute phase, lesions to the globus pallidus are commonly reported (Varrassi et al., 2017). Atrophy of the hippocampus (Gale et al., 1999; Gale & Hopkins, 2004) thalamus (Tuchman, Moser, & Moshe, 1990) and the parietal, occipital, and frontal lobe (Uchino et al., 1994) have also been reported following CO intoxication. Magnetic resonance imaging (MRI) studies commonly report altered signal intensity in the globus pallidus bilaterally (Hedge, Mohan, Lath, & Lim, 2011), and subsequent imaging in the chronic stage of CO poisoning consistently show white matter hyperintensities (WMH) (Hou et al, 2013).

Severe exposures typically result in immediate injury to the globus pallidus, whereas CWM damage occurs within the following hours (O'Donnell, Buxton, Pitkin, & Jarvis, 2000; Porter et al., 2002). The immediate neurological deficits are therefore thought to be caused by acute anoxic encephalopathy and the delayed encephalopathy (DE) and subsequent NS from progressive demyelination of the CWM (Chang et al., 1992). This demyelination, in some cases, may be reversible with studies reporting correlations between improved cognitive function and neuroimaging findings. For example, Wang and colleagues (2016) examined the clinical course and MRI of CO poisoned patients with DE and subsequent NS. They observed improvements in cognitive functioning. However, movement disorders often persisted. The improvements in clinical symptoms were correlated with neuroimaging findings with lesions to the CWM recovering more than globus pallidus lesions, indicating reversible

demyelination rather than irreversible necrosis, which was associated with improved cognitive function. These findings suggest that the pathological lesion underpinning DE and subsequent NS is the diffuse demyelination of the CWM (Wang et al., 2016), with lesions to the CWM more frequently associated with DNS than globus pallidus lesions (Gale et al., 1999; Choi, Kim, Choi, Lee, & Lee 1993).

The common treatment for recognised CO poisoning is the administration of oxygen either under normobaric or hyperbaric conditions (Buckley, Juurlink, Isbister, Bennett, & Lavonas, 2011; Weaver, 2009). The administration of normobaric oxygen (100% oxygen at atmospheric pressure) shortens the half-life of COHb by approximately five-fold, and this is further reduced by the administration of hyperbaric oxygen therapy (HBOT; 100% oxygen at higher than atmospheric pressure) (Buckley et al., 2011). HBOT has been shown to reduce the incidence of cognitive sequelae at six weeks by 46% in CO poisoned patients when compared to normobaric oxygen (Weaver et al., 2002).

1.1.6 Misdiagnosis

CO poisoning is often undetected due to its unnoticeable properties and non-specific symptoms, consequently leading to misdiagnosis (Sykes & Walker, 2016). CO-related hospital admission and mortality rates are therefore likely to be a significant underestimate. Incidence rates of misdiagnosis in CO poisoning have been examined in screening studies of patients presenting with non-specific symptoms. For example, a large prospective study of 1758 patients presenting to emergency departments in England between January and October 2010 with non-specific symptoms found that 4.3% of patients had raised COHb levels (≥2.5% in non-smokers; ≥5% in smokers) (Clarke et al., 2012). Of the 76 identified patients with raised COHb levels, 82% had levels below 10%. This is an important finding as COHb levels of ≥10% are typically used by healthcare professionals to indicate CO poisoning due to previous research suggesting that healthy individuals with COHb levels of below 10% would be asymptomatic (Kales, 1993). Additionally, of the patients identified as positive for CO exposure, CO was not suspected in 80% of the cases by either the patients or emergency clinicians (Clarke et al., 2012). These findings indicate that a number of patients

are potentially misdiagnosed and sent home with the possibility of further exposure and that COHb levels below 10% can result in negative impacts on health. Lower COHb levels, <10%, therefore should not rule out the possibility of CO exposure. Importantly, these studies highlight the need for research that investigates lower-level exposures and the potential associated effects, the focus of this thesis.

Section 1.2: Low-level CO

1.2.1 Endogenous and Exogenous CO

The concentration of CO in the atmosphere ranges between 0.05 and 0.12ppm. In large European city traffic environments, average concentrations over 8 hours are usually below 17ppm, with short lasting peaks up to 53ppm (World Health Organisation (WHO; 1999). Endogenous CO production, predominantly resulting from the degeneration of haem, results in baseline COHb levels of 0.4-0.7% in healthy individuals (Raub & Benignus, 2002, WHO, 1999). This process combined with environmental exposure usually leads to detectable COHb levels of 0.5-1.5% in non-smoking individuals (WHO, 1999). Smokers have higher COHb levels, which are usually around 4%, but heavy smoking can raise COHb readings to as high as 13% (Raub & Benignus, 2002). Generally, levels of <2% in non-smokers and <5% in smokers are regarded as normal (Harper & Croft-Baker, 2004). At these low levels, endogenous CO has known beneficial effects playing a vital role in cellular maintenance, protection, regeneration and survival. Defined as a neurotransmitter in the central nervous system (CNS) it acts as a signalling molecule involved in a range of cellular functions with therapeutic actions including vasodilation, proliferation, anti-apoptotic factors and anti-inflammatory properties (Prockop & Chichkova, 2007). Due to its physiologic and cytoprotective properties, the administration of exogenous low-level CO is currently being studied for neuroprotection in a range of brain pathologies such as traumatic brain injury, hypoxic injury, stroke and epilepsy (for reviews see Mahan, 2012; Queiroga, Vercelli & Vieira, 2015).

1.2.2 Outdoor and Indoor CO Air Quality Guidelines and CO Alarm Standards

1.2.2.1 The World Health Organisation

Levels of COHb depend upon both the ambient air CO concentration and the duration of exposure. The Expert Panel on Air Quality Standard of the WHO (1999) recommended that ambient air CO levels should not exceed levels that would produce blood COHb above 2.5%. According to the WHO guidelines (1999), exposures should conform to the following maximum durations of exposure at different levels: 87 ppm (100 mg/m^3) for 15 min; 52 ppm (60mg/m^3) for 30 min; 26 ppm (30 mg/m^3) for 1 hour; 9 ppm (10 mg/m^3) for 8 hours. More recently, guidelines have been published for indoor air quality (WHO, 2010) to prevent individuals' COHb levels rising above 2%. These recommendations are as follows: 87 ppm (100 mg/m^3) for 15 min; 31 ppm (35 mg/m^3) for 1 hour; 9 ppm (10 mg/m^3) for 8 hours with the addition of 6 ppm (7 mg/m^3) for 24 hours. Importantly, longer-term exposures were addressed, with the addition of a 24-hour guideline in order to protect and minimise any health effects associated with low-level chronic exposure.

It is extremely rare that outdoor ambient CO levels exceed these recommendations in the UK (The Expert Panel on Air Quality Standards (EPAQS; 1994). A more recent report by the Department for Environment, Food and Rural Affairs (DEFRA; 2019) on outdoor UK air quality, reported that ambient CO levels have been compliant with European limit values for many years, with 8 hours average concentrations consistently below 10 mg/m^3 at all monitoring sites. Due to this, relatively few monitoring sites are required to monitor CO concentrations, with only seven sites of which six (Belfast Centre, Cardiff Centre, Edinburgh St Leonards, Leeds Centre, London Marylebone Road and London North Kensington) have operated for at least 10 years.

1.2.2.2 The Health and Safety Executive

The HSE workplace exposure limits (EH40, 2005) detail workplace exposure limits for use of Control of Substances Hazardous to Health. These occupational regulations are in place to protect the health and safety of workers from the risks associated with exposure to hazardous chemicals. In 2011, new and revised workplace exposure limits (WELs) were published in order to assist in controlling

exposure to hazardous substances at work. The guidelines for CO were: long-term exposure limit (8-hr time weighted average (TWA) reference period): 30ppm; short-term exposure limit (15 minute reference period): 200ppm. However, a revised commission directive (EU) was published in 2017 with occupational exposure limits for CO amended to: Long-term exposure limit (8-hr TWA reference period): 20ppm; Short-term exposure limit (15 minute reference period):100ppm.

1.2.2.3 Department of Health (DOH, 2004): Committee on the Medical Effects of Air Pollutants

The department of health's committee on the medical effects of air pollutants (COMEAP), formally known as The Expert Panel on Air Quality Standards (EPAQS), recommended that the WHO (1999) guidelines for outdoor air should be applied to both indoor and outdoor environments, recommending the same concentrations and durations for indoor air quality.

1.2.2.4 European Alarm Standards (British Standards Institution; BSI)

The current European standards CO alarms (BSI EN 50291-1; 2018) require the actuation of an auditable alarm when CO levels reach 50ppm for between 60 and 90 minutes, 100ppm for between 10 and 40 minutes and 300ppm within 3 minutes. Some CO alarms have visual displays indicating the CO level, however, they do not alert occupants to low-level or chronic exposure (Shrubsole, Symonds, & Taylor, 2017). Furthermore, European alarm standards are not in accordance with the WHO (2010) recommendations with levels of 50ppm for between 60 and 90 minutes required prior to alarm activation, significantly higher than the WHO recommendation of 31ppm for 1 hour. The WHO (2010) exposure limits are guidelines only, intended to keep the public safe with limited influence as they are not underpinned by legislation and therefore enforcement in domestic environments is problematic (Shrubsole, Symonds, & Taylor, 2017; APPCOG, 2017).

1.2.3 Ambient CO Concentrations within the Home

Indoor sources of CO, such as gas appliances and smoking habits, contribute significantly to CO exposure and raised CO levels (Cox & Whichelow, 1985; Myers, DeFazio, & Kelly, 1998; Crawford et al., 1990; Knobeloch & Jackson,

1999; Ryan, 1990). Homes without indoor combustion sources typically have CO levels similar to atmospheric ranges (WHO, 1999). Non-smoking households without gas appliances generally have average CO concentrations up to 3.1ppm and with gas appliances up to 5.2ppm. Smoking within the home can raise CO levels up to around 4.5ppm in those without gas appliances and 6.7ppm in those with (WHO, 1999; Institute for Environment and Health (IEH; 1998). However, ambient CO levels up to 38ppm have been found in non-smoking households which were attributed to the use of gas appliances, stoves, or open fires (Cox & Whichelow, 1985). Furthermore, 21% of the occupants in these homes had raised breath CO levels ≥6pmm. Additionally, smoking households without CO generating heating appliances did not exceed CO concentrations of 16ppm. Individuals may therefore be at risk of home exposure irrespective of smoking status, with domestic sources potentially leading to higher CO concentrations than cigarette smoking (Cox & Whichelow, 1985). Other studies have reported raised CO levels in UK homes that contain gas appliances. Ross (1996) measured CO levels for one week and found average concentrations of 2.4ppm in kitchens with gas appliances compared to 0.8ppm in kitchens without. Furthermore, maximum one minute averages of 43.1ppm and maximum one hour averages of 21.4ppm were recorded whilst gas cookers were in use. Moreover, the use of malfunctioning appliances caused one-minute average concentrations to rise to 106ppm and one hour averages to 49.8ppm, significantly exceeding the WHO one hour guideline of 25ppm (Ross, 1996). Stevenson (1985) also found that use of poorly installed or maintained kitchen gas appliances can raise 15-minute average levels to 160ppm, significantly higher than the WHO 15 minute recommendation of 87ppm. Increased COHb levels were also found in the residents of these homes (Stevenson, 1985). However, both of these studies were small, with only five and 14 homes examined respectively (Stevenson, 1985; Ross, 1996). The data therefore does not reflect CO levels in UK homes more generally.

Two larger reports found that 23% of vulnerable homes (13/56) across the UK, and 18% (50/270) in East London, had higher CO levels in the ambient air than those recommended by the WHO (Croxford et al., 2005a; Croxford et al., 2005b). Homes were classed as vulnerable if the occupants were over 60 years of age

or single parent families in receipt of income support. In their first report Croxford et al., (2005a) collected CO readings every 15 minutes for between one and five weeks. Of the 13 homes that exceeded the WHO guidelines, all had 8 hour average concentrations over 9ppm, six had 1 hour concentrations above 26ppm and three had 30 minute concentrations exceeding 52ppm (Croxford et al., 2005a). In their second report, CO measurements were recorded every minute, with averages stored every 15 minutes for 7-32 days (Croxford et al., 2005b). Of the 50 households found to have concentrations exceeding the WHO guidelines, all exceeded the 8-hour average recommendation, 26 exceeded the 1 hour guideline and 10 exceeded the 30 minute recommendation (Croxford et al., 2005b). The elevated CO concentrations in both studies were found to be frequently caused by problems with gas appliances such as gas fires and cookers. A further study of 597 homes in London and South East England reported that 22% of homes had at least one appliance that was deemed at risk (AR) or immediately dangerous (ID) (Croxford, Leonardi, & Kreis, 2008). Furthermore, the prevalence of self-reported neurological symptoms such as headache, confusion and nausea were reported at a higher rate in individuals whose homes had a least one appliance deemed AR or ID (15%), compared to those that did not (7%). McCann et al., (2013) examined the prevalence of community CO exposure in London homes over six months with CO alarms installed in 22, 831 local authority homes between November 2011 and April 2012. A total of 106 alarm incidents were recorded, of which 104 were investigated. Of all investigated incidents, over a third (35%) were due to a problem with a gas appliance and 11% due to misuse of cooking method (McCann et al., 2013).

Other studies however, have found no evidence of raised CO levels with concentrations reported to be within the 8-hour average guideline of 9ppm in 830 UK homes (Raw, Coward, Brown, & Crump, 2004). However, mean concentrations were measured using Draeger color-metric diffusion tubes, which do not provide information on short-lasting peaks in CO levels, as opposed to continuous monitoring (Raw et al., 2004). Henderson, Parry, and Mathews (2006) measured CO levels in 44 homes in South Wales and reported mean CO

concentrations below 1ppm; although short-lasting peaks were observed, none exceeded the WHO guidelines.

In summary, the results of these studies reveal that ambient CO concentrations in a number of UK homes exceed the WHO guidelines, particularly when gas appliances are in use. Therefore, a substantial number of individuals may be exposed to CO within the home at levels higher than those considered safe, potentially resulting in detrimental health impacts. The studies also highlight that increases in ambient CO levels can be transient, making the practice of taking a single measurement inaccurate. That is, elevated levels may not be identified using a single reading and therefore such practices fail to accurately reflect exposure concentrations over time. Repeated readings are therefore necessary to gain awareness of the true nature of the problem (Abelsohn, Sanborn, Jessiman, & Weir, 2002), an approach used in the studies of this thesis.

Previous studies measuring CO levels within the home have typically reported the exposure levels, proportion of homes with low-level ambient CO, and the percentage of homes exceeding the WHO guideline limits. These studies provide data on the magnitude of the problem within UK homes and offer invaluable insight into the number of individuals that are potentially at risk from low-level exposures and are therefore extremely informative. They also offer information of the types of properties and appliances that present the highest risk and highlight geographical and socioeconomic factors that likely affect exposure vulnerability. A few studies have collected health information from occupants such as current symptoms and illnesses. However, detailed health and neuropsychological data are typically not included and therefore evidence of any associated exposure effects is extremely limited. It is clear that further investigation is warranted as the data, although limited, represents significant public health concern (IEH; 1998; Shrubsole, Symonds, & Taylor, 2017). Additionally, data analysis methods need developing that enable examination of any resulting neuropsychological and health effects at various CO concentrations in order to determine thresholds of harm. This is addressed in Study 3 of the thesis (see Chapter 4).

1.2.4 Low-level Acute CO Exposure and Associated Neuropsychological Effects

Low-level or 'less severe' poisoning has been defined by studies using various COHb levels including ≤10% (Sadovnikoff, Varon, & Sternbach, 1992), 10% (Crawford et al., 1990), 1%-11% (Amitai, Zlotogorski, Golan-Katzav, Wexler, & Gross, 1998) and <15% (Chambers et al., 2008). It is generally agreed that COHb levels of below 15% represent less severe poisoning (Chambers et al., 2008). Evidence on the effects associated with acute low-level exposure is limited and the neuropsychological and health impacts that follow are unclear. Experimental studies indicate that slightly raised COHb levels, between 2 and 5%, are associated with adverse cardiovascular effects in both patients with cardiovascular disease and healthy individuals. In patients with coronary artery disease, the onset time of angina was significantly reduced during exercise when exposed to either 50ppm or 100ppm of CO raising COHb levels to between 2.9 and 4.5% (Anderson, Andelman, Strauch, Fortuin, & Knelson, 1973). Patients with cardiovascular disease have been shown to be affected by COHb concentrations as low as 2% during exercise (Allred et al., 1989). An increase of 9% in COHb levels has also been shown to reduce walking distance in patients with chronic bronchitis and emphysema (Calverley, Leggett, & Flenley, 1981). In healthy individuals, COHb levels of below 4% have been reported to decrease exercise performance indicated by a reduced mean exercise time before exhaustion (Aronow & Cassidy, 1975).

Neuropsychological sequelae have also been reported in experimental studies of acute low-level CO exposure at COHb levels of 5-7% (Putz, 1979; Schulte, 1963; Gliner, Horvath & Mihenic 1983; Horvath, Dahms, & O'Hanlon, 1971; Ramsey, 1972). Exposures to CO concentrations as low as 50ppm have been reported to significantly decrease the number of correct responses in an auditory discrimination task (Beard, & Wertheim, 1967). Exposure to 100ppm, raising COHb levels to around 5%, have been reported to impair choice discrimination of colours and letters indicated by increased errors and completion time (Schulte, 1963). Decreased vigilance to visual stimuli has been observed at COHb levels of 6.6% (Horvath et al., 1971) and impaired tracking ability, slowed processing and psychomotor speed and deficits in sustained attention at COHb levels of around 5% (Ramsey, 1972; Putz, 1979; Gliner et al., 1983). However, other

studies have reported no CO-related effects in areas of sustained attention at COHb levels of 5-13% (Roche, Horvath, Gliner, Wagner, & Borgia, 1981; Wright & Shephard, 1978; Benignus, Otto, Prah, & Benignus, 1977), divided attention, psychomotor function and speed at COHb levels of 13-16% (O'Donnell, Chikos & Theodore 1971; Benignus, Muller, Smith, Pieper, & Prah 1990). The majority of these experimental studies have typically used CO concentrations of around 100ppm and durations have been short, lasting around four hours.

Amitai and colleagues (1998) reported significantly impaired memory, learning ability, attention, visuomotor skills, abstracting thinking, and visuospatial planning and processing in a group of students exposed to 17-100ppm (1-11% COHb) compared to controls. The results indicate that acute exposure to low-level CO can result in impairments across a range of cognitive domains, similar to those observed in more severe poisoning (Amitai et al., 1998). However, a measure of intelligence prior to exposure was not included and although the participants were University students, the disciplines studied varied widely. Therefore, there was no control for baseline variability in cognitive performance. Additionally, ambient CO concentrations were used as a marker for COHb level, previously criticised by Bleeker (1999) who highlighted probable misinterpretation. A further study examined the prevalence of cognitive sequelae, depression, and anxiety in patients with less severe (<15% COHb without LOC) compared to more severe poisoning (≥15% COHb or LOC) (Chambers et al., 2008). A high prevalence of cognitive sequelae was observed in both groups at six weeks (37%) six months (33%), and 12 months (31%) with no significant differences between the groups at any time point. Significant group differences were not present in education level or prior psychiatric history, so it is therefore unlikely that pre-morbid psychiatric conditions contributed to the observed sequelae (Chambers et al., 2008).

In relation to affective sequelae, patients who experienced less severe poisoning were found to be twice as likely to have depression compared to those with severe poisoning at six months (19%; 11%), despite the fact that severely poisoned patients had higher rates of intentional poisoning (Chambers et al., 2008). However, at 12 months, depression rates declined in both groups to levels

observed in the normal population. Anxiety levels were also initially higher in the less severely poisoned patients at six weeks, with levels decreasing over time to levels comparable to those observed in the normal population by 12 months (Chambers et al., 2008). However, a control group of healthy individuals was not included nor a measure to estimate pre-morbid functioning (Chambers et al., 2008). Nevertheless, similar results have been reported in studies of patients with traumatic brain injury, in that patients with mild injuries often report higher depression and anxiety than those with moderate to severe injuries, possibly due to an increased awareness in these patients of their cognitive sequelae and the trauma associated with the incident (Uomoto & Fann, 2004; Chambers et al., 2008).

In summary, the literature on the effects associated with acute low-level CO exposure is inconsistent, with some studies reporting negative impacts on health and neuropsychological function, and others finding no evidence of CO-related effects. The inconsistencies within the CO behavioural literature have previously been addressed by meta-analyses and reviews, all of which reached similar conclusions; the evidence is inconsistent, studies lack successful replication and reported results may be due to Type I errors, blinding procedures and publication bias (Benignus, 1993; 1994; Benignus, Muller, & Malott, 1990; Stewart, 1975). Furthermore, the majority of experimental studies were published over 40 years ago and would not adhere to current ethical standards. Additionally, experimental studies examining the neuropsychological effects of acute low-level CO exposure have typically included healthy young adults, who as a group have maximal physiological reserve to compensate for decreases in oxyhaemoglobin availability, and therefore are least likely to show any adverse effects on the CNS (Otto et al., 1979). However, the majority of existing evidence of the effects associated with less severe acute exposures is provided by these early experimental studies, with evidence from other sources extremely sparse. These studies, although extremely dated and unethical, are informative in that they examine and provide evidence of the potential effects associated with low-level acute exposure. Therefore, a review of the experimental literature on acute low-level exposure forms part of this thesis.

The most recent reviews and meta-analyses published in this area are over 25 years old and no clear synthesis exists that evaluates assessments by both primary and secondary cognitive domains. The majority of experimental studies have measured cognitive functioning using a series of extremely dated unstandardised tasks presenting issues with reliability and validity. Furthermore, tasks are often designed to measure a specific primary function, however they invariably measure additional cognitive functions. The impact of these secondary functions has not been previously examined. Contemporary synthesis and detailed examination of the literature by both primary and secondary functions is warranted and may provide further explanation to the inconsistencies within the CO behavioural literature. Therefore, a comprehensive systematic review of the experimental literature on acute low-level exposure was undertaken and forms Study 2 of the thesis (see Chapter 2).

1.2.5 Low-level Chronic CO Exposure and Associated Neuropsychological Effects

Chronic exposures to CO can range from several weeks to years in duration, with intermittent exposure commonly occurring (Weaver, 2009; Myers et al., 1998; Ryan, 1990). Evidence on the health and neuropsychological effects associated with less severe chronic exposure to CO is limited. Present within the literature are numerous anecdotal reports that detail a range of effects that follow such exposures (Knobeloch & Jackson, 1999; Gilbert & Glaser, 1959; Crawford, Campbell, & Ross, 1990; Ryan, 1990; Myers et al., 1998). Ryan (1990) described a case of a 48 year old woman who had been exposed to CO from a malfunctioning furnace with CO levels recorded at 180ppm. The patient experienced headaches, periods of depression, lethargy, and memory problems over a course of three years. Three months after the furnace was replaced, neuropsychological testing revealed deficits in new learning ability and memory, and the patient reported depression and anxiety (Ryan, 1990). Myers et al., (1998) followed seven individuals who were exposed to low-moderate levels of CO from malfunctioning and improperly ventilated domestic appliances for periods ranging from three weeks to three years. Consistent symptoms were reported, including headaches, fatigue, nausea and dizziness and personality changes, and affective disorders, such as depression and anxiety, were high.

Neuropsychological assessment revealed memory impairments and motor slowing in all cases. Improvements were observed with some patients making a full recovery, however mild deficits such as slowed processing speed remained in some cases. Self-reported symptoms also remained high in a few patients, and anxiety and depression commonly persisted (Myers et al., 1998).

Exposure to chronic low-level CO is particularly hard to diagnose due to the non-specific and often subtle symptoms (Harper & Croft-Baker, 2004). Consequently, this often leads to continued CO exposure (Kirkpatrick, 1987; Crawford et al., 1990; Gilbert & Glaser, 1959; Myers et al., 1998; Ross, 1990). Symptoms are similar to those observed in acute poisoning including headache, dizziness, fatigue, nausea, vomiting, confusion, difficulty sleeping and personality disturbance (Myers et al., 1998; Crawford et al., 1990; Kirkpatrick, 1987; Hopkins & Woon, 2006; Gilbert & Glaser, 1959; Knobeloch & Jackson, 1999; Ryan, 1990). These symptoms, in addition to being non-specific, are easily misdiagnosed as viral illnesses, headaches, gastroenteritis, chronic fatigue syndrome, and depression (Knobeloch & Jackson, 1999; Myers et al., 1998; Ryan, 1990). Case reports of patients with chronic CO poisoning evince that reaching the correct diagnosis can be difficult and can subsequently lead to delayed diagnosis and prolonged exposure (Webb & Vaitkevicius, 1997; Myers et al., 1998; Gilbert & Glaser, 1959; Knobeloch & Jackson, 1999). A case report of a 73 year old woman who experienced transient cognitive impairments in the winter months underwent clinical investigations for four months prior to reaching the correct diagnosis (Webb & Vaitkevicius, 1997). Knobeloch & Jackson (1999) document occupants of three homes who had been experiencing symptoms including headaches, dizziness, nausea, and fatigue. Diagnoses included chronic fatigue syndrome, depression, and flu-like illnesses, with CO exposure only considered when contractors reported that the gas appliance ventilation systems had serious problems (Knobeloch & Jackson, 1999). The devastating impact of misdiagnosis is highlighted in a case series of 14 family members who experienced various symptoms over a few months. One patient was admitted to hospital on a few occasions and diagnosed with cerebral transient ischaemic attacks and discharged home. Nine individuals were later found unconscious at the residence

and were subsequently admitted and diagnosed with CO poisoning (Crawford et al., 1990).

However, determining the degree of exposure in case reports is difficult due to the lack of information relating to exposure concentration and duration (Knobeloch & Jackson, 1999; Gilbert & Glaser, 1959; Crawford, Campbell, & Ross, 1990; Ryan, 1990). Furthermore, individuals are commonly exposed to short periods of acute poisoning as well as chronic low-level CO. Therefore, ascertaining which type of poisoning is responsible for any resulting health effects is problematic (Townsend & Maynard, 2002). Clinical assessment tools, such as the carbon monoxide neuropsychological screening battery (CONSB; Messier & Myers, 1991) have been developed for screening in more severe acute CO exposure but are of little use in the assessment of patients with chronic exposure (Myers et al., 1998). Detailed neuropsychological evaluations sensitive to subtle changes in cognitive functioning, that would otherwise potentially be missed, are vital in the assessment and follow up of individuals exposed to CO (Myers et al., 1998; Amitai et al., 1998; Ernst & Zibrak, 1998). Furthermore, research aimed at identifying specific neuropsychological deficits, or patterns of impairment, associated with less severe exposures is vital in order to increase knowledge and identification. One of the main aims of the systematic review undertaken in this thesis, although focused on acute low-level exposure, was to ascertain whether there exists an identifiable pattern of observable deficits associated with less severe exposures (see Study 2, Chapter 2).

Studies examining the effects associated with chronic low-level home exposure are extremely sparse. Volans et al., (2007) collected neuropsychological data from 71 occupants (*M*=53 years) of 270 homes in East London where CO monitoring had been undertaken (Croxford et al., 2005b). Of the subsample selected for neuropsychological testing, ambient CO concentrations exceeded the WHO guidelines in 14 homes, however the majority had mean 15-minute average CO concentrations ≤5ppm (*M*=1.89). These levels therefore represent extremely low-level exposure, when considered in accordance with the WHO (2010) 15 minute exposure guideline of 87ppm and 24 hour guideline of 6ppm. No significant negative CO-related effects were observed. Instead, trends

towards *increased* cognitive performance were found on seven of the 11 tasks, with standardised neuropsychological measures revealing test scores >.05 SD above the mean for a 1ppm increase in mean CO level. These were present in areas of auditory working memory, immediate and delayed visual memory recall, visuospatial ability and problem solving (although all non-significant). It is acknowledged that these deviations are small, with the authors reporting no clear evidence of neuropsychological effects (Volans et al., 2007). However, the exposure concentrations were extremely low and the resulting COHb levels were likely similar to, or slightly higher than, normal baseline levels. The authors reported that of the 39 participants that completed CO breath testing, none had levels exceeding 10% COHb. Extremely low-level exposure to CO may therefore result in similar beneficial effects to those associated with endogenous production and this may explain the slight increases in cognitive performance. However currently this is unknown.

Further evidence on the effects associated with chronic low-level exposure is provided by epidemiological studies that have examined outdoor air pollution levels in relation to hospitalisation and mortality rates. With reports indicating that UK air quality has been consistently within limit values for many years (DEFRA; 2019), it would appear that environmental CO levels would have little to no effect on the health of the UK population. However, higher air pollution levels have been related to increased risk of stroke mortality, with mortality rate ratios found to be 1.26 and 1.32 times higher in the highest and second highest CO pollution areas respectively, when compared to the lowest (Maheswaran et al., 2005). Systematic reviews and meta-analyses also report significant associations between air pollution and heart failure indicated by a 3.52% increase in hospitalisations or mortality rates per 1ppm CO increase (Shah et al., 2013) and risk of MI indicated by an increase of 1.048 per 1mg/m^3 CO increase (Mustafic et al., 2012). Associations between air pollution exposure, including CO, and increased dementia risk have also been reported indicated by an incidence rate ratio 1.36 times greater in the highest CO pollution area compared to the lowest (Chang et al., 2014). Importantly, air pollution has recently been identified as a dementia development risk factor in later life (>65) (Livingston et al., 2020). These studies provide invaluable insight on the health effects associated with

chronic outdoor exposure at the population level, however indoor exposures at the individual level also present significant concern, particularly within the home where higher CO concentrations have been recorded. To our knowledge, the few observational home exposure studies present within the literature have not included longitudinal follow-up of participants, and therefore the longer-term impacts on cognitive functioning over time have not previously been examined. The potential longer-term effects associated with chronic low-level home exposure are explored in Study 4 of this thesis (Chapter 5).

1.2.6 Susceptible Groups within the Population

Poisoning severity depends not only on environmental factors, such as the concentration of CO and exposure duration but also human factors such as age, pre-existing disease and the rate of gas exchange between the environment and the lungs (Sykes & Walker, 2016). The health effects associated with CO are most likely to be present in individuals who are physiologically stressed, resulting in increased susceptibility to CO at low-levels (Raub & Benignus, 2002). The brain and the heart are most susceptible to CO toxicity and hypoxic injury due to their high oxygen demand (Prockop & Chichkova, 2007). High risk groups within the population include the unborn and very young, and older adults, particularly those with pre-existing disease (Raub & Benignus, 2002). Individuals with pre-existing disease such as cardiovascular, respiratory, or hematologic conditions whose ability to adequately regulate oxygen supply or metabolism is compromised, are more susceptible to raised COHb levels. These individuals are likely to develop severe toxicity from lower COHb levels due to their already reduced ability to compensate for decreases in the oxygen carrying capacity of the blood (Raub & Benignus, 2002; Chiew & Buckley, 2014). Older adults as a group may also be more susceptible to CO exposure due to reduced physiological reserve (Harper & Croft-Baker, 2004). Misdiagnosis may also be of particular concern within older adults as they often present with a range of conditions that can account for their symptoms, making it less likely that CO poisoning would be suspected (Harper & Croft-Baker, 2004).

The ageing process is associated with structural and functional cerebral and vasculature changes that can influence cognitive functioning in older adults. For

example, endothelium-dependent vasodilatation and cerebral blood flow (CBF) are known to decline in healthy ageing (Belohlavek et al., 2009; Rodriguez-Manas et al., 2009). Age-related changes to blood vessels can lead to impaired vessel function, including endothelial dysfunction, arterial stiffness and hypo-perfusion, resulting in vascular dysfunction (Xu et al., 2017). These age-related alterations to the vasculature can lead to suboptimal CBF and hypo-perfusion which have been identified as precursors for mild cognitive impairment (MCI) and reported to accurately predict the development of Alzheimer's disease (AD) (David & Taylor, 2004; Belohlavek et al., 2009; Jerskey et al., 2009; Jefferson et al., 2007; Forti et al., 2006). Furthermore, cardiovascular risk factors, such as heart failure, coronary artery disease and atrial fibrillation are more common in older adults and lead to greater decreases in CBF and chronic hypo-perfusion, further compromising the already reduced CBF that is present in ageing (de la Torre, 2012; Leenders et al., 1990; Zhao et al., 2007; Bentourkia et al., 2000; Parkes, Rashid, Chard & Tofts, 2004; Heo et al., 2010).

In summary, older adults may be particularly vulnerable from exposure to substances that further compromise cerebral oxygen supply, such as CO, placing them at a greater risk of damage and cognitive decline, especially those with pre-existing disease. CO may further increase risk of cognitive decline above that associated with the biological and physiological changes related to ageing and disease. However, currently this is unknown. In addition, other factors such as greater time spent at home also increase exposure risk in this group. Older adults are more likely to be retired and some may have restricted mobility resulting in increased time at home, which places an already vulnerable group at higher risk of accidental exposure from domestic appliances (Harper & Croft-Baker, 2004).

Section 1.3: Overview of the Research

Evidence of raised CO concentrations within UK homes is accumulating indicating that a large percentage of homes may have higher levels of CO than those recommended to be safe, with many individuals possibly unknowingly exposed to potentially harmful levels of CO. There is clearly cause for concern as a percentage of the population may be at risk from low-level CO exposures within the home from malfunctioning or poorly ventilated gas appliances or solid

fuel heating devices (Townsend & Maynard, 2002). Furthermore, individuals may be unaware that they are being exposed to low-levels of CO consequently leading to chronic exposure. The exposure may continue for weeks and potentially years until a diagnosis of CO poisoning is suspected in symptomatic individuals or the source of CO is detected. Furthermore, the problem may be of particular concern in the UK as gas appliances are widely used for heating and cooking and homes are often old and therefore contain older appliances (Townsend & Maynard, 2002).

Chronic low-level exposures may be responsible for significant widespread morbidity, but are commonly overlooked not only due to the associated non-specific symptoms but also lack of awareness of the problem (Myers et al., 1998). It is likely that a high number of subacute CO poisonings occur within the population that never come to the attention of medical practitioners (IEH, 1998), and that a proportion of symptomatic patients attending general practitioners are being exposed to CO in the home (Townsend & Maynard, 2002). The APPCOG published a report highlighting the urgent need for research into the effects and prevalence of CO in order to ascertain the magnitude of the problem, people affected, and to improve identification (APPCOG; 2011). Studies aimed at ascertaining the proportion of individuals who are exposed to low levels of CO in the home, and examining the short and long-term effects of chronic exposures, are needed in order to determine whether such exposures are a problem in the UK and, if so, the magnitude of the problem (Townsend & Maynard, 2002; McCann et al., 2013).

Experimental and epidemiological studies, alongside case reports, indicate that adverse physical health and neuropsychological sequelae can follow acute and chronic low-level exposure that can persist after exposure has ceased resulting in long-term impacts. In some cases, complete recovery is achieved. However, symptoms and neuropsychological impairments can remain ranging from mild to severe, that prevent individuals from making a full recovery. These are often overlooked leading to inappropriate and incomplete treatment which can significantly impact upon the lives of patients and families longer term (Myers et al., 1998). However, other experimental studies on acute low-level exposure

report no associated CO-related effects and results from an observational study on chronic exposure present conflicting findings that indicate trends towards slightly increased cognitive performance (Volans et al., 2007). The literature on low-level CO exposure is inconsistent and dated with both experimental studies on acute exposure and case reports of chronic exposure presenting several limitations. It is currently unclear as to whether less severe exposures can cause short or long lasting effects on the brain. Further research is needed in this area where there is a significant knowledge gap.

This thesis examines the presence of low-level CO within a sample of older adult homes in Coventry and aims to determine the short and long-term cognitive effects of chronic low-level exposure in older adults, a group identified as particularly vulnerable. Specifically, the thesis examines whether positive cognitive effects can result from extremely low-level exposure and the thresholds at which detrimental impacts occur, knowledge that is currently unknown. The research was developed from initial concerns from West Midlands Fire Service who often report high levels of confusion in older residents who may be at risk of exposure at levels not sufficient to trigger a CO alarm, but that may still be detrimental to health. CO exposure may therefore be a significant unidentified cause of cognitive impairment that improved awareness, identification and treatment could prevent.

The thesis consists of four studies. Study 1 (Chapter 2) comprises a systematic review of the experimental studies on acute low-level exposure with aims to further explain the inconsistencies within the literature and identify potential cognitive domains most affected by low levels of CO. Study 2 (Chapter 3) consists of the development of a CO outcome measure that permits examination of any resulting neuropsychological effects at different exposure levels. The primary aim in developing this measure was for use in identifying the levels at which potential neuropsychological effects occur. The second aim was to permit the examination of chronic exposure to extremely low-level CO in order to determine whether the beneficial effects associated with endogenous CO, can result from exogenous exposure. Study 3 (Chapter 4) is a cross-sectional observation study of the cognitive effects associated with chronic low-level CO

exposure in older adults. Study 4 (Chapter 5) builds on the findings from Study 3 by examining the long-term cognitive impact of chronic exposures. Of particular interest was whether the relationship between age and cognition is moderated by CO exposure. Finally, Chapter 6 provides a general overview and discussion of the research findings, theoretical and clinical implications, directions for future research, and main limitations.

The main questions addressed in this thesis are:

- Are acute low-level CO exposures associated with cognitive impairments; and if so, is there an identifiable pattern of observable deficits? (Systematic literature review).
- Is chronic exposure to extremely low-level CO associated with positive cognitive impacts?
- Is chronic low-level CO exposure associated with impaired cognitive function, and if so, what are the thresholds of harm?
- Can chronic exposure to low-level CO lead to longer term negative impacts on cognition?
- Does the relationship between CO exposure and cognitive function increase with advancing age?

Chapter 2: Study 1

A Systematic Review of the Experimental Literature on the Cognitive Effects of Acute Low-level Carbon Monoxide Exposure.

2.1 Introduction

Carbon monoxide (CO) poisoning is one of the most common causes of both accidental and intentional poisoning worldwide (Sykes & Walker, 2016). When inhaled, CO enters the bloodstream where it binds to haemoglobin (Hb) forming carboxyhaemoglobin (COHb). The formation of COHb decreases the O_2 carrying capacity of the blood, reducing the availability of O_2 to the tissues and organs, leading to hypoxia (Haldane, 1895a; Raub & Benignus, 2002). The levels of blood COHb formed are dependent upon the concentration of CO, duration of exposure and ambient ventilation (Prockop & Chichkova, 2007). Poisoning severity also depends upon human factors such as age, pre-existing disease and the rate of gas exchange between the environment and the lungs (Sykes & Walker, 2016). The brain and the heart are most susceptible to CO toxicity and hypoxic injury due to their high O_2 demand. Increased cranial pressure and cerebral oedema result from hypoxia (Prockop & Chichkova, 2007). Brain hypoxia also results in oxidative stress, inflammation, necrosis, and apoptosis (Piantadosi et al., 1997). Other pathophysiological mechanisms, not related to hypoxia, may also play a role in CO toxicity. For example, CO binds to intracellular haem proteins, such as myoglobin, causing detrimental changes in cell function (Raub & Benignus, 2002). Structural alterations to myelin basic protein can also occur triggering immunologic responses resulting in progressive demyelination of the cerebral white matter (CWM) and inflammation (Weaver, 2009). Demyelination of the CWM can alter connectivity between separate brain areas disrupting communication between them (Nickel & Gu, 2018).

2.1.1 Neuropsychological Effects of Acute High-level CO Exposure

The majority of research on CO exposure examines severe acute poisoning, the effects of which are well described. Symptoms are non-specific and include headache, fatigue, nausea and dizziness, which are progressively followed by loss of consciousness and ultimately death (Raub & Benignus, 2002).

Neuropsychological sequelae (NS) can also present including a wide range of neurological deficits, cognitive impairments, and affective changes. Symptoms can present immediately after exposure and persist for an undetermined amount of time or can be delayed in onset following apparent recovery of clinical symptoms (Reynolds, Hopkins, & Bigler, 1999). Longer duration of CO exposure (>24 hours) and age (>36) have been found to be potential risk factors in the development of delayed NS (Weaver, Valentine, & Hopkins, 2007). Severe exposures usually result in immediate damage to the globus pallidus (part of the basal ganglia), whereas CWM damage occurs within the following hours (O'Donnell et al., 2000; Porter et al., 2002). The immediate neurological deficits are thought to be caused by acute anoxic encephalopathy and the delayed encephalopathy (DE) and subsequent NS from progressive demyelination of the CWM (Chang et al., 1992). This demyelination may in some cases be reversible with studies reporting correlations between improved cognitive function and neuroimaging findings (Wang et al., 2016).

2.1.2 Low-level CO Exposure

Environmental exposure combined with endogenous CO production leads to detectable baseline COHb levels of <2% in non-smokers and <5% in smokers (Harper & Croft-Baker, 2004). The Expert Panel on Air Quality Standard of the World Health Organisation (WHO; 1999; 2010) published exposure guidelines for both outdoor and indoor air quality which aim to prevent individual COHb levels rising above 2.5% and 2% respectively (see Chapter 1). According to a report by the Department for Environment Food and Rural Affairs (DEFRA; 2019) on UK air quality, outdoor ambient CO levels have been within European limit values for many years with 8 hour average concentrations consistently below 10 mg/m^3 at all UK monitoring sites. However, these guidelines have been exceeded internally in a number of UK homes with 13/56 (23%) across Manchester, Birmingham and Liverpool and 50/270 (18%) in East London reported to have ambient CO levels above the guidelines (Croxford et al., 2005a; Croxford et al., 2005b).

2.1.3 Neuropsychological Effects of Acute Low-level CO Exposure

The WHO (1999; 2010) guidelines are recommendations based on the results of studies revealing that acute low-level CO exposures, resulting in COHb levels of 2-5%, were associated with adverse cardiovascular effects in both patients with cardiovascular disease and in healthy individuals (Allred et al., 1989; Anderson, et al., 1973; Aronow & Cassidy, 1975). Evidence of the neuropsychological impacts associated with acute low-level exposure is inconsistent, with some studies reporting effects at COHb levels of 5% (Gliner et al., 1983; Putz, 1979; Ramsey, 1972) and others reporting no effects at COHb levels as high as 16% (Benignus, Muller, Smith, Pieper, & Prah 1990). However, results from recent studies suggest that both CO-poisoned patients and those chronically exposed to lower level CO are at a higher risk of dementia development (Lai et al., 2016; Nakamura et al., 2016; Wong et al., 2016). Associations between air pollution exposure, including CO, and increased dementia risk have been reported (Chang et al., 2014; Peters, Peters, Booth, Mudway & Anstey, 2019). It is clear that further research into the relationship between lower level CO exposures and the effects on brain function is warranted.

2.1.4 Previous Reviews and Meta-analyses

The most recent reviews and meta-analyses on the behavioural effects of acute low-level CO exposure are over 25 years old (Benignus, 1993; 1994; Benignus, Muller, & Malott, 1990; Stewart, 1975). Stewart (1975) found that the evidence of CO-related cognitive effects, including psychomotor ability, vigilance, arithmetic tasks and driving skill was inconsistent. He surmised that COHb levels below 10% would not be associated with performance deficits on tasks involving judgement and motor coordination due to mechanisms that can efficiently compensate for reductions in the oxygen carrying capacity of the blood. The author concluded that the reported performance deficits in participants with COHb levels of below 5% should be viewed with caution. Benignus et al., (1990) reviewed the behavioural effects of low COHb saturations and, like Stewart (1975), found the evidence to be inconsistent. They reported that none of the studies reporting CO-related effects on behaviour had been successfully replicated, and concluded that COHb levels below 20% would not produce behavioural effects, and if they did, they would be small and not occur

consistently (Benignus et al., 1990). In his 1994 meta-analysis and 1993 review, Benignus reached similar conclusions noting that the behavioural effects were not replicable or reported in studies using higher COHb levels. He suggested that the reported significant results may be due to Type I errors and publication bias. Additionally, meta-analysis results of 43 studies on the behavioural effects of CO revealed that single blind studies were significantly more likely to find CO-related effects than double blind studies (Benignus, 1994). The author concluded that evaluating the literature without consideration of the blinding procedure "implies a much more prevalent effect of CO than is warranted" (page 47).

2.1.5 The Current Review

The literature on the impact of acute low-level CO exposure on cognitive functioning is ambiguous and it is unclear as to whether low-level exposures can cause short term or long lasting effects on the brain. Previous experimental studies have measured cognitive functioning using a series of tasks. These tasks are often designed to measure a specific primary function. However, they invariably measure additional cognitive functions, for example, a visual monitoring task may measure sustained attention (the primary function), but might also assess inhibition (secondary function). The impact of these secondary functions has not been previously examined. Therefore, the current review evaluates the impact of acute low-level CO exposure on cognitive function with all cognitive domains underlying tasks examined. These are evaluated by primary and secondary functions, rather than by primary function only. It is hypothesised that the inconsistencies within the CO behavioural literature may, in part, be due to differences in the areas of cognition assessed. Although task descriptions may only vary slightly, these differences can lead to substantial variations in the underlying cognitive functions required for task completion.

2.1.6 Aims

The aims of the review were twofold: to ascertain whether acute low-level CO exposures are associated with cognitive impairments; and if so, whether there exists an identifiable pattern of observable deficits.

2.2 Method

2.2.1 Literature Search

The experimental literature investigating the relationship between acute low-level CO exposure, COHb levels and cognitive functioning in adults was searched. The search was completed in December 2020. Articles were sourced and identified through searching electronic databases: Academic search complete, PsycInfo, PubMed, SAGE Journals, Scopus, and Web of Science. The search terms are presented in Table 2.1.

Table 2.1. Boolean search terms and combinations

Boolean search term
"Carbon monoxide"
AND
Subacute OR mild OR chronic OR low OR occult
AND
Neuro* OR cogniti* OR psych*
NOT
Animal OR rat OR mice

2.2.2 Inclusion and Exclusion Criteria

The inclusion criteria were: human studies with participants aged 18 years or above; studies published between the years 1960 and 2020; studies that exposed participants to CO, with exposure concentrations and durations resulting in COHb levels below 15%. It is generally agreed that COHb levels of below 15% represent less severe poisoning (Chambers et al., 2008). Studies that used COHb saturations above 15% were included only if lower levels were also examined to enable evaluation of reported effects at the lower concentrations.

Animal studies were excluded along with articles not published in English, case reports, and conference abstracts. Studies examining the neuropsychological effects of acute severe CO poisoning including those investigating efficacy of treatment and neuroimaging findings (defined by one or more of the following: hospital admission, failed suicide attempt, loss of consciousness or a COHb level that would indicate more severe poisoning >15%) were excluded. Additionally, studies investigating other CO-related health effects not relating to cognition (such as cardiac, respiratory and peripheral neuropathy), those examining the effects of smoking, mechanisms of CO toxicology, effects of prenatal CO

exposure in the developing foetus and the effects of CO exposure on paediatric and adolescence development were excluded.

2.2.3 Identification and Selection Procedure

The titles and abstracts of studies were initially screened for eligibility based on the above criteria. Full text articles were then screened and excluded based on the additional criteria: studies not including neuropsychological testing, those investigating severe acute CO poisoning in the 'chronic' or 'subacute' phase, studies where exposure levels were not measured or reported, and multiple reports of the same data set. Article references were also screened and additional articles identified.

2.2.4 Quality Appraisal and Risk of Bias

A quality appraisal was carried out on full text articles for inclusion eligibility using the Mixed Methods Appraisal Tool (MMAT; Hong et al., 2018), by three authors independently (B.L.C., C.A.H. and T.J.C.). Any discrepancies were discussed and agreement reached. Included studies were appraised using the two initial screening questions followed by either Section 2 (quantitative randomised controlled trials) or Section 3 (quantitative non-randomised trials). Each criterion was marked as yes, no or can't tell (if unclear). Non-randomised studies were then assessed using the risk-of-bias in non-randomized studies of interventions tool (ROBINS-I; Sterne et al., 2016) and randomised studies using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2; Sterne et al., 2019). From the results, an overall risk of bias is calculated. Studies were not excluded on the basis of quality or bias risk permitting lower quality papers to contribute to the analysis. However, quality and bias were considered when synthesising the results and drawing conclusions.

2.2.5 Data Extraction and Synthesis

Study methods (experimental design, sample size, age and sex of the participants studied, exposure type, level and duration, mean COHb levels before and after exposure, and the acquisition technique used to measure COHb levels) were initially collated and examined. The studies were then grouped according to the various cognitive domains measured by the tasks. Allocation of the tasks

into their cognitive domains was reviewed and any discrepancies discussed and agreed by all three authors. Following critical appraisal, the results from each of the studies were synthesised and a narrative analysis undertaken. Statistical meta-analysis of the combined data was not possible due to insufficient information in many studies. Effect sizes were calculated for studies where possible.

2.3 Results

The search identified 495 articles. After removal of duplicates, 322 articles remained. Titles and abstracts were reviewed according to the inclusion/ exclusion criteria and 90 articles were retained. After reviewing the full texts, 11 of the studies met the inclusion criteria. The bibliographies of these articles were screened and 36 additional articles identified, of which 15 met the inclusion criteria. These articles potentially were not identified via the search strategy due to the search terms not being present in the article titles or keywords and the articles not being as accessible due to their age. One article was excluded as it reported on the sample size only with no further participant information provided. A total of 26 articles were included in the review (PRISMA diagram Figure 2.1).

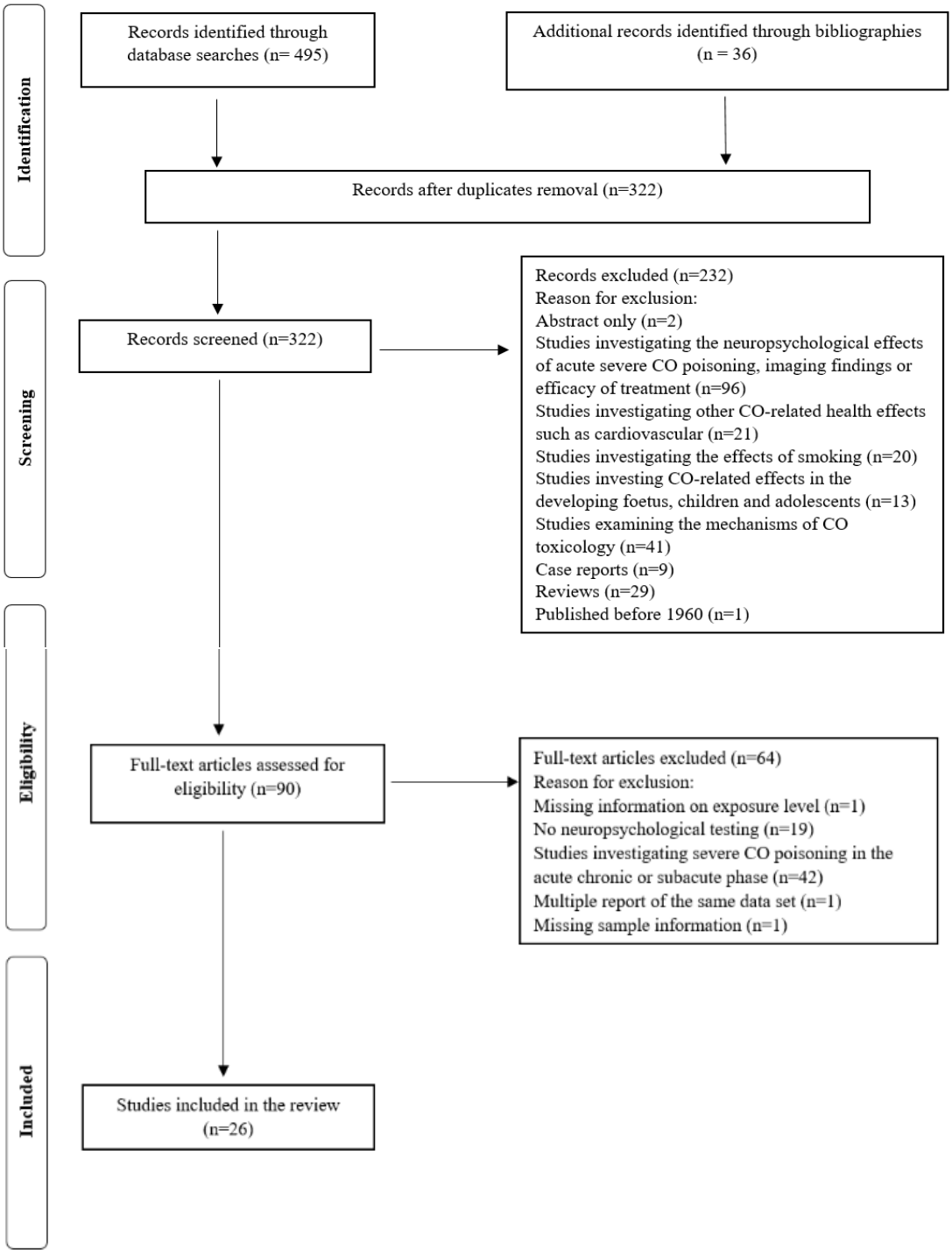


Figure 2.1 PRISMA flow diagram: identification, screening, eligibility and inclusion of the reviewed papers.

2.3.1 Design, CO Concentrations and Exposure Durations

Demographic information, sample size, study design, exposure type, and level and duration of exposure for each of the studies are provided in Appendix 1 (A1) Table A1.1.1. Of the 26 studies included in the review, all were experimental in design and published between 1963 and 1998.

2.3.1.1 Within-participant Studies

Twelve studies used a within participants, repeated measures design wherein participants were exposed to air to establish baseline levels and then were exposed to one or several CO concentrations ranging from 26-800ppm (Beard & Wertheim, 1967; Bunnell & Horvath, 1988; 1989; Gliner et al., 1983; Horvath et al., 1971; McFarland, 1973; O'Donnell, Mikulka, Heinig, & Theodore, 1971a; O'Donnell, Chikos, & Theodore, 1971b; Otto, Benignus, & Prah, 1979; Roche et al., 1981; Rummo & Sarlanis, 1974; Salvatore, 1974). All the CO exposures were acute with the majority of studies exposing participants to CO for durations between 1 and 4 hours. Task durations were not reported in three studies (Bunnell & Horvath, 1988; 1989; McFarland, 1973). However, after examination of the task descriptions and considering the 60-80 minutes exposure prior to testing, it can be assumed that the total exposure duration would have also fallen between 1 and 4 hours. Two studies used shorter exposures of 20 minutes (Rummo & Sarlanis, 1974; Salvatore, 1974), and one used a longer exposure of 7 hours whilst the participants slept (O'Donnell et al., 1971b) (see Table A1.1.1).

2.3.1.2 Between-participant Studies

Three studies utilised a between participants design comparing cognitive performance on a range of tasks between a control and experimental group. Amitai et al., (1998) compared performance between a control group (exposed only to filtered air) and a CO group exposed to 17-100ppm for between 1.5 and 2.5 hours. Schulte (1963) assigned participants to one of several groups, a control group exposed only to air and the remaining groups exposed to CO (100ppm) randomised across 4 testing cycles. The duration of exposure was not reported, only that CO levels were maintained throughout testing. Stewart and colleagues (1970) assigned participants to groups where exposures ranged from 1-24 hours at levels between 25 and 1000ppm (Table A1.1.1).

2.3.1.3 Mixed-Design Studies

Seven studies used a mixed design that included within-participant measures aspects where all participants completed a control condition exposed to filtered air to obtain pre-exposure baselines followed by between-participant comparison by allocation to either a CO exposure group or control group. Within-group comparisons were made between performance pre- and post-exposure and over time (different hours/sittings). The between groups component consisted of comparisons between performance in the different exposure group/s and the controls over time (Benignus et al., 1977; Benignus et al., 1990; Benignus et al., 1987; Putz, 1979; Ramsey, 1972; 1973; Wright, Randell & Shephard, 1973). Four studies employed the same within group measures but rather than a control group, the between groups comparisons were of performance between younger and older adults before and after CO exposure (Groll-Knapp et al., 1982; Harbin, Benignus, Muller, & Barton, 1988) or between pre and post exposure across different exposure settings (Stewart, Newton, Hosko, & Peterson, 1973; Wright & Shepard, 1978). The different exposure concentrations varied between 35 and 9,600ppm. All the exposures were acute with most studies using exposure of 1-5 hours. Three studies used slightly shorter exposures up to 45 minutes (Ramsey, 1972; 1973; Wright, Randell & Shephard, 1973), and one exposed participants for 8 hours whilst they slept (Groll-Knapp et al., 1982) (Table A1.1.1).

2.3.1.4 Studies using Higher CO Concentrations

Seven studies exposed participants to higher levels of CO, five of which used significantly shorter exposure durations raising COHb levels to a maximum of 8% (Rummo & Sarlanis, 1974; Salvatore, 1974), 11% and 17% (McFarland, 1973) 8.5-12% (Ramsey, 1973) and 1-16.6% (Benignus et al., 1990). The studies by Stewart et al., (1970) and Stewart et al., (1973) used high CO concentrations (up to 1000ppm) and included both shorter and longer exposure durations (up to 8 hours) with resulting COHb levels of 2.1-31.8% and 0.4-20% respectively. Therefore, any CO-related effects associated with higher CO concentrations and durations (COHb between 21.9 and 38.1%) are noted but not discussed as they do not represent low-level CO exposure.

2.3.2 Participant Description

All studies examined the effects of CO exposure in healthy adults with the exception of one, which compared the effects of CO exposure between healthy individuals, patients with anaemia and patients with emphysema (Ramsey, 1972). Only eight studies used both female and male participants (see Table A1.1.1). The remaining 18 studies either included only male participants (13 studies), female participants were under-represented (two studies) or gender information was omitted (three studies). The majority of studies included only non-smoking adults as participants, with the exception of six (Amitai et al., 1998; McFarland, 1973; Rummo & Sarlanis, 1974; Schulte, 1963; Stewart et al., 1970; Stewart et al., 1973). In four studies, participants' smoking status was not reported (Benignus et al., 1990; Gliner, Horvath, & Mihenic, 1983; Ramsey, 1973; Wright, Randell, & Shepard, 1973). Ages ranged from 17-43 yrs in the majority of studies, with the exception of three which included those aged 22-55yrs (Schulte, 1963), 20-50yrs (McFarland, 1973) and 17-65yrs (Wright, Randell, & Shephard, 1973). The mean age or age range was not reported in two studies (Beard & Wertheim, 1967; Ramsey, 1972). Two studies compared the effects of CO exposure between younger and older adults. Harbin et al., (1988) compared participants aged 18-28yrs (*m*=22.8) to those aged 60-86yrs (*m*=68.7) and Groll-Knapp et al., (1982) compared participants aged 20-25yrs and 55-72yrs.

2.3.3 COHb Acquisition Technique and Levels, Reported Findings and Effect Sizes.

The carboxyhaemoglobin acquisition technique and mean COHb levels pre and post exposure are presented in Table A1.1.2. Of the 26 studies, 20 obtained blood samples, two used a breathalyser or/and CO-oximeter (Rummo & Sarlanis, 1974; Salvatore, 1974) three estimated levels from formulae (Groll-Knapp et al., 1982; Wright & Shephard, 1978; Wright, Randell & Shephard, 1973) and one study did not obtain COHb levels (Beard & Wertheim, 1967). Tasks and their corresponding cognitive domains, reported findings and effect sizes are also presented in Table A1.1.2. Effect sizes were calculated based on the pooled standard deviation and were classified according to Cohen's criteria (Cohen, 1992): trivial (Cohen's $d \leq .2$), small (> .2), moderate (> .5), large (> .8), and very

large (> 1.3). Effect sizes were not calculated for 12 studies due to insufficient information.

2.3.4 Critical Appraisal and Risk of Bias

The MMAT quality appraisal is presented in Table A1.1.3 and the assessment criteria are presented in Table A1.1.4. There were a total of 18 non-randomised studies, of which 10 (55.6%) were well controlled with confounders in the design and analysis appropriately accounted for, although only half were double blind. The remaining eight studies were poorly controlled, with samples including smokers, COHb levels estimated or reported post-exposure only, CO levels not maintained or monitored, practice effects and sample characteristics not accounted for or full analysis details or outcome data omitted. There were eight randomised studies, of which five (62.5%) were well controlled, with groups comparable in number, sample characteristics and pre-and-post COHb levels. Baseline task performance was corrected for, or thorough practice sessions provided and CO levels monitored and maintained throughout testing. The remaining three studies either omitted group characteristics, included smokers, or COHb levels were estimated or not obtained pre-exposure. All studies provided complete outcome data and were double blind, with the exception of one. The results of the ROB-2 and ROBINS-I (Sterne et al., 2016; 2019) are presented in Table A1.1.5. Of the randomised trials, 50% (4) were considered to be low risk of bias overall compared to only 17% (3) of the non-randomised trials. Furthermore, around 67% (12) of non-randomised trials were categorised as serious risk of bias compared to only 25% (2) of the randomised trials. In summary, non-randomised studies tended to be of poorer quality and presented higher risk of bias.

2.3.5 Cognitive Domains

Study tasks were separated into the areas of cognition assessed. As the majority of studies used several tasks that assessed various aspects of cognition, they are discussed in multiple sections according to the corresponding cognitive functions. A description of the tasks used in each of the studies and the assignment to their corresponding cognitive domains are presented in Table A1.1.6.

2.3.5.1 Visuospatial Ability

Of the four studies examining visuospatial ability, three found no significant CO-related effects at COHb levels of 7 and 10% (Bunnell & Horvath, 1988; 1989) or up to 16.6% (Stewart et al., 1970). Amitai et al., (1998) reported a significant decrease in WAIS block design scores in the experimental group at around 4% COHb when compared to the control group (p=.01; d=.56). However, the task used assesses both visuospatial ability and problem solving. Therefore, given the lack of effect in the other studies, the performance deficits may instead reflect CO-related impairments in problem solving. It is important to note that this was the only unblinded study and blood COHb levels were taken from the experimental group post-exposure only, and so comparisons between pre- and post-exposure COHb levels could not be made. Determining the degree of exposure is therefore difficult, particularly as smokers were included in the sample. Furthermore, the authors report that CO concentrations ranged from 17-100ppm, however the method of monitoring CO levels throughout the 1.5-2.5 hour period prior to testing was omitted. Additionally, all three studies reporting no effects were relatively well controlled, although effect sizes could not be calculated (see Tables A1.1.1; A1.1.2; A1.1.3). In summary, it appears unlikely that acute low-level CO exposure resulting in COHb levels ≤16.6%, would have any effect on visuospatial ability.

2.3.5.2 Sustained Attention

Of the five studies examining sustained attention, two reported no CO-related effects at COHb levels of 5% (Roche et al., 1981) 5.9% and 12.7% (O'Donnell et al., 1971b). However, a large effect size was observed in Roche et al.'s (1981) study (d=-1.17) during the 31-45 minute period on signal detection accuracy indicating increased performance in the control condition. Moderate effect sizes were also observed during the 31-45 and 46-60 minute periods on percentage of false positives (d=-.50) and (d=-.78) respectively, this time signifying *worse* performance in the control. Inspection of the data indicated minimal performance change in the CO condition. O'Donnell et al., (1971a) found a significant effect of CO on 10s time estimation at 3% COHb only, reporting longer time estimations when compared to the control during the 135-150 minute exposure period (p<.05). However, the observed difference was due to a performance decrease

in the control with the exposure condition showing little change. Furthermore, this effect was not observed when COHb levels reached 6.6%. Moreover, in O'Donnell et al., (1971b) study, inspection of the 10s time estimation scores revealed higher accuracy during both CO exposure conditions compared to the control, particularly in the 150ppm condition. Although this effect did not reach significance a moderate effect size was observed (*d*=-.52) (see Table A1.1.2). In contrast, Horvath and colleagues (1971) reported a significant decrease in mean correct responses on a visual monitoring task at 6.6% COHb when compared to the control ($p<.05$). However, this was the only single blind study of the five.

Stewart et al., (1973) reported a significant decrease in time estimation ability of 30s intervals in the exposure conditions up to 20% COHb. However, this effect was not consistent across conditions, observed only in the isolated chamber and not in the group or audiometric booth settings. The COHb level at which this deficit became apparent was not reported. Analysis of the effect sizes suggests that the deficit occurred at COHb levels of 4.01-8% (*d*=-.78). All other effect sizes calculated for the isolated setting were small, suggesting that the significant effect is related to the setting rather than CO exposure (see Table A1.1.2). Moreover, this effect was not observed when estimating 10s intervals up to 20% COHb. Determining the degree of exposure is also difficult as COHb levels were not reported for the groups separately or pre- and post-exposure. This is of particular concern as the study was one of six that used smokers in the sample. Although no other significant differences were reported between the control and exposure conditions across settings, very large effect sizes were observed when estimating both 10 and 30s intervals in the booth setting, (*d*=-1.31) and (*d*=-2.04) respectively. These indicate decreased performance in the CO condition compared to the control. However, performance in the booth setting was generally worse in both the control and exposure conditions when compared to the group and isolated conditions. This suggests that the effects are likely to be due to factors related to the booth setting, with participants confined to a small sound proof booth with no outside visual input. It is therefore plausible that the effects are accounted for, or confounded by, sensory restriction rather than CO exposure (O'Donnell et al., 1971a).

In summary, the reported significant negative CO-related effects are possibly accounted for by the exposure setting (Stewart et al., 1973) or a decrease in performance in the control condition (O'Donnell et al., 1971a). Similarly, the moderate and large effect sizes observed in Roche et al.'s (1981) study appear to be related to variable performance in the control condition. Furthermore, evidence from one study indicates that such exposures may in fact be associated with *improved* performance (O'Donnell et al., 1971b). However, the results were based on an extremely small sample of only four participants. In summary, CO exposure resulting in COHb levels up to 20% would appear to have little or no negative effects on sustained attention.

2.3.5.3 Sustained Attention and Updating Working Memory (WM) (Executive Function)

Of the eight studies assessing sustained attention and updating, six reported no significant CO-related effects at COHb levels of 3.8-17% (Benignus et al., 1977; Benignus et al., 1990; O'Donnell et al., 1971b; Otto et al., 1979; Stewart et al., 1970; Wright & Shephard, 1978). Stewart et al., (1973) reported a significant performance decrease during an auditory time discrimination task between the control and exposure means in the booth setting only, at COHb levels of 9.74% (p<.05). This was not a consistent finding across conditions (isolated chamber, group chamber, and audiometric booth), therefore the effect is again likely to be due to factors related to the booth setting. The small effect sizes observed across all exposure concentrations and conditions, except for in the booth setting, support this (see Table A1.1.2). Furthermore, no significant effects of CO were found during a similar time discrimination task used in the same study, making it difficult to attribute the observed performance decrement to CO exposure.

Beard and Wertheim (1967) reported a significant decrease in correct responses during an auditory time discrimination task at all exposure concentrations (50-250ppm) when compared to the control condition (p<.02). Exposure to 50ppm caused significant performance impairments for both the longer (p<.05) and shorter tone (p<.02). At higher concentrations differences were significant at the p<.01 level when compared to the control. The authors reported a dose related decrease in correct responses with higher CO exposures resulting in greater

performance impairment. However, all participants were tested in an audiometric booth and thus the results may again be accounted for by sensory restriction. This was also one of only two single blind studies. Furthermore, pre- and post-exposure blood COHb levels were not obtained which makes it difficult to ascertain the degree of exposure. Examining the effects of low-level CO exposure without a direct measure of COHb level is problematic and predicting these levels overlooks individual differences such as prior CO exposure, pulmonary diffusing capacity and ventilator volume, all of which may introduce potential sources of error (Horvath et al., 1971).

Effect sizes could only be calculated for three of the eight studies. Based on the available data, it seems reasonable to suggest that CO exposure resulting in COHb levels up to 20% has no effect on sustained attention or areas of updating. In support of this, five of the six studies reporting no CO-related effects were double blind, three of which were well controlled (Benignus et al., 1977; Benignus et al., 1990; Otto et al., 1979) (see Tables A1.1.1; A1.1.2; A1.1.3).

2.3.5.4 Sustained Attention and Inhibition (Executive Function)

One study assessed sustained attention and pre-potent response inhibition using a visual monitoring task (Gliner et al., 1983). Performance levels significantly decreased at COHb levels of 5.8% during the last 30 minutes of testing when compared to performance in the control condition ($p<.05$). Effect sizes could not be calculated. Forming any conclusions about the effects of low-level CO exposure on sustained attention and inhibition is difficult due to the limited number of studies. The significant performance impairments reported by Gliner et al., (1983) may suggest a possible association between impairments in inhibition and low-level CO exposure rather than deficits in sustained attention, since studies on sustained attention failed to find significant CO-related effects (see Sections 3.5.2, 3.5.3). However, the study was single blind and COHb blood samples were only obtained for approximately half of the sample making it difficult to determine the degree of exposure and controlling for individual differences problematic.

2.3.5.5 Divided Attention, Task Switching, Inhibition (Executive Function) and Psychomotor Function

Of the four studies assessing divided attention, task switching, pre-potent response inhibition and psychomotor function using a tracking and concurrent visual monitoring task, one reported no CO-related performance effects (Benignus et al., 1990). Gliner et al., (1983) reported a significant decrease in monitoring performance during the final 30 minutes of exposure (5.8% COHb) when compared to the control but only when the monitoring task was completed singly ($p<.05$). Benignus et al., (1987) reported a significant interaction between CO exposure x hour, whereby CO exposure produced larger tracking errors than exposure to air as a function of time ($p<.01$). Significantly decreased performance at COHb levels of 8% were found following sufficient exposure time. However, when comparisons were made between the two groups at each hour no significant differences were found; neither did task difficulty significantly affect tracking performance. The significant performance decrease within the CO exposure group however, is supported by moderate effect sizes between the control and exposure groups in hour 4 across both task difficulties (see Table A1.1.2).

Putz (1979) found a significant interaction effect between tracking frequency (task difficulty), exposure time (1-4 hours), and exposure group (0, 35, 70ppm) ($p<.01$). Simple main effects tests revealed that the only significant difference was between the control and 70ppm exposure group (5% COHb) during the fourth exposure hour in the high frequency tracking condition. A significant interaction effect was also found between exposure group and exposure time (hour) in reaction times (RTs) on the monitoring task ($p<.05$). Main effects tests revealed that RTs on the monitoring task significantly increased between the second and fourth hour in the 70ppm exposure group when compared to the control ($p<.01$). Effect sizes could not be examined due to limited information.

In summary, exposure to CO resulting in COHb levels between 5 and 8% may significantly affect performance when attention is divided between two concurrent tasks that rely on psychomotor function, task switching and inhibition given sufficient exposure duration. In support of this, Benignus et al., (1990) noted a

trend whereby performance in the CO exposure conditions was near control values at the start of the task but deteriorated as a function of time. All of the exposed group's baseline corrected mean tracking errors were greater than those of the control group and increased in a dose dependent manner (Benignus et al., 1990). A moderate effect size was found in the fourth hour of exposure (see Table A1.1.2). Furthermore, three of the studies were double blind and well controlled with COHb blood samples taken pre-and-post exposure and individual differences in baseline performance either corrected for (Benignus et al., 1990) or thorough practice sessions provided to achieve comparable proficiency on the tasks (Benignus et al., 1987; Putz, 1979). Therefore, the finding seems replicable and robust.

2.3.5.6 Divided Attention, Task Switching (Executive Function) and Psychomotor Function

Of the six studies assessing divided attention, task switching and psychomotor function, five reported no significant CO-related effects at COHb levels of 7-16.6% (Bunnell & Horvath, 1988; 1989; McFarland, 1973; O'Donnell et al, 1971b; Stewart et al., 1970). Rummo and Sarlanis (1974) reported significantly slowed RTs in a driving task at COHb levels of 6-7.6% compared to the control (p<.01) supported by a very large effect size (d=1.77). However, the results were based on a sample of only seven individuals. Forming any firm conclusions is difficult due to the quality of the studies. For example, O'Donnell et al., (1971b) used an extremely small sample of only four participants all of whom had undergone altitude training resulting in greater physiological compensation for decreases in oxyhaemoglobin availability. McFarland's (1973) and Stewart et al.'s (1970) studies were not well controlled, with data omitted or problems with counterbalancing or consistency across sessions. Inspection of the means and effect sizes in Stewart et al.'s (1970) study indicate *better* driving performance in the exposure groups compared to the control. Similarly, a moderate effect size was found in O'Donnell et al., (1971b) study during the high workload task, indicating *greater* tracking accuracy in the 75ppm CO condition compared to the control (see Table A1.1.2). Effect sizes could not be calculated for the remaining four studies.

Based on the available data, low-level CO exposure resulting in COHb levels between 7 and 17% does not appear to have a negative effect when attention is divided between two tasks requiring task switching abilities and psychomotor function. Examination of the data and effect sizes suggest that these exposures may even be associated with *improved* performance. It is noteworthy that these studies failed to find CO-related effects at around 13% COHb, yet studies using very similar experimental methodologies aimed at assessing similar areas of cognition found effects between 5 and 8% COHb (Benignus et al., 1987; Putz, 1979). All of the studies assessed divided attention, task switching and psychomotor function, and although evidence is limited, it seems reasonable to suggest that if an association existed between these exposures and impairments in these areas of cognition then this would be a consistent finding across the studies, particularly as the methodologies were extremely comparable. The main difference between the studies were in the areas of executive function (EF) assessed. Studies reporting significant effects of CO measured the additional EF of inhibition whereas those failing to find a CO-related effect assessed task-switching only. Furthermore, Gliner and colleagues (1983) found a significant effect of CO on performance during a similar inhibition task at COHb levels of 5.8%.

The synthesis in this review points towards an association between low-level CO exposure and impaired inhibition. This, taken together with results of studies reporting no CO-related effects on sustained attention, provides further support for the supposition that the performance impairments observed by Gliner et al., (1983), Benignus et al., (1987) and Putz (1979) may be associated with deficits in inhibition rather than in ability to sustain or divide attention, or in psychomotor function or task switching.

2.3.5.7 Fine Motor Control, Psychomotor Function and Speed

Of the seven studies assessing psychomotor function, four reported no significant CO-related effects up to 16.6% COHb (Bunnell & Horvath, 1988; 1989; Stewart et al, 1970; Wright, Randell & Shephard, 1973). Analysis of the effect sizes in Stewart et al.'s (1970) study revealed that exposures of around 50ppm *improved* performance on the Crawford collar and pin and hand steadiness tasks (see

Table A1.1.2). O'Donnell et al., (1971a) reported no significant CO-related effects over time in tracking ability at COHb levels of 3% and 6.6%. When performance between the conditions were compared, a significant difference was found during the 105-120 time period (p<.05), whereby performance was better during the control compared to both exposure conditions.

Schulte (1963) reported significant positive correlations indicating greater mean completion times and errors with increasing COHb levels following exposure to 100ppm. The author reported that these performance decreases were observable at a COHb level of 3%. However, Schulte (1963) has been criticised for underestimating the COHb levels of his control participants (0.0%) which comprised Firemen working in a large city who were predominantly smokers, and for the extremely high COHb levels reported (up to 20.4%) given that participants were only exposed to 100ppm (O'Donnell et al., 1971a; 1971b). Furthermore, the study was single blind and it is unclear whether pre-exposure baseline levels were obtained causing difficulty in determining the degree of exposure and the COHb level at which the deficits became apparent. In another study, Amitai et al., (1998) found significant performance decreases in the exposure group on both the digit-symbol task (p<.01; d=-.61) and Trail Making part A task (p<.05; d=.43) at 4% COHb when compared to the control group. However, the study was not well controlled (see Section 3.5.1 and see Tables A1.1.1; A1.1.2; A1.1.3).

The main difference between studies reporting a significant effect of CO and those that did not is the additional factor of speed. Three of the seven studies included tasks with a speed aspect (participants were either timed or there was a pre-set completion time), of which two reported significant effects (Amitai et al., 1998; Schulte, 1963). The remaining four studies examined psychomotor function only, with three reporting no significant effects (Bunnell & Horvath, 1988; 1989; Wright, Randell & Shephard, 1973). The reported performance decrements may therefore be related to deficits in psychomotor speed rather than function. This supports the inference that the CO-related effects observed by Gliner et al., (1983), Benignus et al., (1987) and Putz (1979) were not associated with impaired psychomotor function. However, caution must be taken with this

interpretation as neither of the two studies reporting effects were well controlled, neither could effect sizes be calculated for four of the seven studies (see Tables A1.1.1; A1.1.2; A1.1.3). Nevertheless, these exposures appear to have little effect on psychomotor function, but may be associated with impaired psychomotor speed at COHb levels as low as 3-4%.

2.3.5.8 Reaction Time (RT) (Speed of Processing and Psychomotor Speed)

Single task conditions

Of the eight studies employing single tasks, three reported no significant CO-related effects on RTs to visual stimuli at COHb levels of 5% COHb, (Harbin et al., 1988) up to 20% (Schulte, 1963), or during a driving task following a 3.4% COHb increase (Wright, Randell & Shephard, 1973). Although Harbin et al., (1988) reported no significant differences, moderate effect sizes were found indicating slowed RTs in the older adult group following CO exposure (see Table A1.1.2). Ramsey (1972) reported no significant CO-related effects on RT to visual stimuli at COHb levels of 5.4% in any group individually (healthy, emphysema, anaemia) over time or when compared to the control group. When the RTs for all the exposed groups were combined the difference between before and after exposure became significant (p=.02; d=.22). Examination of the within-group differences revealed small effect sizes. Very large effect sizes were found between the exposure and control groups post-exposure. However, these between-group differences were present prior to exposure and therefore are not related to CO (see Table A1.1.2). Salvatore (1974) found significantly increased RTs to visual stimuli at COHb levels of 8% compared to the control condition during the dynamic task condition (moving target) only (p<.25; d=1.33).

Ramsey (1973) reported no significant effects of CO on the Critical Flicker Fusion task (CFFT) over time in either group or between groups. A significant increase in RTs on a visual task was found when comparing pre- and post-exposure means in both the 8.5% and 12% COHb conditions (p<.01), and in both CO groups compared to the control (p<.05). Moderate and large effect sizes were observed in support of these findings (see Table A1.1.2). Bunnell and Horvath (1988; 1989) found no significant CO-related effects on RTs at COHb levels of 7% or 10% on the manikin or Sternberg task. A significant interaction was found

in RTs on a visual search task between COHb level and workload, whereby in the 10% COHb rest condition the average RT was less than in the control condition (p<.01). In contrast, in the 60% VO_2max workload condition at 10% COHb, the average RT was significantly greater when compared to the control (Bunnell & Horvath, 1988). These differences were not observed in their 1989 study. Significantly increased RTs were found during Part 3 of the Stroop task at COHb levels of 7% and 10% when compared to the control but only in the 60% VO_2max workload (p=.04) (Bunnell & Horvath, 1989). However, four of the five studies reporting CO-related effects were either single blind or unblinded, with only one double blind study (Ramsey, 1973).

Divided attention conditions

Of the eight studies employing tasks requiring divided attention, six reported no CO-related effects on RTs during tracking and concurrent monitoring tasks at COHb levels of 5.9 -17% COHb (Benignus et al., 1987; Bunnell & Horvath, 1988; 1989; McFarland, 1973; O'Donnell et al 1971b) or during a driving task up to 16.6% (Stewart et al., 1970). O'Donnell et al., (1971b) also found no CO-related effects on the CFFT. Putz (1979) reported significantly increased RTs on a monitoring task at 5% COHb between the second and fourth hour compared to the 3% COHb and control group (p<.01). Rummo and Sarlanis (1974) reported significantly slowed RTs during a driving task in the CO condition at COHb levels of 6-7.6% when compared to the control (p<.01). Moderate to large effect sizes were observed over time with the exception of the 60 minute time period (see Table A1.1.2). Although no significant differences were found in O'Donnell et al.'s (1971b) study, a moderate effect size was observed at 5.9% COHb indicating slowed RTs in the moderate workload condition only. In contrast, small to moderate effect sizes were found in Stewart et al.'s (1970) study indicating faster RTs across all exposure groups when compared to the control. Stewart et al (1973) found no significant effects of CO on RT under sustained attention conditions at COHb levels up to 20%.

Overall, effect sizes could only be calculated for seven of the 15 studies examining RTs and therefore conclusions are limited. The evidence is inconsistent, with a total of seven of fifteen studies reporting some significant

negative CO-related effects on RTs at COHb levels of 5-12%, and eight studies reporting no effects with COHb level increases as little as 3.4% or at much higher levels of 17%. Significant CO-related effects were not found on the CFFT up to COHb levels of 12.7% (Ramsey, 1973; O' Donnell et al., 1971b), suggesting that the observed deficits may be associated with impaired psychomotor speed rather than processing speed. However, five of the seven studies (71.4%) reporting significant effects were single blind. Nevertheless, examination of the effect sizes, where possible, appears to support the finding that a CO-related deficit in psychomotor speed may exist.

2.3.5.9 Sensory, Short-term and Working Memory

Of the three studies assessing working memory (WM), one reported no significant performance effects at COHb levels of 5.9% and 12.7% (O'Donnell et al., 1971b). Schulte (1963) found significant positive correlations between the number of errors and COHb level (r=.59) and between mean completion time and COHb level (r=.67) on a mental arithmetic task. The author reported greater performance decrements with increasing COHb levels that became apparent at concentrations of 1-2%. Healthy individuals have baseline COHb levels up to 2%, it is therefore unlikely that such impairments would be detectable at these low levels. Additionally, O'Donnell et al., (1971b) reported no CO-related effects on a very similar mental arithmetic task or on an additional task assessing WM. Amitai et al., (1998) found a significant performance deficit in the 4% COHb exposure group compared to the control group in working semantic memory only (p=.01; d=-.86). No significant performance effects were found on the digit span backward (WAIS), working figural memory (Wechsler Memory Scale; WMS) or immediate recall (Rey Auditory Verbal Learning Test; RAVLT) with small effect sizes observed.

Three studies assessed sensory memory, two of which reported no significant performance effects at COHb levels of 7 and 10% (Bunnell & Horvath, 1988; 1989). McFarland (1973) found no significant effects during a driving task at COHb levels of 17% in either condition (30 or 50 mph). However, exposed participants did require significantly more roadway viewing time for processing and storage of visual information at 50mph in the CO condition, compared to the

control. One study assessed short-term memory and reported significant differences between the control and 4% COHb exposure group on the digit span forward (p=.02; d=-.52) (Amitai et al., 1998). Forming any definitive conclusions on acute low-level CO exposure and these aspects of memory is difficult due to the limited amount of evidence, quality of the studies and limited effect sizes (see Sections 3.5.1, 3.5.6, 3.5.7 and Tables A1.1.1; A1.1.2; A1.1.3). However, it would appear that both sensory and WM are not affected by these exposures. Studies finding no CO-related effects on updating (Section 3.5.3) support this.

2.3.5.10 Learning Ability and Long-term Memory

Two studies examined aspects of learning ability and long-term memory, both of which reported some CO-related effects. Amitai et al., (1998) used the WMS and reported significant differences between the control and 4% COHb exposure group in long-term semantic memory (p=.01; d=-.57) and long-term figural memory (p=.02; d=-.53). The RAVLT was also used as a measure of long-term memory processing and learning. No significant differences were reported, a finding supported by the observed small effect sizes. However, the study was not well controlled (see section 3.5.1 and Tables A1.1.1; A1.1.2; A1.1.3).

Groll-Knapp et al., (1982) used a memory test where a list of words was recalled at 6 minutes and again after 8 hours of sleep following a 3-minute learning period. In the exposure condition the younger adult group were exposed to 100ppm of CO for an 8-hour sleep period (10% COHb) and the older adult group were exposed to 95ppm (8% COHb). The only finding of significance was in the younger group who recalled significantly more words in the morning than the evening under the control condition (p<.05). The authors concluded that this may suggest an association between CO exposure and deficits in memory consolidation. However, this performance improvement was not observed in the older adult control condition, and therefore likely reflects impaired consolidation in the older adult group due to age-related effects on learning. Furthermore, if such an effect existed following CO exposure, indicated by better performance in the control condition, the effect likely would have been observed in the control condition across both age groups particularly in a potentially high-risk older adult group. Moreover, COHb levels were only reported post-exposure and were

estimated for the younger adult group with blood samples only obtained from the older adult group. Therefore, comparisons could not be made between COHb levels prior to and after exposure, nor could the degree of exposure be accurately determined. Additionally, the significant impairments in long-term semantic and figural memory reported by Amitai and colleagues (1998) were not replicated on similar tasks measuring long-term memory processing and aspects of learning. The evidence on the effects of low-level CO on learning ability and long-term memory is inconsistent and forming any conclusions is difficult due to the quality and limited number of published studies.

2.3.5.11 Cognitive Flexibility (task switching) and Interference (inhibition and selective attention)

Of the three studies assessing cognitive flexibility and interference, one found no significant differences between the control and 4% COHb exposure group (Amitai et al., 1998). Two studies used a three-part Stroop word-colour task (Bunnell & Horvath, 1988; 1989). Part 1 measures simple RTs, whereas Parts 2 and 3 involve aspects of EF, specifically interference (inhibition and selective attention). However, Part 3 also requires cognitive flexibility requiring participants to adapt to a new response set. Only performance on Part 3 of the task was significantly affected by CO indicated by decreased total scores and greater average differences in number of responses between Part 2 and 3 observed in both CO conditions (7 and 10% COHb) when compared to the control (p<.01) (Bunnell & Horvath, 1988). Bunnell and Horvath (1989) reported a significant interaction effect between COHb and physical workload (60% VO_2max) on Part 3 total scores, reflecting increased RTs in the CO conditions when compared to the control (p<.05). The consistent finding across studies was that performance on Part 2 of the tasks was unaffected by CO, whereas negative performance effects were observed on Part 3. This suggests an association between low-level CO exposure and reduced ability to adapt to a new response set (Bunnell & Horvath, 1989).

2.4 Discussion

2.4.1 Summary and Discussion of Findings

Evidence from 26 experimental studies investigating the cognitive effects of acute low-level CO exposure was reviewed. The literature was dated, with studies

published between 1963 and 1998. No recent literature was found. Of the 26 studies, 25 included healthy adults as participants with the majority (19) aged 17-43yrs. Although differences in CO concentrations and exposure durations between studies make comparison difficult, some general observations can be made. Most studies used CO concentrations ranging between 17 and 250ppm (15) with short exposure durations typically lasting 0.75-5 hours (21).

Acute low-level CO exposure appears to have no effect on visuospatial ability at COHb levels up to 16.6%, or on sustained attention and areas of updating (WM) up to 20%. The results revealed minimal CO effects on sensory and WM memory at COHb levels as low as 4% or up to 17%. The evidence of the effects of acute low-level CO on learning ability and long-term memory is limited and forming any conclusions difficult. The two studies assessing these areas of cognition reported some CO-related effects between 4 and 10% COHb, suggesting a potential relationship between such exposures and deficits in these functions. However, further research is warranted to validate these findings.

It would appear that acute low-level CO exposure resulting in COHb levels up to 17% has no effect on divided attention, task switching or psychomotor function. However, exposures resulting in COHb levels of 5-8% may be associated with impaired inhibition. The methodological strengths of these studies add support to this inference, with three of the four studies double blind and well controlled. There is also a potential association between acute low-level CO exposure (7-10% COHb) and reduced cognitive flexibility. Two studies (Bunnell & Horvath, 1988; 1989) found performance on Part 2 of a Stroop task, requiring inhibition and selective attention, to be unaffected by CO, yet performance deficits were observed on Part 3 which requires the additional function of task switching. This suggests that impaired inhibition may result only during complex tasks that depend on additional EF abilities. Studies reporting CO-related effects employed tasks that required both inhibition and task switching abilities with one exception (Gliner et al., 1983). It is possible that a direct association exists between CO exposure and impaired inhibition. However, it is also plausible that such impairments arise only during complex tasks that rely on inhibitory control and task switching simultaneously. This increase in cognitive demand may result in

reduced cognitive control, with CO-related impairments observable across multiple EFs or that arise from impaired inhibitory control subsequently affecting other EF abilities.

Executive function is separated into three core constructs: inhibition, updating and monitoring of WM, and cognitive flexibility. These constructs are commonly viewed as separate subcomponents with unique variance reflecting the distinct abilities associated with a particular construct. However, they are also considered to be interrelated with shared variance indicating significant overlap and dependence upon common underlying abilities (Miyake et al., 2000; Miyake & Friedman, 2012). Inhibition control relies on information being held in WM relating to relevant and irrelevant information to inhibit the appropriate response and achieve a desired goal (Diamond, 2013). Inhibitory control also supports WM through the suppression and deletion of irrelevant and previously relevant information from WM and resisting interference (Hasher & Zachs, 1988; Zachs & Hasher, 2006). Cognitive flexibility relies on both inhibition to deactivate previous rules or perspectives, and WM to activate or load new information (Diamond, 2013).

The key finding of the review is the association between inhibition and CO exposure. Studies that examined other EF components such as WM (including updating) and task switching found no CO-related effects when tasks primarily relied on these constructs. The interrelated nature of EF constructs may offer an explanation for the findings whereby impaired inhibition results from increased cognitive load when tasks demand both inhibitory processes and additional EF abilities. Subsequently, deficits in other EF components may become evident as these rely to a certain degree on efficient inhibitory control. This may also provide an explanation for the possible deficits in problem solving observed by Amitai et al., (1998), with higher-order EFs dependent and built on these core EF components. Therefore, any impairments in the core EF abilities are likely to result in deficits in high-order EFs (Collins & Koechlin, 2012; Lunt et al., 2012).

An alternative explanation for the review findings arises from the viewpoint that inhibition is multifaceted comprising various constructs of inhibitory processes

that rely on distinct brain regions (Hung, Gaillard, Yarmak & Arsalidou, 2018). These constructs include pre-potent response inhibition, resistance to distractor interference and resistance to proactive interference (Friedman and Miyake, 2004; Nigg, 2000). These tasks are commonly used interchangeably to assess inhibition but have been found not to correlate, indicating the presence of distinct aspects of inhibitory control as opposed to a single underpinning mechanism (Noreen & Macleod, 2015). Therefore, the tasks employed by the reviewed studies may, to a degree, be measuring different aspects of inhibitory processing thus explaining the discrepancies in findings. However, further research is needed to aid understanding of the potential relationships between inhibition, other EFs and acute low-level CO exposure.

The results also revealed possible associations between impaired psychomotor speed and acute low-level CO exposures at COHb levels of 3-4%. This finding is supported by studies reporting significant CO-related effects on RT at COHb levels of 5-12%. However, it is important to note, that five of the seven single blind studies (71.4%) reported significant effects on RTs compared to only two of the eight double blind (25%).

It has been suggested that exposures to lower levels of CO may not pose as much risk as higher exposures due to physiological compensation. In response to decreases in the oxygen carrying capacity of the blood, compensatory mechanisms are triggered to maintain oxygen supply to the central nervous system (CNS) including increased cardiac output and cerebral blood flow, cerebrovascular vasodilation and increased oxygen consumption in muscle (Raub & Benignus, 2002). Small increases in COHb levels to around 5-10% have been found not to impair oxygen metabolism. Therefore, if CO-related effects on the CNS are caused by hypoxic mechanisms, any subsequent neuropsychological effects at these low COHb levels would be small (Raub & Benignus, 2002). A total of 16 of the 26 reviewed studies here reported some CO-related effects, of which 13 examined COHb levels up to, but often below 12%. The significant CO-related behavioural effects reported by some studies may have therefore been Type I errors, or resulted from underreporting of non-

significant findings or unintentional leaks in blinding (Raub & Benignus, 2002; Rosenthal, 1979).

In his meta-analysis of 43 studies on the effects of CO on behaviour, Benignus (1993) found that studies carried out under single blind procedures were significantly more likely to find CO-related effects (75%) compared to those studies utilising double blinding (26%). Of the 26 reviewed studies here, 10 were single blind and two unblinded, of which ten (83%) reported some significant CO-related effects, compared to only six (43%) of the 14 double blind studies. However, in their more recent review, Benignus et al., (2002) concluded that "it is difficult to explain such effects from well planned and executed studies" (p930) and "none of the reported CO behavioural effects in humans are, without further work, entirely credible."(p927) (Raub & Benignus, 2002). The results of the current review indicate that some of the inconsistencies within the CO behavioural literature are due to slight differences in the cognitive domains assessed. Our analysis of the multiple cognitive domains, rather than by primary function only, resulted in a synthesis sensitive to subtle cognitive differences, a previously unexplored method within the literature. This approach has subsequently revealed associations between low-level acute CO exposures and specific cognitive functions including psychomotor speed, inhibition and long-term memory and provides an alternative explanation for the inconsistent findings within the literature.

2.4.2 Implications for Future Research

The majority of studies on the neuropsychological effects of acute low-level CO exposure have typically included healthy (predominantly male) young adults, who as a group have maximal physiological reserve to compensate for decreases in oxyhaemoglobin availability, and are least likely to show any adverse effects on the CNS (Otto et al., 1979). Individuals with compromised ability to adequately regulate oxygen supply or metabolism are likely to be most susceptible to raised COHb levels and develop severe toxicity from lower concentrations. High risk groups within the population include the unborn and very young, and older adults particularly those with pre-existing disease (Chiew & Buckley, 2014; Raub & Benignus, 2002). Previous experimental studies have reported the detrimental

effects of acute low-level CO exposure on the cardiovascular system within susceptible groups such as patients with coronary artery disease (Anderson et al., 1973). However, research is needed that examines the neuropsychological effects of these exposures within high-risk groups. Focus should be directed to the effects of such exposures on inhibition from a multifaceted viewpoint and include conditions of increased cognitive demand wherein tasks are dependent on simultaneous EF abilities. This would develop understanding on whether deficits result as a direct effect on specific aspects of inhibition or whether the relationship is moderated or mediated by an additional EF when these are required concurrently. The effects of such exposures on higher-order EFs, such as planning and problem solving, also warrants attention. The findings of this review suggest possible impairments in long-term memory and psychomotor speed which also present potential areas of future research.

Studies on the effects of prolonged chronic low-level home exposures (>24 hours), as opposed to the acute exposures reviewed here (≤24 hours), are extremely limited. The effects of such exposures whereby the body is compensating for a prolonged period of time are unknown, with tolerance and adaptation mechanisms potentially minimising risk to the CNS. Indoor sources of CO such as gas appliances contribute significantly to CO exposure, with studies reporting ambient CO levels above the WHO (2010) guidelines, particularly whilst gas appliances are in use (Croxford et al., 2005a; Croxford et al., 2005b). Case reports document neuropsychological sequelae such as deficits in memory, learning ability and motor slowing following chronic CO exposure within the home (Myers et al., 1998; Ryan, 1990). These exposures may be therefore be responsible for significant widespread morbidity particularly in high-risk groups such as older adults not only due to increased susceptibility but also due to increased time spent within the home (Harper & Croft-Baker, 2004; Myers et al., 1998). Studies aimed at ascertaining the proportion of individuals who are exposed to chronic low level CO in the home, examining the potential long-term effects of COHb accumulation over time and physiological responses to chronically elevated COHb levels are needed.

It is notable that following examination of the effect sizes, possible associations between low-level exposure and *increased* performance in areas of sustained and divided attention, task switching and psychomotor function were found (O'Donnell et al., 1971b; Stewart et al., 1970). These findings, however, should be interpreted with caution due to the extremely small sample size in one of the studies (n=4) (O'Donnell et al., 1971b) and neither of the studies were well controlled. However, in their study of the effects associated with chronic exposure within the home, Volans and colleagues (2007) observed trends towards increased cognitive performance in areas of auditory working memory, immediate and delayed visual memory recall, visuospatial ability and problem solving (although all were non-significant, >.05 *SD*). Chronic exposure to extremely low-level CO may therefore result in temporary improvements in cognition function. There is evidence in support of this with endogenously produced CO known to have beneficial effects. Identified as a neurotransmitter, endogenous CO is involved in a range of cellular functions exhibiting both physiologic and cytoprotective properties. Therapeutic actions include vasodilation, proliferation, anti-apoptotic factors and anti-inflammatory properties, with the administration of exogenous low-level CO currently being studied for neuroprotection in a range of brain pathologies (for reviews see Mahan, 2012; Queiroga, Vercelli & Vieira, 2015). These beneficial effects may therefore be present following inhalation of low-level CO. These effects if present, may be observed in specific groups only, such as older adults who may benefit most from the potential physiological and protective properties due to the biological and physiological changes associated with ageing and disease. However, any potential beneficial effects are likely short lasting with prolonged exposure, and the burden this places on the body's resources, reaching a point where harm is initiated.

The level and durations at which acute and chronic low-level exposures become harmful to health are likely to be different with some degree of variation due to individual differences in the population of study. The studies included in this review typically used CO concentrations of 100ppm with short durations. Under chronic conditions, these would not represent low-level exposure, particularly in reference to the WHO indoor air guidelines (2010) and to concentrations

previously reported in UK homes. The toxic effects of CO are known to occur via hypoxia independent mechanisms such as inflammation and immunologic responses (Weaver, 2009). Lower CO exposures are unlikely to cause a hypoxic state severe enough to cause immediate damage but may result in a certain degree of CWM demyelination given sufficient exposure time, potentially disrupting neurocognitive networks. Whether the effects of low-level exposures are long lasting and whether chronic exposures can lead to demyelination or more severe damage such as irreversible necrosis is unknown. Adaptation, tolerance and compensatory mechanisms and the potential beneficial properties of low-level exogenous CO may play a protective role up to a certain CO dose and duration, but the point at which these mechanisms become ineffective and the exposure becomes toxic is unknown. Future research should be directed towards the level and duration at which both acute and chronic low-level CO exposure shifts from being beneficial to harmful and the resulting neuropsychological effects and corresponding neuroimaging findings. This should be conducted with consideration of, and adherence to, ethical guidelines to ensure individuals are not put at risk in environments with potentially harmful levels of CO.

2.4.3 Limitations

Synthesis of the studies by cognitive domains sometimes resulted in only a few studies examining the same aspects of cognition. Consequently, the conclusions drawn were based on a limited amount of evidence. The quality of the included studies also adds some degree of uncertainty to the results, with the majority of studies omitting pertinent data either relating to sample characteristics, methodology, analysis or results. Effect sizes could not be computed for around half of the included studies and therefore a meta-analysis was not possible. A further limitation relates to the acquisition technique and measurement of COHb levels. Of the 26 included studies, 22 obtained direct COHb measurements, of which only 13 acquired samples both pre- and post-exposure. The importance of directly measuring pre-exposure baseline COHb levels has been discussed previously. Predicting COHb levels from formulae or acquiring samples post-exposure only, introduces potential sources of error relating to physiological individual differences and prior CO exposure. This makes determining the degree

of exposure problematic, particularly as smoking participants were included in six of the studies. Additionally, most studies did not use standardised, validated and reliability tested measures and a third were not well controlled, presenting problems with randomisation, counterbalancing and individual differences all introducing potential sources of error. Moreover, most studies were over four decades old, women were underrepresented and around half were single blind and used extremely small samples. Thus, most studies had poor design and control measures and were unethical.

2.4.4 Conclusion

In summary, the results of the review suggest that acute low-level CO exposures are not associated with impaired visuospatial skills, ability to sustain or divide attention, sensory and working memory, or psychomotor function. A pattern of deficits emerged that suggests these exposures may be related to impaired long-term memory, psychomotor speed and impaired inhibition, particularly when task switching is required. However, it is acknowledged that these inferences are based on the review of a small number of studies, the majority of which were carried out over 40 years ago. Nevertheless, it would appear that impaired inhibition, psychomotor and processing speed is a consistent finding across the reviewed studies and should be the focus of further research.

Study 2 details the development of a data analysis method that was necessary to examine CO data alongside neuropsychological data in a way that would permit the examination of varying levels of CO, including extremely low-levels, in order to determine whether positive effects do follow chronic low-level exposures and at what levels, and crucially to identify thresholds of harm.

Chapter 3: Study 2

A Method to Analyse Carbon Monoxide Exposure Data in Relation to Cognitive Outcomes: Accounting for Exposure Patterns, Duration and Severity.

3.1 Introduction

Experimental studies indicate associations between acute low-level carbon monoxide (CO) exposures and adverse cardiovascular effects in both patients with cardiovascular disease and in healthy individuals at carboxyhaemoglobin (COHb) levels between 2 and 5% (Aronow & Cassidy, 1975; Anderson et al., 1973; Allred et al., 1989). Neuropsychological deficits may also follow at COHb levels of 5-7% including impaired vigilance, tracking, processing speed, and attention (Horvath, Dahms, & O'Hanlon, 1971; Gliner, Horvath, & Mihenic, 1983; Ramsey, 1972; Putz, 1979). However, other studies report no CO-related effects on cognitive performance at levels COHb levels of 5-16% (Roche et al., 1981; Wright & Shephard, 1978; Benignus, et al., 1977; 1990; O'Donnell, Chikos & Theodore 1971b). Previous reviews and meta-analyses addressing these inconsistencies have all reached similar conclusions and highlight the lack of successful replication, potential for Type I errors and problems relating to blinding procedures and publication bias (Benignus, 1993; 1994; Benignus, Muller, & Malott, 1990; Stewart, 1975). Results from the systematic review in this thesis indicated that impaired long-term memory, psychomotor speed and inhibition were relatively consistent findings, when study tasks were examined by both primary and secondary cognitive functions (see Study 1). However, potential associations between acute low-level exposure and *increased* performance in areas of sustained and divided attention, task switching and psychomotor function were also observed when the effect sizes of two studies were examined (O'Donnell et al., 1971b; Stewart et al., 1970). The majority of studies on acute low-level exposure however, are over four decades old, include extremely small samples and were not well controlled or ethical. Nevertheless, they informed the publication of outdoor and indoor exposure guidelines by the Expert Panel on Air Quality Standard of the World Health Organisation (WHO, 1999; 2010) (see Chapter 1).

Evidence on the effects associated with chronic low-level home exposure is limited. Numerous case reports document neuropsychological impairments such as deficits in memory, learning and motor slowing, following chronic low-level CO exposure within the home (Ryan, 1990; Myers et al., 1998). However, there is often uncertainty about the duration and level of exposure with reported durations ranging from weeks to several years and CO levels usually unknown. Determining the degree of exposure and the levels at which the observed impairments became apparent in case studies is therefore difficult. Subsequently, the ascription of particular symptoms to various CO levels in case reports is not viable. Furthermore, the results of an observational study on chronic low-level exposure found trends towards *increased* cognitive performance with increasing CO (Volans et al., 2007). Although no significant effects were observed, with the authors reporting no clear evidence of neuropsychological effects, these findings add to the inconsistencies within the literature, further complicating the determination of effects associated with low-level exposure. This research area presents many challenges that have likely contributed to the lack of published studies over recent years. Ethical considerations relating to the safe administration and monitoring of CO levels and intervention protocols are fundamental to the challenge, particularly when studying susceptible populations.

More recently, epidemiological studies have examined the relationship between chronic low-level CO exposure and health by focusing on outdoor air pollution levels in relation to hospitalisation and mortality rates. These studies indicate that air pollution may be associated with increased risk of stroke, myocardial infarction (MI) and heart failure (Maheswaran et al., 2005; Shah et al., 2013; Mustafic et al., 2012). Associations between air pollution exposure, including CO, and increased dementia risk have also been reported, indicated by an incidence rate ratio 1.36 times greater in the highest CO pollution area compared to the lowest (Chang et al., 2014). Furthermore, air pollution has recently been identified as a dementia development risk factor in later life (>65) (Livingston et al., 2020).

Epidemiological studies provide invaluable insight into the associations between outdoor CO exposure and health conditions at the population level, however

individual indoor exposures also present significant concern. Indoor sources of CO such as gas appliances and smoking habits contribute significantly to raised CO levels (Cox & Whichelow, 1985; Myers, DeFazio, & Kelly, 1998; Ryan, 1990). Evidence is accumulating of elevated CO levels within UK homes. For example, two reports found that 13/56 (23%) of homes across Manchester, Birmingham and Liverpool and 50/270 (18%) in East London had ambient CO levels exceeding the recommended guidelines, particularly whilst gas appliances were in use (Croxford et al., 2005a; Croxford et al., 2005b). Of the homes found to have raised CO levels, all exceeded the recommended 8 hour average level of 9ppm, 32 exceeded the recommended 1 hour level of 26 ppm, and 13 exceeded the recommended 30 minute level of 52ppm (Croxford et al., 2005a; Croxford et al., 2005b). Associations between self-reported neurological symptoms and the use of unsafe gas appliances have also been reported (Croxford et al., 2008). Other studies however, have found no evidence of raised CO levels with concentrations reported to be within the 8 hour average guideline of 9ppm in 830 UK homes (Raw et al., 2004) and mean concentrations below 1ppm with short lasting peaks none of which exceeded the WHO guidelines in 44 homes in South Wales (Henderson, Parry, & Mathews, 2006). However, mean concentrations were either measured using Draeger color-metric diffusion tubes which do not provide information of short-lasting CO peaks (Raw et al., 2004) or measurements are examined in relation to the WHO guidelines only (Henderson, Parry, & Mathews, 2006). Furthermore, the majority of these studies are based on data that is extremely dated.

Previous studies that have measured CO levels within the home typically report on exposure levels, the proportion of homes with low-level CO and the percentage of homes exceeding the WHO guideline limits. These studies provide data on the magnitude of the problem within UK homes and offer invaluable insight into the number of individuals that are potentially at risk from low-level exposures and therefore are extremely informative. They also offer information of the types of properties and appliances that present the highest risk and highlight geographical and socioeconomic factors that likely affect exposure vulnerability. From this, interventions can be directed to those most vulnerable in society. However, they do not provide detailed health status information of the

occupants and therefore any associated exposure effects are not investigated. Furthermore, CO levels are usually examined using time weighted averages for comparison with the WHO guidelines. Whilst this method is useful in determining whether individuals are exposed to levels of CO above those recommended, it does not facilitate the analysis of short-lasting peaks as these are averaged out over set time periods. Furthermore, lower-level exposure, below the guidelines, are typically not examined.

Epidemiological studies typically use survival analysis, such as Cox proportional hazards models, with the time to an event of interest examined. The method facilitates the examination of the effect of multiple variables upon the time to a specified event, such as time to hospital admission, disease progression, diagnosis and death. The hazard is the probability of the event occurring at a particular time, or is experienced close to that point in time, based on a set of covariates (Clark, Bradburn, Love & Altman, 2003; Cox, 1972). Poisson regression is another commonly used method to examine the effect of a set of covariates on an outcome measure, that is, count data. For example, when estimating the effects of risk factors or intervention on hospital admission rates or number of days admitted (Weaver, Ravani, Oliver, Austin, & Quinn, 2015; Harris, Lamping, Brown, & Constantinovici, 2002; Williams et al., 1990). These data analysis methods however, are not suitable for use in the current thesis with neuropsychological functioning, the outcome, measured on continuous scales. The data could have been examined in relation to the effect of CO exposure on the probability of an event occurring, such as identification of mild cognitive impairment (MCI) (for example, indicated by scores of 88 and below on the ACE-III) (Takenoshita et al., 2019). However, the literature is limited and the evidence available inconsistent, with some studies reporting negative neuropsychological effects and others indicating potential positive effects. The research is therefore exploratory and aims to examine the effects of various CO levels on neuropsychological function, without pre-set expectations of resulting effect directions, in order to increase knowledge and understanding in an area where there is a significant knowledge gap.

It is clear that further research is needed that is directed towards establishing whether extremely low-level exogenous CO can result in beneficial effects, similar to those associated with endogenous production, and if negative effects do follow, determining the thresholds of harm. These thresholds are likely to be different depending on the exposure duration and individual differences in the population of study, such as age and health status. For example, older adults are identified as particularly vulnerable to CO due to the biological and physiological changes associated with ageing and disease and are likely to develop toxicity from lower concentrations. Similarly, any potential beneficial effects are likely to be dependent upon these same factors, with the potential physiological and protective properties of exogenous CO, if present, observed in vulnerable groups only such as older adults (see Chapter 1).

If we are to move towards identifying 'safe' levels of exposure, detailed analyses of exposure patterns over time are needed. Analysis of changes in both indoor and outdoor CO levels, including low-level transient increases along with more continuous rises, and how these correlate with health outcomes, present research opportunities in an area where there is a significant knowledge gap. At an individual level, examining indoor CO levels in relation to neuropsychological and health data from small samples of the population and outdoor CO levels across larger samples in relation to hospital admission and mortality rates provide investigation methods. The timing of such research has never been more imperative due to a combination of factors, most prominent being the impact of the COVID-19 pandemic. Individuals in developed countries spend a large majority of their time indoors, specifically at home (Kornartit, Sokhi, & Ravindra, 2010), and following the national lockdown businesses continue to encourage working from home, potentially further increasing the amount of time spent within the home environment. Furthermore, changes to the UK housing stock are simultaneously occurring in order to achieve climate change targets by reducing greenhouse gas emissions (HM Government, 2010; EU, 2011; The Department of Energy and Climate Change; DECC, 2014). Building properties such as energy efficiency, ventilation and geometry all have an impact on indoor air pollution. Extensive retrofitting such as increased insulation and airtightness has already been initiated (DECC, 2012) and although these alterations may result in a

reduction in outdoor pollution, through reduced fuel consumption, they are likely to have a negative impact on indoor air quality. However, the effects of retrofitting on indoor CO levels and the potential increased risk of exposure are yet to be explored. Nevertheless, they present significant public health concerns (Shrubsole, Symonds, & Taylor, 2017).

3.1.1 The Current Study

Evidence reviewed above indicates the presence of low-level CO in a significant number of UK homes at concentrations exceeding those recommended to be safe. These exposures have been associated with detrimental health effects and therefore represent a significant public health concern. Furthermore, the non-specific symptoms and unnoticeable properties of CO combined with lack of awareness lead to undetected exposures and misdiagnosis resulting in continued exposure (Kirkpatrick, 1987; Crawford et al., 1990; Gilbert & Glaser, 1959; Myers et al., 1998; Ross, 1990). Moreover, of great concern is the evidence from epidemiological studies that indicate even low-level air pollution including CO, below the recommended guidelines, are associated with adverse health effects (see Shah et al., 2013; Mustafic et al., 2012 for reviews). This suggests that even extremely low-level CO exposure may in fact be harmful given sufficient exposure time. In relation to indoor exposures, particularly at home, examination of the short and long-term effects of COHb accumulation over time on health and neuropsychological function is needed. From a neuropsychological perspective, studies investigating and identifying potential risk factors for cognitive decline and dementia development such as CO exposure are paramount. Additionally, the potential beneficial effects of extremely low-level exposure also necessitates further examination.

It is clear from the data analysis methods discussed above that the identification of an appropriate method is needed that enables the examination of varying levels of CO, including extremely low-levels. This would aid understanding of whether exogenous CO can result in beneficial effects in certain groups, and if so, the levels at which these effects occur and their duration. Importantly, the detailed analysis of CO data at various concentrations combined with neuropsychological and data at the individual level would make a huge

contribution towards the determination of thresholds at which low-level exposures become harmful. It is likely that any potential beneficial effects are short lasting with prolonged exposures reaching a point where harm is initiated. This information would be invaluable in informing policy, guidelines and safety technology, ultimately keeping the public safe. The current paper outlines the development of an analysis approach suitable for analysing the data collected within this thesis that enables the potential effects of low-level CO exposure on cognitive functioning to be examined at various CO levels. Furthermore, the method facilitates the separation of different exposure patterns and severities and the inclusion of zero readings in turn permitting investigation of how these factors relate to changes in functioning and health. Several CO outcome measures were developed and tested in multiple analyses. The methods underpinning each and the rationale underlying selection of the final measure are presented.

3.2 Method

3.2.1 Participants

The data used for the purpose of developing the analyses measures were collected as part of a cross-sectional and longitudinal study of home exposure in older adults and included data from 106 older adults (≥59 years) residing in Coventry, UK. A total of 97 homes were visited with multiple occupants taking part in nine of the homes (see Study 3 and 4; Chapters 4 and 5).

3.2.2 Procedure

Participants were recruited via liaison with West Midlands Fire Service. “Contact and Connect” is a free service provided by Coventry AgeUK, available to individuals over the age of 50 who reside in Coventry. The service aims to identify individual needs and make the appropriate referrals to local services to maximise independence and quality of life. Contact and Connect works alongside a range of partners including the NHS, Coventry City Council and West Midlands Fire Service. West Midlands Fire Service carry out ‘safe and well’ visits in response to referrals made to them. During these visits, older adults (≥60 years of age) residing in Coventry were informed of a research project investigating the possible health effects of sub-alarm levels of CO within the home. The study

therefore employed a community sampling method that minimised any bias from the selection of symptomatic individuals whose difficulties have been attributed by them, or by a medical professional to exposure to CO (Gupta & Horne 2001, Gupta, Perharic, Volans, Murray, & Watson, 1997). The Fire Service were provided with training sessions by the researcher regarding participant recruitment prior to the commencement of the study and a leaflet containing brief study information and researcher contact information to hand out to residents (see Appendix 2 (A2); A2.1). Individuals were not excluded based on any factors relating to socioeconomic status including property type, tenure, benefit status and geographical region or on health status, home appliances and smoking behaviour. The inclusion of all electric homes, without potential sources of CO, were incorporated in the project to function as a control group for comparison purposes. Fire officers revisited the properties of research volunteers where they signed the first part of a two-stage consent process indicating that they agreed to the Fire Service sharing their personal information with, and to be contacted by, the researcher to arrange their participation in the study (see A2.2). During these home visits, participants were given a detailed participant information sheet to read prior to arranging an appointment with the researcher, and the CO data loggers and alarms were installed (see A2.3). Home visits with the researcher were scheduled and the second stage of the consent process carried out along with neuropsychological testing (see A2.4). Participants were given a detailed debrief following participation (see A2.5). The fire service recorded CO levels during their first visit and any properties with CO levels ≥20 ppm were not informed of the research and therefore excluded; in accordance with the Health and Safety Executive Workplace Exposure Limits (HSE; 2020), the fire service raise an incident at CO levels of ≥20 ppm. Following a 1-month period, the CO data loggers were collected from the properties. The data were downloaded via the USB port to EasyLog software and levels were initially checked for safety purposes by the Fire Service prior to being shared with the researcher. In one case, the monthly readings revealed prolonged exposure to CO at levels considered to be unsafe by the Fire Service. This individual's data were removed from the analysis and the Fire Service provided intervention. Repeated CO monitoring and testing was carried out at seven months post the initial visit to enable analysis of changes in CO levels and functioning over time. Fire officers

re-visited the properties at seven months, prior to the visit from the researcher, replaced the data loggers, checked CO alarms and provided an intervention that included health and safety information regarding CO sources, safety and prevention, and the associated health risks (see A2.6).

3.2.3 Equipment

3.2.3.1 CO Alarms

FireAngel CO-9X Wireless Carbon Monoxide Alarms were used. These alarms are CE marked and Kitemarked to BS EN 50291-1 meeting European health and safety requirements. An 85dB warning alarm is triggered if exposure rises above the following sensitivity levels: 50ppm for between 60 and 90 minutes, 100ppm for between 10 and 40 minutes and within 3 minutes at ≥300ppm. The alarms have a seven year sealed battery and warranty and were given to all participants to keep them safe both throughout the research and thereafter.

3.2.3.2 CO Data Loggers

Lascar electronics EasyLog carbon monoxide data loggers (EL-USB-CO300) were used. The standalone data logger samples and stores up to 32,510 readings with a range of 0 to 300ppm (±5ppm accuracy) and operating temperature between -10 and +40 ^{O}C. The sensor life of the loggers is four years and battery life three months, which were replaced before redeployment to each property. Sampling rates can be set between 10 seconds and five minutes. The data loggers were placed in the home to continuously sample the ambient CO concentrations over one month, and were programmed to record and store an average reading every five minutes. The loggers were placed in the room the resident indicated they spent the majority of time and was typically the living room. Previous studies aiming to measure occupant CO exposure have positioned data loggers in the main living area of the residence at head height of a seated individual (Croxford et al., 2005a; 2005b). Similarly, in the current study, they were placed out of direct sunlight and draughts, away from direct CO sources and at head height whilst seated where possible, but often had to be placed slightly higher on shelves. The main source of CO was often in the kitchen (e.g. the boiler) however, in terms of individual exposure the main living area of the house was considered to be the most representative position. The loggers do

not contain a visual display or alarm and contain two lights only, one that flashes green signalling sampling and the other amber indicating low battery life. This was explained to the occupants and the loggers were positioned with the lights facing the wall so that they were as discreet as possible. Occupants did not receive any real-time feedback on CO levels to minimise any behaviour alterations that may result from exposure knowledge. This was important not only for neuropsychological testing but also to capture individuals' natural behaviour within the home.

3.2.3.3 Toxico Personal Alarm

A Honeywell ToxiRAE 3 (PGM-1700) personal CO monitor was used by the researcher for her own safety. The ToxiRAE 3 has a 3-electrode micro-sensor that displays the CO level with a range from 0 to 1999ppm and a resolution of 1ppm. Operating temperature for intermittent use is -22 to +140 ^{o}F. Limit levels for alarm activation are user set and include high, low, short-term exposure limits (STEL) and time weighted averages (TWA). When exceeded, an audible 95dB alarm is activated with a 6-LED flashing visible alarm and vibration with a <12 second response time. The number of auditory beeps, flashes and vibrations per second depend on the CO level that has been exceeded. The Fire Service maintained the alarm, replacing batteries and recalibrating when required.

3.2.4 CO Data Preparation

Once downloaded via EasyLog software, Excel data files containing five minute average CO recordings for each property over the sampling duration were produced. Data loggers were often left in properties for over the month duration due to Fire Service availability. Therefore, the first stage in preparing the data for analysis was to trim the files so that the number of readings per property were consistent. Files were trimmed to exactly 28 days resulting in 8064 readings per property. The start of logger recording was delayed for around eight hours, allowing time for the Fire Service to ensure that they were in the properties prior to commencement of recording. However, recording continued once collected up until download and so the end of the files were trimmed. This accounted for any outdoor exposure such as road pollution once removed from the property and

indoor exposure within the fire station prior to being downloaded. Numerous CO outcome measures were then developed from the 8064 readings.

3.2.5 Data Analysis Plan

In order to develop a method for use in analysing the data at different exposure levels, various CO outcome measures were examined. Initially, CO levels were examined in relation to the WHO (1999; 2010) guidelines. This is the most commonly used method when examining CO levels within the home. The data were converted into simple moving averages over the stated time periods (15 minutes, 30 minutes, 1-hour, 8-hours and 24 hours) and examined according to each recommendation. The CO data were transformed into time series data using the centred moving average with a span of 12 for 1-hour, 96 for 8-hours and 288 for 24-hours and sequence charts plotted. Comparisons were also made between the CO levels in this study and the results from Croxford et al's (2005a; 2000b) studies (due to similar methodologies). Following this, measures of central tendency, dispersion and the total CO exposure (readings summated over the 28 days) were considered and are explored. CO ranges were then developed based on both the WHO guidelines (1999; 2010) and the range within the collected data. This permitted the data to be separated into various exposure levels. The ranges included 0ppm, 0.5-3ppm, 3.5-6ppm, 6.5-9ppm and ≥9.5ppm. Finally, four additional measures were developed including the total CO exposure and percentage in each specified range, and the total number of readings and percentage within each range. All measures, including the rationale underpinning their development and appropriateness for use in analyses, are discussed.

3.3 Results

3.3.1 CO Levels in Relation to the WHO Guidelines

None of the homes had simple moving averages above the WHO (1999; 2010) guidelines at either time point. A small number of properties were close to reaching the 8 and 24 hour guideline limits, with results from the two nearest properties revealing 8 hour moving averages of 8.56ppm and 8.99ppm and 24 hour moving averages of 5.13ppm and 5.43ppm. The exposure levels for 1-hour and 8-hour moving averages for one of these properties are presented in Figure 3.1, and the 24-hour moving average for the same property in Figure 3.2. These

Figures also provide a visual representation of the exposure detail that is lost when averaging data over time. This is most noticeable when averaging over longer time periods and can be seen clearly in Figure 3.2. The CO levels frequently peak up to approximately 14ppm however, due to the inclusion of lower and zero readings when simple moving averages are calculated, the CO level rarely exceeds 2.5ppm.

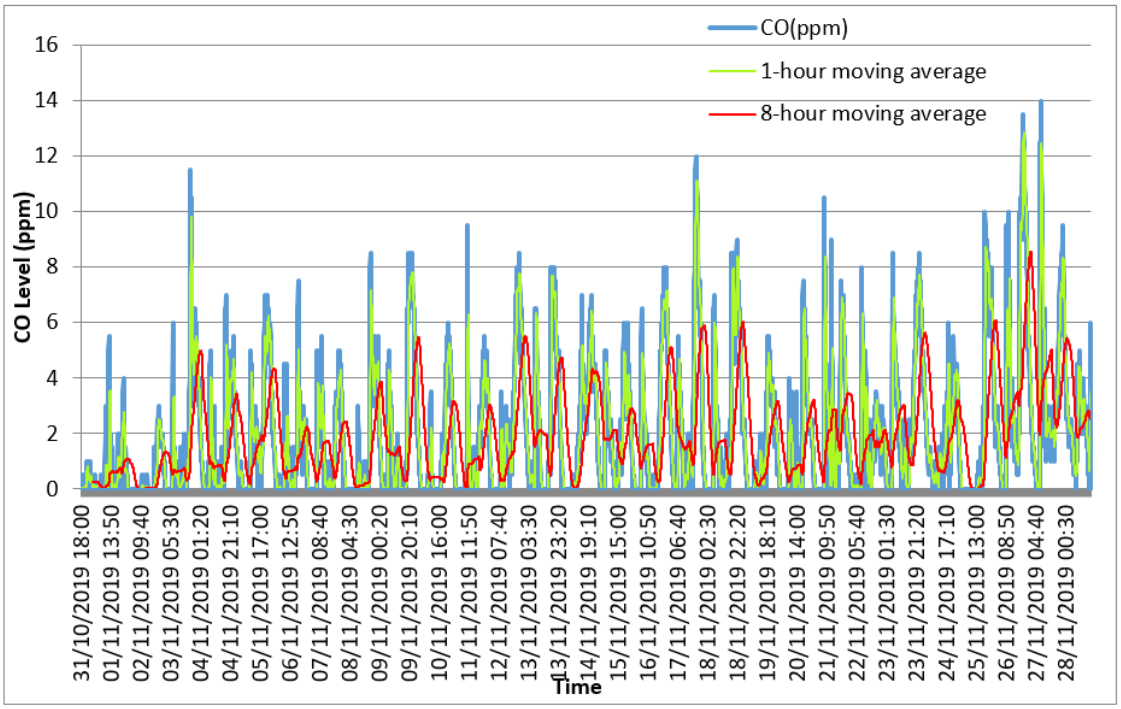


Figure 3.1. The blue line represents the exposure levels over 28 days, the green line is the 1-hour simple moving average (SMA) and the red line is the 8-hour SMA. It can be seen that the highest 1-hour SMA is approximately 13ppm, which is much lower than the recommended WHO (2010) guideline of 31ppm. The 8-hour SMA is typically below 6ppm but spikes up to 8.56ppm close to the 9ppm guideline (WHO, 1999; 2010).

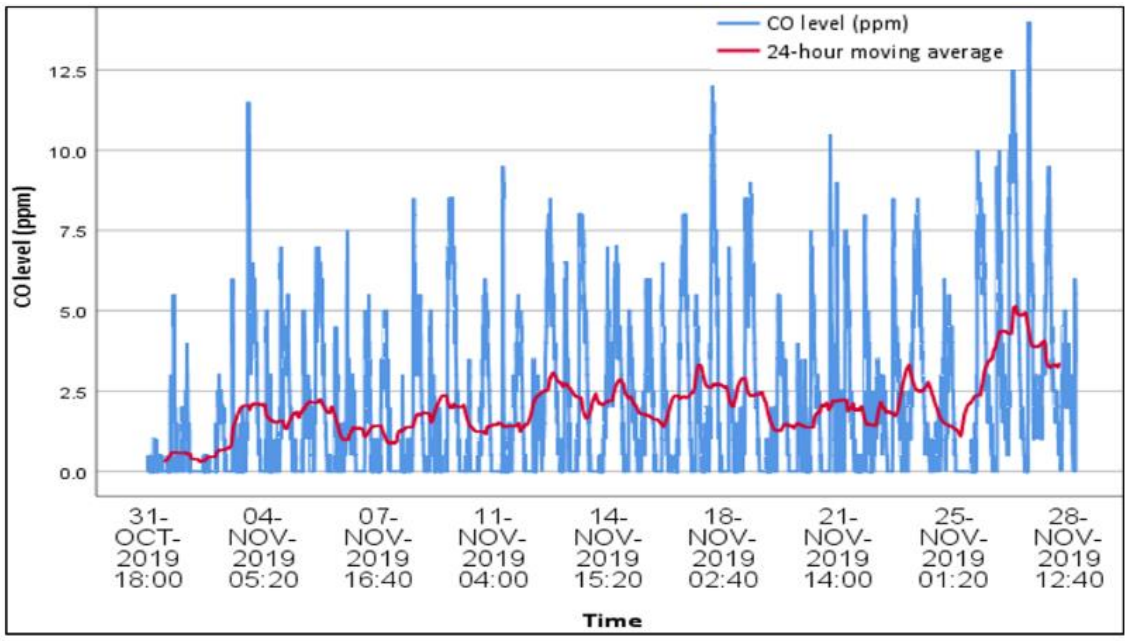


Figure 3.2. The blue line represents the exposure levels over 28 days and the red line is the 24-hour simple moving average (SMA). It can be seen that the highest 24-hour SMA is between 1.5-3ppm for the majority of the 28-day period but spikes up to 5.13ppm close to the 6ppm guideline (WHO, 1999; 2010).

As none of the properties had CO levels exceeding the WHO guidelines, frequency count data were calculated for comparison purposes that indicates the number of homes with CO levels exceeding the recommended limits, where concentrations peaked over these levels only, but the raw data or simple moving averages were not maintained for the stated durations. This data therefore represents the number of homes with CO concentrations above the recommended concentrations only. This information is presented in Table 3.1 alongside the results from Croxford et al.'s (2005a; 2005b) studies.

Table 3.1. Number of homes with simple moving average CO levels above the WHO (1999) guidelines in Croxford et al.'s (2005a; 2005b) studies and the number of homes with CO levels above the WHO (1999;2010) guideline limits for the current study at Time 1 (T1) and Time 2 (T2).

	Croxford et al., 2005a	**Croxford et al., 2005b**	**Current study T1**	**Current study T2**
Total number of homes	56	270	97	73
87 ppm for 15 min[1, 2]	0	0	0	0
52 ppm for 30 min[1]	3 (5.4%)	10 (3.7%)	0	0
26 ppm for 1 hour[1]	6 (10.7%)	26 (9.6%)	1 (1.0%)	0
31 ppm 1 hour[2]	----------	----------	0	0
9 ppm for 8 hours[1,2]	13 (23.2%)	50 (18.5%)	14 (14.4%)	11 (15.1%)
6 ppm for 24 hours[2]	----------	----------	24 (24.7%)	16 (21.9%)

[1] WHO (1999) guidelines for outdoor air
[2] WHO (2010) guidelines for indoor air

Overall, when compared to the results from Croxford et al.'s (2005a; 2005b) studies, there was a lower prevalence of homes with raised CO levels. None of the homes in this study had CO levels that exceeded 52ppm, compared to 5% and 4% of homes exceeding the guideline of 52ppm for 30 minutes in their (2005a) and (2005b) studies, respectively. Similarly, only 1% of homes had CO levels exceeding 26ppm in the current study compared to approximately 10% of homes in both their (2005a; 2005b) studies exceeding this level for a 1 hour duration. Comparisons between studies in relation to the 9ppm 8 hour guideline revealed a higher prevalence of homes exceeding these limits with 23% and 19% in Croxford et al., (2005a; 2005b) studies, compared to 14% and 15% in the current study at Time 1 and Time 2 respectively. Finally, in the current study, 25% and 22% of homes had CO levels that exceeded 6ppm at time 1 and time 2 respectively. It is important to note that unlike the results presented from Croxford et al.'s (2005a; 2005b) studies, none of the homes in the current study exceeded the exposure limits for the stated durations; the percentages represent short-lasting peaks above the guideline concentrations only. However, the results do reveal the presence of low-level CO within a proportion of UK homes, which under chronic conditions may impact health. The higher prevalence of homes with CO concentrations observed in Croxford et al.'s (2005a; 2005b) reports may be due to the areas of study which included Manchester, Birmingham, Liverpool and London, all of which fall within the 10 largest UK cities, in terms of population size (ONS, 2021). Another potential explanation is the implementation of legislation such as the Gas Safety (Installation and Use) Regulations (HSE; 1998) that require annual gas safety checks by a Gas Safe registered engineer in premises rented by local authorities, housing association and the private sector. Additionally, the Smoke and Carbon Monoxide Alarm regulations (2015; 2022) stipulate that CO alarms must be installed in all social and privately rented households in rooms where there is a solid burning combustion appliance (2015), and more recently any room where there is a fixed combustion appliance (excluding gas cookers) (2022). Such legislation has likely improved CO safety

within homes and subsequently reduced CO levels from 2005 when Croxford and colleagues reports were published compared to the current studies.

3.3.2 Mean and Standard Deviation of CO Levels

Following the examination of CO levels in relation to the WHO (1999; 2010) guidelines, attention was directed towards the identification of an appropriate outcome measure that would enable the analysis of the CO data in relation to the neuropsychological data (see Chapters 4 and 5). Initially, measures of central tendency were considered such as the mean, median and mode. However, for the majority of data files, these measures summated to between 0 and 1ppm due to the high frequency of zero readings over the 28 day period, with mean CO levels of <1ppm in 97% of all data files at both time points (see Table 3.2).

Table 3.2. CO data file mean, frequency and cumulative percentage for T1 and T2.

T1 (*n*=97)			T2 (*n*=73)		
Mean (ppm)	Frequency (n)	Cumulative %	Mean (ppm)	Frequency (n)	Cumulative %
.00	50	47.2	.00	43	55.1
.01	15	61.3	.01	4	60.3
.02	8	68.9	.02	5	66.7
.03	2	70.8	.03	2	69.2
.04	1	71.7	.04	7	78.2
.05	4	75.5	.05	4	83.3
.06	2	77.4	.08	1	84.6
.07	7	84.0	.10	2	87.2
.08	1	84.9	.11	2	89.7
.09	1	85.8	.15	1	91.0
.10	1	86.8	.18	2	93.6
.11	1	87.7	.21	1	94.9
.13	1	88.7	.25	1	96.2
.17	2	90.6	.30	1	97.4
.22	1	91.5	1.36	1	98.7
.26	1	92.5	1.98	1	100.0
.49	2	94.3			
.53	1	95.3			
.56	1	96.2			
.83	1	97.2			
1.05	1	98.1			
1.39	1	99.1			
1.59	1	100.0			

It can be seen from Table 3.2 that around 97% of the data files for both T1 and T2 had a mean CO level below 1ppm. However, the graphical representation of the data presented extensive variability in exposure patterns, with some files revealing a continuous extremely low-level exposure and others a majority of zero readings with higher short-lasting peaks. The variability of the CO data over

time was not accurately represented in these measures of central tendency and therefore could not be used for analysis purposes. Measures of dispersion were then considered, specifically the standard deviation, and were calculated for each data file (see Table 3.3).

Table 3.3. CO data file standard deviation, frequency and cumulative percentage for T1 and T2.

T1 (*n*=97)			T2 (*n*=73)		
SD (ppm)	Frequency (n)	Cumulative %	SD (ppm)	Frequency (n)	Cumulative %
.00	36	34.0	.00	31	39.7
.01	3	36.8	.01	1	41.0
.02	3	39.6	.03	3	44.9
.03	3	42.5	.04	1	46.2
.04	1	43.4	.05	4	51.3
.05	1	44.3	.06	1	52.6
.06	1	45.3	.08	2	55.1
.07	2	47.2	.09	2	57.7
.08	4	50.9	.12	2	60.3
.09	3	53.8	.13	2	62.8
.10	1	54.7	.17	2	65.4
.11	1	55.7	.19	1	66.7
.12	1	56.6	.21	1	67.9
.14	2	58.5	.23	2	70.5
.16	3	61.3	.24	1	71.8
.17	1	62.3	.27	2	74.4
.18	1	63.2	.28	1	75.6
.21	1	64.2	.33	1	76.9
.22	3	67.0	.37	1	78.2
.23	2	68.9	.40	3	82.1
.25	1	69.8	.48	1	83.3
.27	2	71.7	.51	1	84.6
.30	1	72.6	.52	2	87.2
.32	4	76.4	.54	2	89.7
.34	2	78.3	.56	1	91.0
.35	1	79.2	.58	1	92.3
.37	1	80.2	.70	1	93.6
.39	1	81.1	.71	1	94.9
.40	1	82.1	.79	1	96.2
.41	1	83.0	1.33	1	97.4
.44	2	84.9	1.35	1	98.7
.45	1	85.8	2.43	1	100.0
.48	1	86.8			
.51	1	87.7			
.62	1	88.7			
.72	3	91.5			
.85	1	92.5			
.96	1	93.4			
1.21	1	94.3			
1.29	1	95.3			
1.60	1	96.2			
1.64	1	97.2			
1.94	2	99.1			
2.35	1	100.0			

It can be seen from Table 3.3 that the standard deviation represented the data more accurately, revealing more variability and spread; however, similar problems arose with between 93 and 96% of the data files falling within 1 standard deviation of the mean. Furthermore, the standard deviation was unable to separate different exposure patterns when entered into the analysis and therefore did not provide an accurate representation of the observed data.

3.3.3 Total CO Exposure Value

The total CO exposure was then calculated by summating the 8064 CO readings over the month. Every observed CO concentration was multiplied by the number of readings at that level and then summated providing a figure that represented the total monthly exposure. For example, a data file containing a total of 10 readings at 7ppm equated to 70ppm. This process was repeated for each observed CO level and added together providing a total CO exposure value for each data file (property). However, a large number of zero readings were observed in several of the data files, and there was large variance between files in the number of readings at 0ppm. This was problematic as the total CO exposure value was formed by multiplying the number of readings at each level, and therefore this measure did not account for readings at 0ppm or variance between the files in the number of these readings. In addition to analysing CO peaks, zero readings within the data files equally reveal information about the exposure. The total exposure value did not permit analysis of these readings, nor did it separate different exposure patterns within the data. Details relating to the exposure type and severity were therefore lost in the analysis. The different exposure patterns observed between data files are presented in Figures 3.3-3.6, which represent CO data over 1-month from four different properties. Figures 3.3 and 3.4 show a continuous extremely low-level exposure with the majority of CO readings between 1 and 4ppm and fewer 0ppm readings. Figures 3.5 and 3.6 reveal exposures with the majority of readings at 0ppm, with short-lasting higher CO peaks up to around 17ppm.

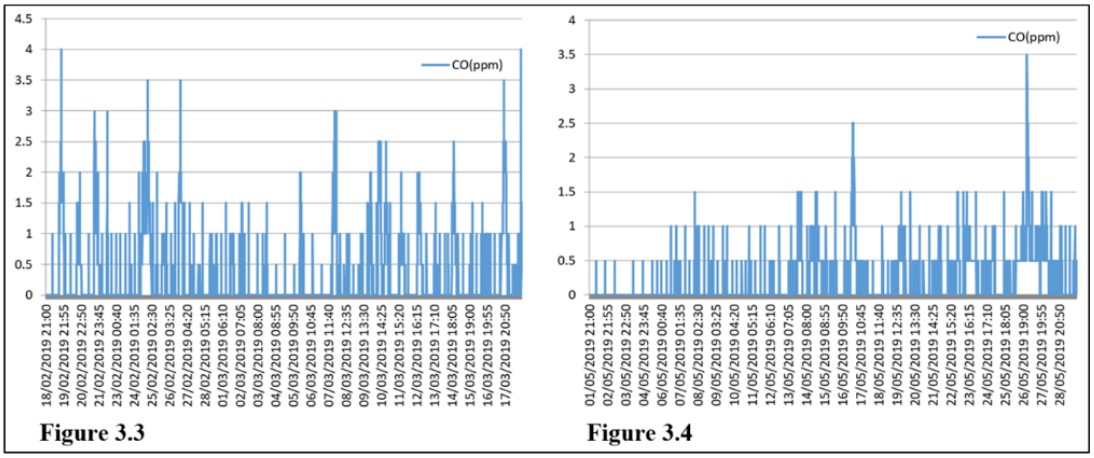


Figure 3.3 Figure 3.4

Figures 3.3 and 3.4. CO levels over 1-month showing a continuous extremely low-level exposure. The majority of CO readings over the month are extremely low-level, between 0-4ppm, with very few zero readings.

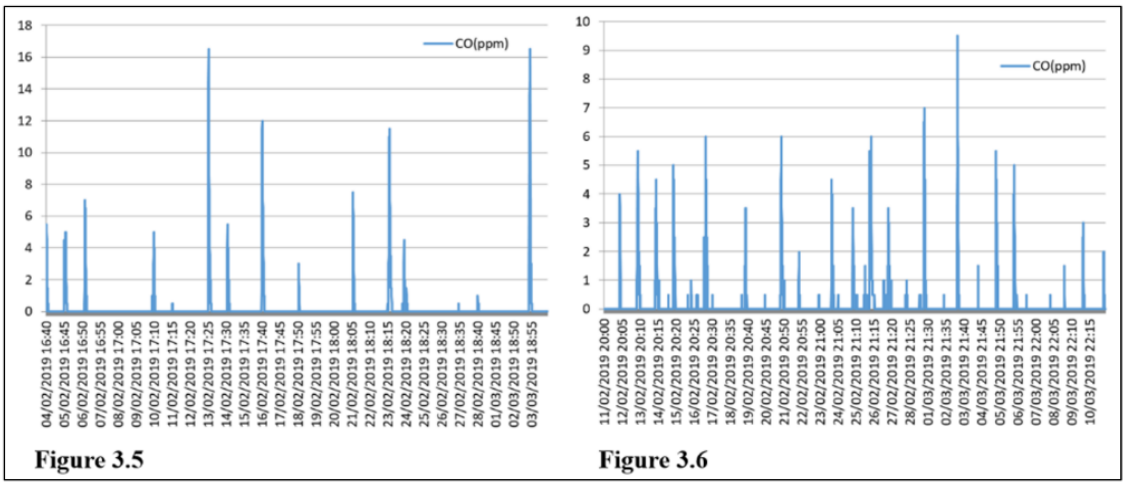


Figure 3.5 Figure 3.6

Figures 3.5 and 3.6. CO levels over 1-month showing higher short lasting CO peaks up to around 17ppm with a higher percentage of zero readings.

A main aim of developing a CO outcome measure was that it would facilitate the examination of potential cognitive effects associated with different exposure types and severities. The application of the total CO exposure value as a measure in analyses did not permit analysis of zero readings but also concealed these different exposure types. To demonstrate this, the total CO value, mean, range and percentage of zero readings for Figures 3.3-3.6 are presented in Table 3.4.

Table 3.4. Mean, range, Total CO exposure and percentage of zero readings for Figures 3.3-3.6.

	Figure	Range (ppm)	Mean (ppm)	Total CO exposure (ppm)	Zero readings (%)
Low continuous	3.3	0-4	0.26	2104.0	76.5
	3.4	0-3.5	0.17	1367.0	73.9
Short lasting higher peaks	3.5	0-16.5	0.22	1766.5	93.8
	3.6	0-9.5	0.17	1406.5	90.7

Interpretation of Table 3.4 indicates that the mean and total CO exposure values can summate to similar totals for extremely different CO exposures. Comparison of the means and total CO exposure for Figures 3.3 and 3.5 reveal very similar means of .26 and .22 and total CO exposure values of 2104 and 1767 respectively. This can also be observed across Figures 3.4 and 3.6 with mean values of .17 and total CO exposure values of 1367 and 1407 respectively. However, the higher readings observed in Figures 3.5 and 3.6 (up to 16.5ppm) represent a different exposure pattern compared to the extremely low readings (up to 4ppm) observed in Figures 3.3 and 3.4. The percentage of zero readings over the month also highlight this difference with variability observed between exposures; those with short lasting higher peaks revealed a greater number of zero readings (approx. 92%) compared to the extremely low-level continuous exposures (approx. 75%). These observations provide evidence that both the mean and total CO exposure value were unsuitable for analysis purposes as they overlook potential differences between various exposure patterns and severities, subsequently omitting important exposure detail from the analysis.

3.3.4 The development of CO Ranges

Carbon monoxide ranges were developed in an attempt to address the analysis problems detailed above. The introduction of ranges into the data preparation was underpinned by the concept that separation of the CO data into specified ranges would permit the separate examination and analysis of any associated effects at various CO levels. This would be extremely useful to determine ‘safe’ levels of exposure. It was also anticipated that this method would account for different exposure patterns in the analyses and therefore reveal important information relating to exposure type and severity. The development of the ranges was based both on the observed range within the data and the WHO indoor air quality guidelines (2010). The highest CO peak in the data was 29ppm

and so we focused on the two lowest WHO guidelines (6ppm for 24 hours; 9ppm for 8 hours) and ranges were subsequently developed with equal differences between them. The final ranges were 0.5-3ppm, 3.5-6ppm, 6.5-9ppm and ≥9.5ppm. Due to the limited number of homes with CO readings above 9ppm, the final range incorporated all readings ≥9.5ppm. This allowed for an adequate number of homes within the highest range to be included in the analyses.

3.3.4.1 Total CO Exposure and Percentage Values between Specified Ranges

The total CO exposure value was separated into the total CO that fell within each range. This was also converted to a percentage based on the individual monthly data file total, with the percentage of CO readings separated into the specified ranges. It was thought that this method would highlight different exposures, in that extremely low-level continuous exposures would reveal a majority of CO readings in the lowest ranges compared to exposure containing short lasting higher peaks that would show a certain amount of CO spread across the higher ranges. The total CO exposure separated into the specified ranges and percentage conversion for six data files (A to F) are presented in Table 3.5 which represent CO data over 1-month from six different properties.

Table 3.5. Total CO over the month between specified ranges and percentage.

Data File	Total CO exposure	Total CO 0.5-3	Total CO 3.5-6	Total CO 6.5-9	Total CO 9.5-30	% 0.5-3	% 3.5-6	% 6.5-9	% 9.5-30
A	12789.5	4120.5	5002.5	2096.0	1570.5	32.22	39.11	16.39	12.28
B	11202.5	9159.5	1243.0	286.5	513.5	81.76	11.10	2.56	4.58
C	4486.50	3678.00	743.50	65.00	.00	81.98	16.57	1.45	.00
D	3975.00	749.50	871.50	789.50	1564.50	18.86	21.92	19.86	39.86
E	604.00	117.00	155.00	150.50	181.51	19.37	25.66	24.92	30.05
F	8.00	1.00	.00	7.00	.00	12.50	.00	87.50	.00

Similar total CO exposure values can be observed in data files A and B (11,202-12,789ppm). However, by separating the exposures into ranges, two very different exposure types emerge. Data file A contains a lower amount of CO in the lowest range 4120.50 (32%) compared to data file B where the majority of the total CO exposure falls within this range 9159.50 (82%). Conversely, approximately 3667 (29%) of the total exposure falls in the higher ranges (6.5-30ppm) in data file A, compared to only 800 (7%) falling within this range in data

file B. Data file A therefore represents an exposure with short lasting higher peaks, whereas data file B represents an extremely low continuous exposure. This separation of exposure patterns can be observed between data files with much lower CO exposure totals, demonstrated in data files C and D that have similar but much lower values (4,000-4,500ppm). A high amount of the total exposure falls within the lowest range in data file C (82%) with only 1.5% falling in the higher ranges between 6.5 and 30ppm revealing a continuous extremely low-level exposure pattern. Data file D however, represents an exposure with short lasting peaks with only 19% of total CO falling in the lowest range and with 60% in the higher ranges. This process therefore separates varying exposures patterns, regardless of exposure severity, that can be entered and analysed, separately. Furthermore, exposure severity is also reflected in the total CO within each range, with higher totals indicating more severe exposures.

The percentage of total CO in each range was also considered as a potential outcome measure. However, as percentages were calculated based on individuals' total exposure values, there was extensive variability between these values. Without a consistent baseline value, or relative frequency, percentage conversion is problematic. This is illustrated in data files D and E, which have extremely different exposure totals of 4,000ppm and 600ppm respectively. When converted to a percentage of total CO within each range, the values are similar and if entered into analyses in this format the exposures would appear comparable. Information relating to exposure severity is therefore lost. The impracticality of this measure is also demonstrated in data file F, where the total CO exposure value is extremely low at 8ppm, of which 7ppm fell within the 6.5-9ppm range. Percentage conversion transforms this into a very high percentage of CO within this range (88%) when in actuality the exposure was minimal at 7ppm. Therefore, although this measure separates varying exposure patterns, exposure severity information is lost when the CO data is presented in this format. Furthermore, both the total CO exposure and percentage values do not account for the zero readings as the value is based on the total monthly exposure. The inclusion of these readings was considered important as they provide details relating to exposure pattern and severity.

3.3.4.2 Total Number of Readings and Percentage Values between Specified Ranges

The two final measures were calculated based on the total number of readings that fell within each range and were converted to percentages. The first measure is essentially frequency count data with percentage conversion translating these values onto a continuous scale. Importantly, the values when converted to percentages represent relative frequencies as they are calculated using the total number of readings (8064), a consistent baseline number across data files. Furthermore, presenting the data in this format permitted the inclusion and analysis of zero readings. The number and percentage of readings at 0ppm was added to the ranges. The final ranges were therefore: 0ppm, 0.5-3ppm, 3.5-6ppm, 6.5-9ppm and 9.5-30ppm. The number of data files that had CO readings within each of the ranges detailed above were 70, 39, 25 and 15 respectively. The total number of readings within each range and percentage conversion are displayed in Table 3.6 for the same data files presented in Table 3.5.

Table 3.6. Total number of readings over the month and percentage conversion between specified ranges.

Data File	Total readings 0	Total readings 0.5-3	Total readings 3.5-6	Total readings 6.5-9	Total readings 9.5-30	% 0	% 0.5-3	% 3.5-6	% 6.5-9	% 9.5-30
A	3725	2796	1121	285	138	46.19	34.67	13.90	3.53	1.71
B	1006	6672	302	38	47	12.47	82.73	3.74	.47	.58
C	5050	2827	179	9	0	62.62	35.05	2.22	.11	.00
D	7093	553	193	102	124	87.95	6.86	2.39	1.26	1.54
E	7911	84	34	20	16	98.09	1.04	.42	.25	.20
F	8062	2	0	1	0	99.96	.03	.00	.01	.00

When the percentage of readings within each range is calculated, the different exposure patterns observed within the data continue to be separated. For example, 83% of readings in data file B fall within the 0.5-3ppm range (continuous extremely low-level exposure) compared to only 35% in data file A (short lasting higher peaks). These percentages are extremely comparable to those presented in Table 3.5 for the 0.5-3ppm range, however, there are large differences in the higher ranges between the outcome measures. The percentage of readings between 6.5 and 30ppm account for 6% and 1% of the total readings for data file

A and B respectively. These are extremely different to those previously calculated using the total CO exposure value (29% and 7%) for the same data files (see Tables 3.5 and 3.6). Calculated using relative frequency, the percentage of readings represent the data more accurately with only 423 (6%) in data file A and 85 (1%) in B of the total 8064 readings falling in the higher ranges. This measure also provides exposure severity information which is reflected in the observed values, with higher figures indicating greater exposure at the specified level.

The importance of accounting for exposure severity has been discussed previously and illustrated using data files D and E and the total exposure values (see Table 3.5). These data files represent a low exposure (data file E: 600ppm) and a much higher exposure (data file D: 4,000ppm). However, the total CO exposure value converted to percentages results in similar values across all ranges suggesting they are of comparable severity (see Table 3.5). The percentage of readings reflects this variance in exposure severity with a higher percentage of readings across all ranges in data file D when compared to E. Data file D has 746 (9%) readings between 0.5 and 6ppm and 226 (3%) between 6.5 and 30ppm, compared to 118 (1.5%) and 36 (0.5%) for the same ranges in data file E. Therefore, when these percentages are entered into analyses, it is clear that data file D represents greater exposure. The inaccurate interpretation of data file F is also corrected by using this measure, with a total exposure value of only 8ppm over the month, of which 7ppm (88%) fell within the 6.5-9ppm range. Percentage conversion based on the percentage of readings translates this to .01% in the 6.5-9ppm range which accurately represents the exposure accounting for the majority of readings at zero (99.96%).

Furthermore, the inclusion of zero readings in percentage conversion reveals additional exposure detail. For example, zero readings account for 46% and 12% of the total readings in data file A and B respectively. These percentages alone suggest that Data file A represents an exposure containing a large amount of zero readings with the remaining CO readings spread across the ranges (short lasting higher peaks) and data file B a continuous extremely low exposure with fewer zero readings (see Figures 3.2-3.6). The combined examination of the zero data points and the separate readings in each specified range provides an

extremely informative method for analysing CO data in relation to exposure pattern and severity. Importantly, the CO data in this format can be analysed in combination with health data facilitating the detailed examination of exposure level, pattern, and severity and the impact of these factors on health.

3.4 Discussion

The current paper details the methods underpinning the development of several CO outcome measures designed for the analysis of the associated effects of low-level CO exposure on neuropsychological functioning. Each measure was tested in multiple analyses, with the percentage of CO readings between specified ranges selected as the method that provided the most reliable analyses. The results show promise, providing an alternative way to analyse carbon monoxide data in relation to neuropsychological data. The detailed examination process led to a CO measure that is sensitive to identifying varying exposure patterns whilst accounting for exposure severity. The method also provides a technique to incorporate zero readings in the analyses revealing additional detail relating to exposure pattern and severity. Furthermore, separation of the CO data into specified ranges enables the associated effects to be examined at different exposure levels. This alternative approach may assist in determining whether beneficial effects can result from extremely low-level exposures, and if so, identifying the level and duration at which these effects become apparent and the areas of cognition affected. Importantly, the method facilitates the examination of the levels at which harm is initiated and the impact of exposure pattern and severity on health and neuropsychological function. Examination of these factors may provide crucial information on whether certain exposure types are more harmful, highlight areas of cognitive function most affected and identify the levels at which specific effects become apparent. It could be hypothesised that exposures comprising a majority of zero readings with transient higher peaks may be more harmful when compared to an extremely low continuous exposure based on the protective role adaptation, tolerance and compensatory mechanisms may play under chronic exposure conditions. However, the level and duration at which these mechanisms become ineffective and the exposure

becomes toxic are currently unknown as are the impacts of different exposure patterns.

Thresholds of harm for acute and chronic low-level exposures are likely to be different with some degree of variation due to individual differences in the population of study. Identifying 'safe' exposure levels for both the healthy population and susceptible groups is vital if we are to move towards keeping the public safe. Reports measuring CO levels within homes have lacked neuropsychological testing and examine CO concentrations in relation to the WHO (1999) guidelines only. Experimental studies of acute low-level exposure have typically included small samples of healthy young adults, the majority of which were carried out over 40 years ago. Case reports of chronic low-level exposure are based on an individual's self-reported experience and often lack information relating to the duration and level of exposure. Epidemiological studies provide great insight into outdoor low-level chronic exposures at the population level, revealing associations between air pollution and stroke, MI, heart failure and increased risk of dementia development (Maheswaran et al., 2005; Shah et al., 2013; Mustafic et al., 2012; Peters et al., 2019). These studies indicate that even small increases in CO, below the recommended limits, may be associated with adverse health effects under chronic conditions. In support of this, evidence from case reports on chronic low-level exposure indicate the presence of neuropsychological impairments such as memory and attention deficits (Nakamura et al., 2016). However, epidemiological studies do not provide detailed health status information at the individual level, thus any subsequent inferences and conclusions drawn are limited.

It is clear that future research is warranted that aims to identify the level and duration at which both acute and chronic low-level exposures shift from potential beneficial effects to toxicity, the associated health and neuropsychological effects at various concentrations and the impact of different exposure patterns. The methods outlined here provide a promising technique that may facilitate the determination of more accurate thresholds at which low-level exposures become harmful to cognitive functioning. Importantly, the method permits the separation of varying exposure patterns, accounts for exposure severity and provides an

analysis technique that incorporates zero readings and enables the examination of potential effects at various exposure levels. Therefore, the influence of these exposure factors on cognitive function can be thoroughly investigated in the current thesis which in turn may provide new evidence to underpin exposure guidelines. Studying groups within the population that are most susceptible to low-level exposures, such as older adults and those with pre-existing disease, in order to determine 'safe' exposure limits is imperative. This information would be invaluable in informing policy, guidelines and safety technology in order to keep those most vulnerable safe. The WHO (1999; 2010) guidelines are informed and underpinned by extremely dated research, the majority of which was carried out over four decades ago. It is clear that research is needed in order to assess whether these guideline limits require revision. The methods detailed provide a potential approach to analyse CO data at various levels that may, in turn, provide new evidence of the thresholds at which CO exposure becomes harmful to cognitive functioning in older adults. Furthermore, previous guidelines vary depending on the publication body causing some degree of confusion. Therefore, the development of new evidence based exposure limits that are consistent across publication bodies would alleviate this confusion resulting in unified approach to protecting the public across all relevant partners.

3.4.1 Limitations

The data analysis method detailed above does have some limitations. Firstly, the CO ranges were selected pragmatically, based on the CO range within the collected data and the WHO (1999; 2010) guidelines. Whilst the WHO (1999; 2010) guidelines are based on findings that indicate CO concentrations above those recommended are harmful, much of the evidence is extremely dated. However, with evidence other than from these studies sparse, it was decided that ranges would be developed with consideration of the available evidence. Moving forward, future studies are needed on the neuropsychological and health effects associated with CO at various exposure concentrations and durations in order to provide evidence to underpin the selection of particular ranges. A further limitation of the analysis method is that by separating the CO data into specified ranges, the risk of Type 1 errors is increased due to the greater number of significance tests required for each of the ranges. This risk would have be

reduced if fewer ranges were used, for example 0.5-6 and 6.5-30ppm, and is a consideration for future research. An alternative approach to analysing the data would have been to identify exposure patterns within the data and examine differences between them on levels of functioning. For example, comparison of a continuous extremely low-level exposure versus an exposure containing short-lasting higher CO peaks. However, this would have required categorising different exposure patterns, in which a considerable amount of exposure detail is lost. Nevertheless, this approach represents an alternative method for future research.

Study 3 applies this analysis method in the examination of the cognitive effects of chronic low-level CO exposure in older adults. Investigation of potential effects at various exposure concentrations, including extremely low-level CO, is combined with detailed neuropsychological assessment data with aims to contribute towards determining whether beneficial effects are associated with less severe exposures, and critically, thresholds of harm.

Chapter 4: Study 3

A Cross Sectional Study of the Cognitive Effects of Chronic Low-level CO Exposure in Older Adults.

4.1 Introduction

When inhaled, carbon monoxide (CO) enters the bloodstream where it binds to haemoglobin (Hb) forming carboxyhaemoglobin (COHb). The formation of COHb reduces the oxygen carrying capacity of the blood, decreasing oxygen delivery to the tissues and organs leading to hypoxia (Haldane, 1895a; Raub & Benignus, 2002). The brain and the heart are most susceptible to CO toxicity and hypoxic injury due to their high oxygen demand (Prockop & Chichkova, 2007). The symptoms of acute severe poisoning have previously been well described and include headache, fatigue, nausea and dizziness, which are progressively followed by loss of consciousness and ultimately death (Raub & Benignus, 2002). Neuropsychological sequelae (NS) can also present, including a wide range of neurological deficits, cognitive impairments, and affective changes. However, less is known about the health and neuropsychological effects of low-level exposure. These exposures have been defined at various COHb concentrations but there is general agreement that levels below 15% represent less severe poisoning (Chambers et al., 2008). Healthy individuals have baseline COHb levels of 0.4-0.7% resulting from endogenous CO production. This, combined with environmental exposure usually leads to baseline COHb levels of <2% in non-smokers and <5% in smokers (Harper & Croft-Baker, 2004; Raub & Benignus, 2002).

4.1.1 Low-level Acute Exposure

Evidence indicates the presence of neuropsychological effects following acute low-level exposure such as impaired tracking ability, sustained attention and slowed processing and psychomotor speed at COHb levels of 5-7% (Horvath et al., 1971; Ramsey, 1972; Putz, 1979; Gliner et al., 1983). However, other studies have reported no CO-related effects on areas of cognition including sustained and divided attention and psychomotor and processing speed at COHb levels between 5 and 16% (Roche, et al., 1981; Wright & Shephard, 1978; Benignus et al., 1977). These inconsistencies have been previously addressed by meta-

analyses and reviews, all of which reached similar conclusions: the evidence is inconsistent; studies lack successful replication; and reported results may be due to Type I errors, blinding procedures and publication bias (Benignus, 1993; 1994; Benignus, Muller, & Malott, 1990; Stewart, 1975). Results from the systematic review of the acute low-level exposure literature in this thesis indicated that the reported inconsistencies may, in part, be due to differences in the areas of cognition assessed across the studies. When both primary and secondary cognitive domains were evaluated, results indicated that CO-related impaired inhibition was a consistent finding across the reviewed studies, particularly when tasks required simultaneous task switching abilities. The review also revealed potential CO-related long-term memory impairments and psychomotor speed deficits (see Study 1; Chapter 2). Additionally, examination of effect sizes in two of the reviewed studies (O'Donnell et al., 1971b; Stewart et al., 1970) indicated possible associations between low-level exposure and *increased* performance in areas of sustained and divided attention, task switching and psychomotor function. However, it is important to note that the sample size in one of these studies was extremely small (n=4) (O'Donnell et al., 1971b) and neither of the studies were well controlled. Therefore, caution should be taken when interpreting these findings. Furthermore, the majority of experimental studies on acute exposure were published over 40 years ago, had poor design and control measures and would not be acceptable by current ethical standards. Nevertheless, exposure guidelines published by the Expert Panel on Air Quality Standard of the World Health Organisation (WHO; 1999; 2010) are based on these studies and aim to prevent individual COHb levels rising above 2.5% and 2% respectively.

4.1.2 Low-level Chronic Exposure

Studies on the neuropsychological effects associated with chronic low-level exposure are limited. Whether these exposures can lead to short or long-term effects is therefore unclear. The current study examined the cognitive impacts of chronic low-level exposure in a group of older adults, who as a group, are identified as particularly vulnerable to CO. Evidence of the detrimental neuropsychological effects, less severe prolonged exposure may present, are detailed in numerous anecdotal reports. For example, deficits in learning ability

and memory, depression and anxiety have been reported three months post-exposure in a 48 year old woman exposed to CO from a malfunctioning furnace (Ryan, 1990). Furthermore, Myers et al., (1998) reported memory impairments, motor slowing and depression and anxiety in seven individuals exposed to low-moderate levels of CO from malfunctioning appliances for between three weeks to three years. However, determining the degree of exposure in case reports is difficult due to the lack of information relating to exposure concentration and duration. Furthermore, individuals may be exposed to short periods of acute poisoning at higher levels as well as low-level chronic exposure. Therefore, ascertaining which type of exposure is responsible for any resulting health effects is problematic (Townsend & Maynard, 2002).

Further evidence of the potential detrimental effects chronic exposure to low-level CO may pose, is provided by epidemiological studies with reported associations between outdoor air pollution and increased risk of stroke (Maheswaran et al., 2005), myocardial infarction (MI) (Shah et al., 2013), and heart failure (Mustafic et al., 2012), indicated by higher hospital admission and mortality rates. Importantly, associations between air pollution exposure, including CO, and increased dementia risk have also been reported (Chang et al., 2014) with air pollution recently identified as a dementia development risk factor in later life (>65) (Livingston et al., 2020). These results indicate that chronic exposure to CO, at levels below the recommended guidelines, may increase the risk of adverse physical health and cognitive effects.

Studies examining the neuropsychological effects associated with chronic low-level exposure in the home are extremely limited with only a few published studies to date. Saenz, Wong and Ailshire, (2018) examined the cognitive effects of indoor home exposure in 13,000 older adults (>50 years) in Mexico. They reported significantly lower cognitive performance in the exposed individuals in areas of verbal learning and recall, orientation and attention, after adjusting for age, sex, educational level, wealth, housing quality, chronic diagnoses and smoking behaviour. However, indoor air pollution was assessed according to the occupant's primary cooking fuel, with the use of wood or coal categorised as exposure to pollution as opposed to gas. This reliance on indirect measurement

of air pollution raises several major limitations; concentrations of nitrogen oxide, sulphur dioxide, CO and particulate matter can accumulate indoors from combustion sources and cooking (Linaker et al., 1996; Ström, Alfredsson, Malmfors, & Selroos, 1996) and without direct measurement, it is unclear whether any resulting effects are associated with exposure to one, or a combination of, these pollutants. Additionally, the categorisation of gas appliance use as a control or comparison of lower exposure is problematic with gas appliances commonly reported to contribute significantly to raised CO levels within the home (Stevenson, 1985; Ross, 1996; Croxford et al., 2005a; Croxford et al., 2005b). Furthermore, cognitive functioning was assessed using the Cross-Cultural Cognitive Examination (CCCE; Glosser et al., 1993), a dementia screening tool that has been previously criticised on quality and diagnostic accuracy (see Appels & Scherder, 2010 for systematic review). It is therefore extremely unlikely to be sensitive to subtle changes in cognitive function.

Volans et al., (2007) examined the effects of indoor home CO exposure using detailed neuropsychological data from 71 occupants (*M*=53 years) of the 270 homes in East London where continuous CO monitoring had been undertaken (Croxford et al., 2005b). No significant negative CO-related effects on cognition were observed. Instead, trends towards increased cognitive performance were found on seven of the 11 tasks, with standardised neuropsychological measures revealing test scores >.05 SD above the mean for a 1ppm increase in mean CO level. These were present in areas of auditory working memory, immediate and delayed visual memory recall, visuospatial ability and problem solving, whilst controlling for pre-morbid IQ, smoking, education and distraction level during testing (although all non-significant, >.05 *SD*). However, it is acknowledged that these deviations are small, with the authors reporting no clear evidence of neuropsychological effects (Volans et al., 2007).

4.1.3 Susceptible Groups

The majority of studies on the neuropsychological effects of acute low-level CO exposure have typically included healthy young adults, who are least likely to show any adverse effects on the central nervous system (CNS) (Otto et al., 1979). If we are to advance knowledge of the levels at which low-level exposures

present risk to health and neuropsychological function, research examining the effect of chronically elevated COHb levels, specifically in vulnerable groups, is needed. High risk groups within the population include the unborn, very young, and older adults, particularly those with pre-existing disease (Raub & Benignus, 2002). Individuals with pre-existing disease such as cardiovascular, respiratory, or hematologic conditions whose ability to adequately regulate oxygen supply or metabolism is compromised, are most susceptible to raised COHb levels. These individuals have reduced ability to compensate for any decreases in blood oxygen carrying capacity following COHb formation and are therefore likely to develop severe toxicity from lower concentrations (Raub & Benignus, 2002; Chiew & Buckley, 2014).

Older adults are also at a higher risk of exposure from domestic appliances due to increased time spent within the home consequent upon retirement or mobility restrictions (Harper & Croft-Baker, 2004). Furthermore, age-related structural and functional changes to the vascular system are likely to further increase exposure vulnerability in older adults. For example, endothelium-dependent vasodilatation and cerebral blood flow (CBF) are known to decline in healthy ageing (Belohlavek et al., 2009; Rodriguez-Manas et al., 2009). Age-related changes to blood vessels can lead to impaired vessel function, including endothelial dysfunction, arterial stiffness and hypo-perfusion, resulting in vascular dysfunction (Xu et al., 2017). These age-related alterations to the vasculature can lead to suboptimal CBF and hypo-perfusion which have been identified as precursors for mild cognitive impairment (MCI) and reported to accurately predict the development of Alzheimer's disease (AD) (David & Taylor, 2004; Belohlavek et al., 2009; Jerskey et al., 2009; Jefferson et al., 2007; Forti et al., 2006). Furthermore, cardiovascular risk factors, such as heart failure, coronary artery disease and atrial fibrillation are more common in older adults and can lead to greater decreases in CBF and chronic hypo-perfusion, further compromising the already reduced CBF that is present in ageing (de la Torre, 2012; Leenders et al., 1990; Zhao et al., 2007; Bentourkia et al., 2000; Parkes et al., 2004; Heo et al., 2010). Older adults, as a group, may therefore be particularly vulnerable to exposure from substances that further compromise cerebral oxygen supply, such as CO, especially those with pre-existing disease.

4.1.4 The Current Study

The literature on low-level CO exposure is inconsistent and dated with both experimental studies on acute exposure and case reports of chronic exposure presenting several limitations. Nevertheless, these studies alongside results from epidemiology studies indicate that adverse physical health and NS can follow acute and chronic low-level exposure. These findings present significant concern, especially when considered alongside accumulating evidence of raised CO concentrations in a number of UK homes, with domestic appliances, particularly gas, contributing significantly to elevated CO levels (Stevenson, 1985; Ross, 1996; Croxford et al., 2005a; Croxford et al., 2005b). Moreover, individuals in developed countries spend a large majority of their time indoors, specifically at home (Kornartit et al. 2010). Exposure to CO within the home may therefore be responsible for significant widespread morbidity with individuals potentially exposed to higher CO concentrations than those considered safe. The problem may also be of particular concern within the UK, with gas appliances widely used for heating and cooking and homes are often older and may contain dated appliances (Townsend & Maynard, 2002).

The unnoticeable properties of CO combined with the associated non-specific symptoms all contribute to difficult diagnosis with individuals and medical professionals often unaware of the exposure. Consequently, this leads to chronic exposure that may continue for weeks and potentially years until CO exposure is suspected in symptomatic individuals, or the CO source is detected (Kirkpatrick, 1987; Crawford et al., 1990; Gilbert & Glaser, 1959; Myers et al., 1998; Ryan, 1990). Further adding to the complexity within the CO behavioural literature, are the potential positive CO-related effects on neuropsychological function, with review findings and results from one study potentially indicating better performance (see Chapter 2 and Volans et al., 2007). It is important to note that the reported CO levels in Volans and colleagues (2007) study represent extremely low-level exposure, with 15-minute average concentrations in the majority of studied homes ≤5ppm (M=1.89). At these low levels, endogenous CO has known beneficial effects playing a vital role in cellular maintenance, protection, regeneration and survival (Prockop & Chichkova, 2007). Due to its physiologic and cytoprotective properties, the administration of exogenous low-

level CO is currently being studied for neuroprotection in a range of brain pathologies (for reviews see Mahan, 2012; Queiroga, Vercelli & Vieira, 2015). Extremely low-level exposure to CO may therefore result in similar beneficial effects to those associated with endogenous production. However currently this is unknown.

It is currently unclear as to whether less severe exposures can cause short term or long lasting effects on the brain. Further research is needed in an area where there is a significant knowledge gap. Research directed towards establishing whether extremely low-level exogenous CO can result in beneficial effects and if negative effects do follow, determining the associated neuropsychological effects and thresholds of harm is crucial. These thresholds are likely to be different depending on the exposure duration and individual differences in the population of study, such as age and health status. For example, older adults are identified as particularly vulnerable to CO due to the biological and physiological changes associated with ageing and disease and are likely to develop toxicity from lower concentrations. Similarly, any beneficial effects may be dependent upon these same factors, with the potential physiological and protective properties of exogenous CO, if present, observed only in vulnerable groups such as older adults who may benefit most from any resulting therapeutic effects.

If we are to move towards identifying ‘safe’ levels of low exposure, research examining exposure level, duration and pattern, such as low-level transient increases along with continuous rises, and how these correlate with neuropsychological outcomes, is needed. The effects of chronic exposures whereby the body is compensating for a prolonged period of time are unknown. Exogenous CO along with tolerance and adaptation may play a protective, and potentially beneficial role, in minimising risk to the CNS up to a certain dose and duration, but the point at which these mechanisms become ineffective and the exposure becomes toxic are unclear. Increased understanding of the effects associated with chronically elevated COHb levels, specifically in vulnerable groups, is required if we are to advance knowledge of the potential beneficial effects of exogenous CO and the levels at which these exposures present risk to health and neuropsychological function.

4.1.5 Aims and Hypotheses

Therefore, the primary aim of the study was to measure continuous CO levels within a sample of homes in order to examine the relationship between chronic low-level CO exposure and cognitive function in an older adult sample who, as a group, are identified as specifically vulnerable. It is anticipated that the analysis method detailed in Chapter 3 will permit the examination of effects at various exposure concentrations, including extremely low-level CO, and this combined with neuropsychological assessment data will contribute towards determining whether beneficial effects are present, and critically, thresholds of harm.

The effects associated with low-level chronic exposures, if present, are likely to be subtle in comparison to those observed in severely poisoned patients. Detailed neuropsychological evaluations that are sensitive to slight cognitive changes are therefore vital in the assessment of individuals exposed to CO (Myers et al., 1998; Amitai et al., 1998; Ernst & Zibrak, 1998). A thorough neuropsychological battery was administered, assessing multiple areas of cognition, including long-term and short-term memory, attention, psychomotor speed, visuospatial ability and processing speed. Given evidence from the literature review (Chapter 2), the three core executive functions (EFs), working memory (WM), inhibitory control and cognitive flexibility, and higher-level EFs including planning and problem solving are also a targeted set of functions (see Diamond, 2013 for a detailed review on EFs). During neuropsychological testing, it is important to control for pre-morbid levels of functioning, by ascertaining an individual's ability prior to the onset of cognitive deterioration. These measures assess aspects of cognition that are thought to be preserved with ageing, such as vocabulary and knowledge of language rules, and are therefore crucial in assessing accurate degrees of cognitive decline (de Oliveira, Nitrini, Yassuda & Brucki, 2014). These baseline levels can then be controlled for, or compared to, current levels of functioning. Demographic factors known to impact cognitive function such as age and education level, alongside health covariates including physical and psychiatric diagnoses, levels of anxiety and depression and information relating to smoking status and behaviour within the home were also controlled for in order to account for potential confounders.

Whilst current evidence on the effects associated with chronic exposure is extremely limited, a few observations can be drawn from the existing literature. Firstly, memory impairments and psychomotor speed deficits appear to be relatively consistent findings following acute low-level exposure (see Chapter 2) and chronic exposure (Gilbert & Glaser, 1959; Ryan, 1990, Myers et al., 1998; Nakamura et al., 2016). Additionally, deficits in EF, specifically pre-potent response inhibition, may follow acute low-level CO exposure (see Chapter 2). It is therefore likely that, if cognitive deficits do present following chronic low-level exposure, impaired memory, inhibition and psychomotor speed may result. Furthermore, due to the biological and physiological changes related to ageing and disease, any negative CO-related effects are likely to strengthen with advancing age. Additionally, if positive effects do result following extremely low-level CO exposure, it is anticipated that they will be observed in the current study due to the group of older adults studied who potentially may benefit most from any associated physiological and protective properties. Furthermore, trends towards improved performance in areas of auditory working memory, immediate and delayed visual memory recall, visuospatial ability and problem solving were found in a study of chronic home exposure with extremely similar methodology (Volans et al., 2007). Therefore, if positive effects are observed they may likely present in similar areas.

Hypothesis 1 (H_1) At a certain unknown dose, chronic low-level CO exposure will be associated with impaired cognitive function.

H_2 If CO-related deficits are observed these will be present in, but not limited to, aspects of memory, inhibition and psychomotor speed.

H_3 The strength of any potential relationship between low-level CO and cognitive function will increase with advancing age.

H_4 Extremely low-level exposure to CO will be associated with positive effects on cognitive function including auditory working memory, aspects of long-term memory and visuospatial ability and problem solving.

4.2 Method

4.2.1 Study Design

The study was designed as a cross-sectional observational study that incorporates a correlational design.

4.2.2 Participants

A sample of 106 older adults aged 58 to 97 years (*M*=75.60, *SD*= 8.40) residing in Coventry were recruited via liaison with West Midlands Fire Service (see Chapter 3 for details). With observational studies on the effects associated with chronic low-level CO exposure extremely sparse, effect size could not be computed based on previous research. As the research only examined low-levels of CO, and due to Fire Service safety intervention protocols, relatively small variation in the data were anticipated, thus a small to moderate effect size was expected (0.25). The effect size alongside an alpha value of 0.05 and a power of 0.80 were used to calculate the sample size using G Power (Faul, Erdfelder, Buchner, & Lang, 2009). The results indicated that the highest sample size needed would be a total of 130 participants, which was increased to a sample of 150 participants to allow for a 13% attrition rate.

The inclusion criteria were: individuals residing in Coventry; ≥60 years of age; and fluent in English language. All participants were aged ≥60 years, with the exception of one who was 58 years old. The age criterion was based on the anatomical brain changes observed in ageing, with the overall volume of the brain reported to decline with age at an approximate rate of 5% per decade after age 60 (Hedman et al., 2012). Furthermore, late-onset AD is typically described by an onset age of 65 years or older (Rabinovici, 2019). The exclusion criteria were: individuals who had experienced an acute CO poisoning episode; and those lacking mental capacity to consent or understand participation in the study, according to the Mental Capacity Act (MCA; 2005). Individuals were not excluded based on any existing physical medical conditions or on factors relating to socioeconomic status including property type, tenure, benefit status and geographical region or on health status, home appliances and smoking behaviour. Participants with CO levels of 20ppm or above in their homes on the initial visit from the Fire Service (the level at which an incident is raised by the

Fire Service) were not informed of the research and therefore excluded. The study employed a community sampling method, minimising any bias from the selection of symptomatic individuals whose difficulties have been attributed by them, or by a medical professional, to exposure to CO (Gupta & Horne 2001, Gupta et al., 1997).

4.2.3 Measures

4.2.3.1 Neuropsychological Measures

Global cognitive function was assessed using the Addenbrooke's Cognitive Examination III (ACE-III; Noone, 2015). The ACE-III provides information on general level of impairment and assesses five cognitive domains: attention, memory, verbal fluency, language, and visuospatial abilities. It is scored out of 100, with higher scores indicating better cognitive functioning. The ACE-III is a reliable and widely used clinical tool with the cognitive domains showing significant correlation with standardised neuropsychological assessments of attention, memory, language and visuospatial ability (Noone, 2015).

The National Adult Reading Test (NART; Nelson, 1982) was used as a measure of pre-morbid IQ which assesses vocabulary and knowledge of language rules, areas reported to be preserved with ageing when declines are present in other cognitive domains (Schaie & Willis, 1993). Participants are required to read aloud a list of 50 irregularly spelt English words with increasing difficulty. The NART is scored on correct pronunciation with the total number of errors recorded. The NART has been reported to have good reliability and validity (O'Carroll, 1987; Crawford, Parker, Stewart, Besson, & DeLacey, 1989). The results from the test will be used as an indicator of pre-morbid cognitive function and will be incorporated into the analyses as a control for baseline performance.

Selective attention (resistance to distractor interference), divided attention and processing speed were assessed using the Useful Field of View test (UFOV; Ball, Beard, Roenker, Miller & Griggs, 1988). The UFOV is a computer-based task that consists of three subtests. The first task is a measure of processing speed whereby a silhouette of either a car or a truck is displayed on a screen for a short duration followed by a screen displaying both of the images. The participant is

required to identify which of the two images appeared on the previous screen. The stimuli are presented in a randomised order and displayed for progressively shorter durations (500-17ms) until the participant can no longer correctly identify which of the two images they were shown. The second task assesses divided attention and requires the participant to identify a stimulus in the centre of the screen and locate a simultaneously presented car displayed in the periphery. The stimuli and presentation details are the same as in the first task with the addition of the secondary stimuli presented randomly in 1 of 8 periphery locations. Participants are asked to identify the stimuli in the middle of the screen and the position of the car on the periphery. The third task assesses selective attention and is the same as the second except the car displayed in the periphery is embedded in a screen of 47 distractor triangles. Across all tasks, the software automatically adjusts the stimulus presentation time, until a stable measure is established. Final scores reflect the display duration at which the participant accurately identified the correct stimulus 75% of the time, with lower scores indicating better performance. The UFOV has shown good reliability and validity (Edwards et al., 2005).

Visuomotor speed was assessed using the Trail Making Test part A (TMTA) (Reitan & Wolfson, 1985). The TMTA is a paper-based task which involves the participant connecting 25 numbered circles in sequential order as quickly as possible. The task is scored in terms of completion time with lower values representing better performance. Executive functioning, specifically cognitive flexibility and inhibition (resistance to pro-active interference), was measured using part B of the TMT. The task involves the participant alternating between connecting circled numbers and letters in order (i.e. 1, A, 2, B) as quickly as possible. The completion time from the TMTA is subtracted from the completion time of TMTB, with the resulting time used as the TMTB score. The TMT is commonly included as part of neuropsychological assessment and has been found to be sensitive to a range of neurological impairments (Spreen & Strauss, 1998).

Immediate and delayed recall and recognition were assessed using the logical memory subtest of the Wechsler Memory Scale (WMS-IV; Wechsler, 2010).

Depending on the participant's age, the WMS-IV adult battery (16-69 years) or the older adult battery (65-90 years) was administered. Participants aged ≤69 years were assessed using the adult battery. In the older adult battery, the participant is read story A twice and B once and is asked to recall any information immediately after each reading. The units are summated to form the immediate recall total scored out of 53. The participant is asked to try and remember the stories as they will be asked about them later. Following 30 minutes, the participant is asked to recall any information from story A and then B with the number of recalled units scored out of 39 forming the delayed long-term memory recall score. In the final part of the task, participants respond yes/no to a series of questions about the stories with the number of questions answered correctly forming the recognition memory scores. Higher scores represent better performance across all parts of the task. The older adult battery procedure and scoring is similar, however, story B and C are administered and are read only once to the participant during the immediate recall part of the task.

The block design task from the WAIS-III was used as a measure of visuospatial ability and problem solving. The task involves the participant rearranging a set of two-coloured (red and white) cubes that have various patterns on different sides in order to match a target two-dimensional geometric pattern within a specified time limit. There is a total of 14 patterns with higher scores awarded to faster completion times. Higher scores therefore indicate better performance scored out of a maximum of 68. The task ended when three consecutive scores of 0 were recorded.

The Hospital anxiety and depression scale (HADS; Zigmond & Snaith, 1983) was used as a measure of anxiety and depression. The scale consists of 7 items relating to anxiety and 7 to depression that are scored on a 4-point Likert scale with each item scored from 0 to 3. The 7 individual item scores are summated separately to form the total scores with higher scores reflecting greater levels of anxiety and depression. The HADS has been reported to have good reliability and validity (Bjelland, Dahl, Haug, & Neckelmann, 2002).

A questionnaire including demographic, medical (such as pre-existing physical and psychiatric diagnoses) and property information (such as home appliances and behaviour within the home) was administered (see Appendix A2.7). This information was included in order to control for the potential decline in cognitive functioning associated with pre-existing physical conditions and the impact psychiatric disorders can have on performance. In addition to the NART, education level, smoking status and hours spent within the home per day were also recorded for incorporation as control variables in the analyses. Information relating to property type, home appliances and cooking behaviour was collected in order to examine potential sources of CO and is reported elsewhere in a paper in preparation that is outside this thesis.

The final four measures were administered using Inquisit Lab and programmed by Millisecond Software using a Lenova ThinkPad L470 laptop with a 14" display monitor. Viewing distance could not be controlled due to the visits taking place within homes where variance in furniture and participant mobility and health were encountered and appropriate adjustments made. However, in all cases, participants indicated that they could clearly see the screen and were comfortable throughout testing. The Sustained Attention to Response Task was used to assess sustained attention and inhibition (pre-potent response) (SART; Robertson et al., 1997). The task includes 225 individual number presentations between 1 and 9 (25 of each) displayed in a random order. The numbers are presented centre screen with five varying font sizes (48, 72, 94, 100, and 120-point) that are also randomised. Participants are instructed to respond by pressing the spacebar to all digits (GO stimuli) except for the number 3 (NOGO stimulus) where no response is required and to respond as quickly and accurately as possible. Dependent variables included: mean reaction time (RT) across all GO trials (≥200ms), intra-individual variability using the coefficient of variation (*SD*/mean RT) and SART errors (responses to the NOGO stimulus). Anticipations (RTs <100ms), omissions (no response during a GO trial) and RTs for Go trials with latencies of 100-199ms (classified as ambiguous) were not analysed (see Carriere et al., 2010 for administration and scoring details).

Auditory short-term memory was assessed using the forward digit span (individual tries to repeat digits forward) and auditory WM using the backwards digit span (individual tries to repeat digits backward) from the Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV; Wechsler, 2010). The forward digit span starts with a list of 3 digits and increases in a 1:2 staircase with a correct response increasing the subsequent list by 1 digit, and 2 consecutive incorrect responses reducing the length by 1 digit. A total of 14 trials were administered. The procedure for the digit span backwards is the same with the exception of starting with a list length of 2 digits. The maximum list length correctly recalled prior to two incorrect lists of the same length (two-error maximum length) were recorded.

Visual WM was assessed using The CORSI block span task (Corsi, 1972). The task consists of 9 blue blocks presented in fixed locations on a black screen that individually light up yellow in a pre-fixed sequence. Participants are asked to remember the exact sequence and are required to click on the boxes in the same order they were presented. The sequences start with 2 boxes and can increase up to a sequence of 9 with 2 trials presented per block sequence length. If one of the two sequences was entered correctly, the next two trials of an increased sequence length were administered with a maximum of 16 sequences presented. The task ended when the participant failed to recall two sequences of equal length. The block span score represents the length of the last correctly repeated sequence. A second measure was also calculated by multiplying the block span by the number of correct trials to gain a total score. This measure reflects performance on both trials of equal length and is suggested to be more reliable than block span scores alone (see Kessels et al., 2000 for detailed administration and scoring details).

The planning and problem solving aspect of Executive Function was assessed using The Tower of London task (TOL; Shallice, 1982). Participants are required to figure out and plan how to move 3 different coloured balls on three pegs in such a way to achieve a specific solution pattern. A specific target pattern is displayed which must be achieved within a limited amount of moves from the starting position. Target patterns increase in difficulty throughout the task.

Participants are given 3 attempts at each problem. Unsuccessful completion of the problem scores 0 and the next problem is automatically presented. Successful completion on the first trial scores 3 points, second trial 2 points and the third 1 point. The total score is the sum of points across all 12 problems with a maximum score of 36 (see Krikorian, Bartok & Gay, 1994) for detailed administration information and scoring). Response times for planning and execution were not analysed due to the researcher controlling the mouse in cases of poor mobility. Instructions and practice trials were administered prior to the commencement of each task which were discarded from the analyses.

Blood pressure and levels of CO levels within exhaled breath (ppm) were also measured.

4.2.3.2 Equipment

CO Alarms

FireAngel CO-9X Wireless Carbon Monoxide Alarms were used throughout the study in order to keep the participants safe from higher levels of CO exposure than is considered safe according to current alarm guidelines. The CO alarms were left in the properties after study completion. For information relating to specification and alarm activation thresholds see Chapter 3.

CO Data Loggers

Lascar electronics easy log carbon monoxide data loggers (EL-USB-CO300) were used to continuously record the ambient CO concentrations within the home over a 1 month duration. Average recordings were taken every 5 minutes resulting in a total of 8064 readings per home. For information relating to specification, sampling rate, accuracy, placement and CO data preparation see Chapter 3.

Toxico Personal Alarm

A Honeywell ToxiRAE 3 (PGM-1700) personal CO monitor was used in order to keep the researcher safe when entering properties with potential CO in the ambient air and to record the CO level during the assessment (see Chapter 3 for specification details).

Breathalyser

A Bedfont Micro-Smokerlyzer (AWR-BM+01) was used as a physiological measure of CO levels in exhaled breath (ppm) in order to determine the degree of exposure. The monitor contains an electrochemical sensor and automatically converts CO readings (ppm) to COHb% with a concentration range of 0-250ppm and a response time of <20 seconds. Sensor life: 2-5 years, accuracy: +/- 2%, sensitivity: 1ppm and operating temperature: 0-40°C. The device contains an anti-bacterial filter and one-way valve to reduce cross-contamination and alerts the user when replacement is required. Single use mouth pieces were used. Participants were required to inhale and hold their breath for 15 seconds prior to exhaling into the monitor. These devices are simple to use, are non-invasive, compact and portable, only take a few seconds to use, and have been validated (Kurt et al., 1990). Battery replacement and calibration was carried out by the Fire Service when required.

Blood Pressure Monitor

A BDFA electronic LCD digital display blood pressure monitor was used as a physiological marker of health. The monitor has a measuring range of 0-280 millimetres of mercury (mmHg) with a measurement accuracy of +/-3 mmHg.

4.2.4 Informed Consent and Ethical Approval

A two-phase consent process was undertaken with West Midlands Fire Service carrying out the first phase with volunteers signing an 'expression of interest' form in which they agreed to the Fire Service sharing their contact details with the researcher. The second phase was carried out by the researcher where informed written consent for study participation was obtained. The study received ethical approval by the Faculty of Health and Medicine research ethics committee, Lancaster University. Reference number: FHMREC17082 (see A2.8).

4.2.5 Procedure

Participants were recruited via liaison with West Midlands Fire Service. Following deployment of the CO data loggers and alarms by the Fire Service, home visits with the researcher were scheduled at a time during the four weeks that the data loggers were in place. Health and mental screening questionnaires and

neuropsychological testing were carried out. The tasks were carried out in a fixed order as follows: General information questionnaire, HADS, CASP, ACE-III, WMS, NART, TMTAB, WAIS-BD, WMS, CORSI, WAIS DSF DSB, TOL, SART and UFOV. Due to the number of measures, the order of assessments were not counterbalanced. However, due to the lengthy nature of the assessments, regular breaks were taken to avoid fatigue and boredom and the more repetitive tasks were carried out towards the end of testing. The general information questionnaire was carried out first to allow for a rapport to be built and to put participants more at ease prior to neuropsychological testing. In cases where participants had restricted mobility/dexterity, the laptop was placed in front of the participant whilst the researcher controlled the mouse under direction. This only affected performance measures on the TOL task, with reaction times removed from the analysis. All participants completed the SART task without assistance. Participants were given a detailed debrief following participation. The CO data loggers were collected from the properties after they had been in place for a total of one month. The data were downloaded and initially checked for safety purposes by the Fire Service prior to being shared with the researcher. The study was double blind with both the researcher and participants unaware of exposure status (see Chapter 3 for full procedure details).

4.2.6 Statistical Analysis

In order to examine the hypotheses that chronic low-level CO exposure would be associated with impaired cognitive function, particularly memory inhibition and psychomotor speed (H_1 and H_2), and that positive CO-related effects, if present, would be observed at extremely low levels of CO in areas including auditory WM, aspects of long-term memory and visuospatial ability and problem solving (H_4), correlation analyses were initially carried out. Correlations between the CO ranges and age, hours spent within the home, pre-morbid IQ, anxiety, depression, physical and psychiatric diagnoses (control variables) were examined in order to assess the relationships, and any multicollinearity, between these variables prior to further analysis. Correlations between the neuropsychological measures and control variables were carried out in order to determine the variables that were associated with the neuropsychological measures so that their variance could be controlled for in further analyses.

Finally, correlation analyses were undertaken between the neuropsychological measures and the percentages of CO in each range in order to determine the relationship between CO exposure, at various levels, and functioning (see Chapter 3 for details on CO outcome measures).

Regression models were then developed from the results of the correlation analysis with control variables entered into Block 1 when they were significantly correlated with the cognitive measures. These were subsequently dropped from the model when their contribution was not significant, with the exception of age, in order to increase the degrees of freedom. Carbon monoxide data were analysed in specified ranges (0ppm, 0.5-3ppm, 3.5-6ppm, 6.5-9ppm and 9.5-30pmm) with the percentage of readings in each used in the analysis. These were entered into the regression models separately due to Multicollinearity (for details on CO data preparation and rationale see Chapter 3). The main effects of interest, the percentage of CO readings within each range, were entered into Block 2 to examine H_1, H_2 and H_4. In order to answer H_3 that the relationship between age and cognition would be moderated by CO exposure, in that, the relationship would increase with advancing age, an interaction term between the percentage of CO readings and age was entered in Block 3. In cases where significant interactions were found, the percentage of CO was separated into two groups (low/no CO; higher CO) in order to permit further examination of the effects by plotting interaction graphs between age and the cognitive scores separated by CO group. Interaction graphs were also plotted by age group, with two groups created (young older adults: 58-74 years (*n*=50); old older adults: 75-97 years (*n*=56) in order to examine the interaction effect between CO exposure and cognitive performance by age group. The age groups were determined by median split.

4.2.7 Data Processing

The raw data were entered into IBM SPSS Statistics 26 (2019) for analysis.

4.2.7.1 Missing Data

There was an extremely small amount of missing data, only 2 cases were missing across the UFOV tasks. Analyses were run without these cases when examining CO-related effects on UFOV scores only.

4.2.7.2 Data Transformations

Prior to correlation analysis, variables were assessed for normality by inspection of histograms, Q-Q plots, skewness and kurtosis values and tests of normality (Kolmogorov-Smirnov test). Data transforms were used when required on the cognitive and mental health variables with transformation chosen based on Field (2013). Transformed variables were used in correlation analyses for normality and in regression analyses to correct for linearity and homoscedasticity problems. The interpretation of the direction of effect for reflected variables, are reversed and are presented as such (i.e. positive correlations for reflected variables are interpreted as negative) (Field, 2013).

4.2.7.3 Assumption Testing and Bias from Outliers and Influential Cases

Outliers greater than ±3 SDs were removed from the correlation and regression analyses. In the regression models, the influence of a case on the ability of the model to predict that case was also assessed using studentized deleted residual (difference between adjusted predicted value and observed value divided by the standard error). Residuals ±3.29 were removed from the analysis (see Field, 2013). Additionally, the influence of a case on the model's ability to predict all cases (the full model) was assessed using Cook's and leverage values. Leverage cut off points of >0.5 were used with values exceeding this removed from the analyses (see Huber, 1981). Cook's distance values above 1 indicate potentially large influence and represent cause for concern and so were removed from the regression analysis (Cook and Weisberg, 1982). Independence of observations (residuals) were assessed by the Durbin Watson statistic which was approximately 2 for each regression, indicating no correlation between the residuals. Linearity and homoscedasticity were assessed by visual inspection of the studentized residuals and unstandardized predicted values plot and partial regression plots. There was no evidence of multicollinearity, as assessed by correlations <.80, VIF values >4.0 and tolerance >0.2 (Field, 2013; Hair et al.,

2010). The assumption of normality of the residuals was assessed by a histogram of the standardized residuals and a normal P-P plot. The removal of influential cases from the analyses did not lead to a large number of omitted cases, with all analyses run with ≥100 observations.

4.2.7.4 Mean Centring

All of the control and predictor variables were mean centred for regression analysis, by subtracting the mean from all observations for each variable, in order to reduce multicollinearity. This enabled the examination of interaction effects between age and CO exposure on cognitive function.

4.3 Results

4.3.1 Descriptive Statistics

Descriptive statistics are provided in Table 4.1. It can be seen that the mean age for male participants (*M*= 74.0 years) was slightly lower than for female participants (*M*= 76.3 years). Years in education ranged between 9 and 21, with a mean of 12.7 years, and NART errors between 1 and 46 with a mean of 21.7, with higher scores indicating lower pre-morbid IQ.

Table 4.1. Mean, standard deviation and range for age, education level, NART errors and gender.

	Age (yrs)	**Education (yrs)**	**NART (errors)**	**Age by gender (yrs)**	
				M	**F**
N	106	106	106	33	73
Range	58-97	9-21	1-46	58-92	60-97
M	75.60	12.73	21.73	74.00	76.33
SD	8.40	2.24	10.32	9.04	8.06

NART= National adult reading test

4.3.2 Mean, Standard Deviation and Range for Ambient, Breath and COHb Levels

Descriptive statistics are presented in Table 4.2 for ambient, breath and COHb level by smoking status. Breath CO (ppm) and COHb levels are reported as an indication of exposure severity, with only smoking status controlled for in the analyses. It can be seen that smokers had a higher level of CO in their breath (*M*=14.67ppm) compared to non-smokers (*M*=2.51ppm), as would be expected.

The mean ambient CO level was also higher in the homes of smokers (*M*=0.26ppm) compared to those of non-smokers (*M*=0.07ppm).

Table 4.2. Mean, standard deviation and range of CO measures by smoking status.

Smoking status	Ambient CO (ppm)	Breath CO (ppm)	COHb (%)
Smoker			
N	9	9	9
Range	.00-13.50	5.00-22.00	1.00-4.20
M	.26	14.67	2.79
SD	.50	4.64	.87
Non-smoker			
N	97	97	97
Range	.00-29.00	1.00-7.00	.20-1.40
M	.07	2.51	.50
SD	.21	.97	.19

4.3.3 Mean and Standard Deviation for Independent and Dependent Variables

Means and standard deviations for all variables are displayed in Table 4.3. Means are presented for the untransformed variables and therefore trimmed means (5%) are also reported (the highest and lowest 5% of the data were excluded and means calculated from the remaining 90% of data points). These were included in order to examine the influence of outliers on the mean. Comparison between the two measures revealed only small differences indicating that the outliers did not have a large influence on the overall mean.

Table 4.3. Mean and standard deviation for control, predictor and dependent variables.

Variable	Mean (SD)	5% trimmed mean
Age (yrs)	75.60 (8.40)	75.53
Hours spent in the home	20.98 (2.51)	21.15
NART Errors	21.73 (10.32)	21.54
Depression	4.27 (2.93)	4.17
Anxiety	5.76 (4.02)	5.49
Physical diagnoses (N)	1.70 (1.46)	1.59
Psychiatric diagnoses (N)	.25 (.61)	.14
% of CO readings at 0ppm	94.71 (14.70)	97.45
% of CO readings between 0.5-3ppm	4.68 (13.68)	2.22
% of CO readings between 3.5-6ppm	.43 (1.60)	.15
% of CO readings between 6.5-9ppm	.11 (.43)	.02
% of CO readings between 9.5-30ppm	.07 (.29)	.01
TMTA	53.48 (20.84)	52.00
TMTB	142.38 (82.50)	133.37
TMTBA	88.90 (69.58)	80.95
ACE-III Total	85.55 (9.26)	86.16
WAIS-BD	27.91 (10.69)	27.55
WMS-IR	28.91 (8.56)	29.10
WMS-DR	16.00 (7.19)	15.93
WMS-R	18.90 (3.07)	18.89
SART-RT	514.35 (100.10)	513.20
SART Errors	10.20 (5.37)	10.03

SART RTIIV	.31 (.08)	.31
CORSI-BS	4.77 (.90)	4.79
CORSI-BSTS	31.95 (13.10)	31.38
TOL	29.59 (3.90)	29.95
WAIS-DSF	5.68 (1.10)	5.66
WAIS-DSB	4.23 (1.17)	4.21
UFOV-PS	46.89 (48.93)	38.99
UFOV-DA	192.63 (152.48)	185.32
UFOV-SA	304.22 (136.82)	306.95

PPM= parts per million; TMT= trail making task; ACE-III= Addenbrookes cognitive examination-III; WAIS-BD=Welschler adult intelligence scale block design; WMS-IR=Welschler memory scale immediate recall; WMS-DR= delayed recall; WMS-R= recognition; SART-RT= Sustained attention response time mean reaction time; IIV= Intraindividual variability; CORSI-BS= CORSI block span; BSTS= block span total score; TOL= tower of London task; WAIS-DSF= digit span forward; WAIS-DSB= digit span backwards; UFOV-PS= useful field of view processing speed; DA= divided attention; SA= selective attention.

4.3.4 Bivariate Pearson Correlations

Exploratory correlation analyses were run in order to determine whether any of the CO ranges were correlated with the cognitive variables. Correlations between the control variables and predictor variables (CO ranges) are presented in Table 4.4 and correlations between the control and predictor variables and the cognitive measures are displayed in Table 4.5.

4.3.4.1 Correlation Analyses between Control Variables and CO Ranges

Interpretation of Table 4.4 indicates a significant correlation between the percentage of CO readings at 0ppm and physical diagnoses (p<.01), wherein as the CO readings at 0ppm decreased, indicating greater exposure, the total number of physical diagnoses increased. The percentage of CO readings from 0.5-3ppm was also significantly correlated with physical diagnoses with increased CO readings in this range related to greater number of physical diagnoses. Significant relationships were observed between the number of hours spent in the home per day and NART errors (p<.01), age (p<.001), anxiety (p<.05) and depression (p=.01). These correlations indicate that increased numbers of hours spent within the home, per day, are associated with greater NART errors (lower pre-morbid IQ), higher levels of anxiety and depression and older age. The percentages of CO at each range were significantly correlated with each other, as was depression and anxiety, and depression and number of physical diagnoses at the p<.001 and p<.01 level.

Table 4.4. Correlations between control variables and CO ranges.

	N	1	2	3	4	5	6	7	8	9	10	11
(1) % CO readings 0ppm												
(2) % CO readings 0.5-3ppm	106	-.990***										
(3) % CO readings 3.5-6ppm	106	-.530***	.406***									
(4) % CO readings 6.5-9ppm	106	-.441***	.312**	.957***								
(5) % CO readings 9.5-30ppm	106	-.382***	.277**	.733***	.837***							
(6) Age	106	.087	-.065	-.176	-.168	-.095						
(7) Hours spent in the home	106	-.148	.154	.019	.010	.092	**.415*** **					
(8) NART	106	-.047	.071	-.111	-.159	-.142	.104	**.257** **				
(9) Anxiety	106	-.106	.106	.053	.038	.029	-.052	**.205***	.115			
(10) Depression	106	-.048	.049	-.007	.041	.079	.073	**.290** **	.116	.495***		
(11) Physical Diagnoses	106	**-.249** **	**.249** **	.102	.099	.136	-.083	.062	.187	.087	.271**	
(12) Psychiatric Diagnoses	105	-.122	.124	.025	.028	.117	-.028	.054	.003	.187	-.023	.034

*p <.05, **p <.01, ***p <.001

Table 4.5. Correlations between the control variables and CO ranges and the cognitive measures.

	% CO 0ppm	% CO 0.5-3ppm	% CO 3.5-6ppm	% CO 6.5-9ppm	% CO 9.5-30ppm	Age	HSH	NART	Depression	Anxiety	Physical diagnoses	Psychiatric diagnoses
TMTA	-.019	.049	-.168	-.180	-.137	.496***	.372***	.280**	.129	-.051	-.009	.025
TMTB	-.039	.066	-.139	-.171	-.118	.490***	.417***	.487***	.171	.148	.049	.067
TMTBA	-.047	.068	-.098	-.130	-.079	.411***	.358***	.479***	.133	.157	.057	.085
ACE-III Total	.048	-.082	.172	**.226***	.173	-.277**	-.417***	-.699***	-.081	-.029	-.094	.035
WAIS-BD	-.002	-.037	**.211***	**.293****	**.239***	-.235*	-.348***	-.577***	-.153	-.106	-.078	-.129
WMS-IR	.084	-.100	.047	.085	.084	-.320**	-.475***	-.521***	-.136	-.199*	-.065	-.028
WMS-DR	-.013	.002	.080	.085	-.008	-.422***	-.431***	-.436***	-.108	-.052	-.110	.039
WMS-R	**-.203***	**.202***	.101	.092	.041	-.366***	-.303**	-.347***	-.091	-.003	.034	.102
SART-RT	.007	.010	-.098	-.125	-.109	.350***	.240*	.189	.008	-.023	-.128	.071
SART Errors	-.010	.006	.027	.030	.042	-.065	-.008	.171	.025	.032	.271**	-.113
SART RTIIV	.035	-.035	-.005	-.047	-.023	.052	.038	.153	-.015	-.115	.082	-.112
CORSI-BS	.006	-.040	**.192***	**.246***	.158	-.151	-.237*	-.278**	-.145	-.094	-.127	-.072
CORSI-BSTS	.017	-.051	.180	**.248***	.191	-.184	-.199*	-.352***	-.082	-.135	-.089	.036
TOL	**-.195***	.171	**.238***	**.234***	.175	-.127	-.015	-.110	.090	.051	.183	-.135
WAIS-DSF	.102	-.117	.021	.063	.124	-.171	-.127	-.374***	-.110	-.037	-.144	-.051
WAIS-DSB	-.089	.061	**.194***	**.236***	.190	-.186	-.248*	-.514***	.038	-.069	-.019	-.032
UFOV-PS	.085	-.079	-.073	-.091	-.045	.352***	.385***	.337***	.071	-.019	.013	-.001
UFOV-DA	.031	-.009	-.137	-.170	-.093	.477***	.330**	.370***	.109	-.043	-.043	-.004
UFOV-SA	.020	.028	**-.291****	**-.319****	**-.226***	.607***	.327**	.388***	.057	-.051	.089	-.008

*p <.05, **p <.01, ***p <.001

PPM= parts per million; HSH= hours spent in the home; TMT= trail making task; ACE-III= Addenbrookes cognitive examination-III; WAIS-BD=Welschler adult intelligence scale block design; WMS-IR=Welschler memory scale immediate recall; WMS-DR= delayed recall; WMS-R= recognition; SART-RT= Sustained attention response time mean reaction time; IIV= Intraindividual variability; CORSI-BS= CORSI block span; BSTS= block span total score; TOL= tower of London task; WAIS-DSF= digit span forward; WAIS-DSB= digit span backwards; UFOV-PS= useful field of view processing speed; DA= divided attention; SA= selective attention.

4.3.4.2 Correlation Analyses between Control Variables and Neuropsychological Measures

Interpretation of Table 4.5 indicates that correlations between age and the majority of the cognitive variables were significant at varying levels (p<.001-p<.05), with advancing age associated with poorer performance in areas of psychomotor and processing speed, cognitive flexibility, divided and selective attention, visual spatial ability, problem solving and immediate and delayed recall and recognition. Greater number of hours spent within the home per day and NART errors were also significantly associated with lower performance across the majority of cognitive variables at varying levels (p<.001-p<.05). Additionally, higher anxiety and depression scores were significantly correlated with greater number of hours spent in the home (p<.05). The only significant correlation between the cognitive and mental health variables was between anxiety and immediate memory recall with increased levels of anxiety associated with lower scores (p<.05). Similarly, only one significant correlation between the number of physical diagnoses and cognitive measures was observed, with greater number of SART errors, indicating poorer sustained attention and inhibitory control, associated with higher number of physical diagnoses (p<.01).

4.3.4.3 Correlation Analyses between CO Ranges and Neuropsychological Variables

Significant correlations were found between the percentage of CO readings at 0ppm and WMS-R and TOL scores, with greater CO readings at 0ppm, indicating lower exposure, associated with lower performance scores (p<.05). These results indicate a positive CO-related effect in areas of memory recognition and planning and problem solving. A significant association was found between WMS-R scores and the percentage of CO readings from 0.5-3ppm, with higher scores associated with greater percentage of CO readings in this range (p<.05). This also indicates a positive CO-related effect with greater number of CO readings, signifying higher exposure, related to higher (better) memory recognition scores. Significant correlations between the percentage of CO readings from 3.5-6ppm and WAIS-BD, CORSI-BS, WAIS-DSB, TOL (p<.05) and UFOV-SA (p<.01) scores were found with higher percentage of CO readings associated with better performance on each of these measures. Similarly, these findings suggest that the greater exposure from 3.5-6ppm is related to increased

performance in areas of visuospatial ability and problem solving, visual and auditory WM, planning, problem solving, selective attention and resistance to distractor interference. Greater percentage of CO readings from 6.5-9ppm were also found to be significantly associated with better performance across a range of measures including ACE-III, CORSI-BS and TS, TOL, WAIS-DSB (p<.05) and WAIS-BD and UFOV-SA (p<.01) scores. Finally, the highest CO range, from 9.5-30ppm, was significantly correlated with WAIS-BD and UFOV-SA scores, indicating better performance with greater percentage of CO in this range (p<.05). These findings suggest a positive effect of CO, with greater exposure associated with increased scores on the WAIS-BD task (visuospatial ability and problem solving) and lower scores on the UFOV-SA (selective attention), indicating better performance across both tasks.

In summary, positive CO-related effects on cognition were found in areas of memory recognition, planning, problem solving, visual and auditory WM, selective attention and visuospatial ability. These findings provide contradicting evidence in relation to the hypotheses that low-level chronic CO exposure would be associated with impaired cognitive function (H_1 & H_2). However, the observed CO levels were extremely low and thus support is provided for H_4, with extremely low-level CO associated with positive CO-related effects on cognition, particularly in auditory WM, memory recognition, visuospatial ability and problem solving.

4.3.5 Regression Models

In order to further examine H_1, H_2 and H_4 that chronic low-level CO exposure would be associated with impaired cognitive function, particularly memory, inhibition and psychomotor speed, and that extremely low-level exposure would be associated with positive effects in areas including auditory WM, aspects of long-term memory and visuospatial ability and problem solving, hierarchical multiple regression models were developed. These were based on the results of the correlation analyses and specifically focused on the significant correlations between the CO readings and neuropsychological measures. Control variables were dropped from the models when their contribution was not significant in order to increase the degrees of freedom and increase power. Age, hours spent within the home and NART errors were significantly correlated with the majority of the

cognitive variables and were controlled for along with anxiety, depression, total physical and psychiatric diagnoses and smoking status in Block 1.

The contribution of each CO range was examined in separate models and entered into Block 2 and the interaction between age and CO was entered in to Block 3 in order to examine H_3 that the strength of the relationships between low-level CO and cognitive function would increase with advancing age. Due to the number of cognitive variables assessed, regression models are reported only when CO exposure significantly contributed to the variance explained by the model and for the specific significant ranges only.

4.3.5.1 Regression on WAIS Block Design (WAIS-BD) (visuospatial ability and problem solving)

Model 1: Control variables

The first model was statistically significant, R^2=.406, F(3,99)=22.509, p<.001; adjusted R^2=.387, explaining 40.6% of the variance in WAIS-BD scores. NART errors and age were significant predictors within the model.

Model 2 & 3: Percentage of CO readings at 0ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 did not lead to a significant increase in explained variance (R^2 *change*=.012, F(1,98)=1.974, p=.163). The inclusion of the interaction term in Model 3 led to a significant increase in variance explained (R^2 *change*=.041, F(1,97)=7.336, p=.008). The final model was significant, R^2=.458, F(5,97)=16.408, p<.001; adjusted R^2=.430, explaining 45.8% of the variance in WAIS-BD scores. Age, NART errors and the interaction between age and the percentage of CO readings at 0ppm were significant predictors within the model.

Model 2 & 3: Percentage of CO readings from 0.5-3ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 did not lead to a significant increase in explained variance (R^2 *change*=.010, F(1,97)=1.635, p=.204). The inclusion of the interaction term in Model 3 led to a significant

increase in variance explained (R^2 *change*=.078, F(1,96)=14.460, p<.001). The final model was significant, R^2=.485, F(5,96)=18.071, p<.001; adjusted R^2=.458, explaining 48.5% of the variance in WAIS-BD scores. Age, NART errors, smoking status and the interaction between age and the percentage of CO readings from 0.5-3ppm were significant predictors within the model.

Model 2 & 3: Percentage of CO readings from 3.5-6ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 did not lead to a significant increase in explained variance (R^2 *change*=.018, F(1,95)=2.852, p=.095). The inclusion of the interaction term in Model 3 led to a significant increase in variance explained (R^2 *change*=.024, F(1,94)=3.895, p=.051). The final model was significant, R^2=.431, F(5,94)=14.241, p<.001; adjusted R^2=.401, explaining 43.1% of the variance in WAIS-BD scores. Age, NART errors, smoking status and the interaction between age and the percentage of CO readings from 3.5-6ppm were significant predictors within the model.

Model 2 & 3: Percentage of CO readings from 6.5-9ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a significant increase in explained variance (R^2 *change*=.032, F(1,97)=5.549, p=.021). Model 2 was significant, R^2=.436, F(4,97)=18.778, p<.001; adjusted R^2=.413, explaining 43.6% of the variance in WAIS-BD scores. NART errors, smoking status and the percentage of CO readings from 6.5-9ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in variance explained (R^2 *change*<.001, F(1,96)=.043, p=.836).

Model 2 & 3: Percentage of CO readings from 9.5-30ppm and interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a significant increase in explained variance (R^2 *change*=.055, F(1,99)=9.865, p=.002). Model 2 was significant, R^2=.445, F(4,99)=19.855, p<.001; adjusted R^2=.423, explaining 44.5% of the variance in WAIS-BD scores. NART errors, hours spent within the home and the percentage of CO readings from 9.5-30ppm were significant

predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in variance explained (R^2 *change*<.001, $F(1,98)=.073$, $p=.788$).

Table 4.6. Regression models with the percentage of CO readings between each range predicting variance in WAIS Block Design (WAIS-BD) scores and the interaction effect between age and CO at each level.

WAIS-BD	Variable (β)						R^2	F
	Age	NART	Smoking	HSH	CO	Age*CO		
0ppm								
Model 1	-.198*	-.589***	-.120				.406	22.509
Model 2	-.178*	-.603***	-.126		-.111		.417	17.542
Model 3	-.223**	-.608***	-.143		.080	.278**	.458	16.408
0.5-3ppm								
Model 1	-.203*	-.571***	-.122				.397	21.531
Model 2	-.193*	-.579***	-.132		.101		.407	16.662
Model 3	-.299***	-.550***	-.163*		-.082	-.344***	.485	18.071
3.5-6ppm								
Model 1	-.156	-.577***	-.181*				.390	20.428
Model 2	-.153	-.555***	-.165*		.136		.407	16.330
Model 3	-.352**	-.542***	-.160*		.077	-.257*	.431	14.241
6.5-9ppm								
Model 1	-.147	-.594***	-.211*				.404	22.159
Model 2	-.126	-.568***	-.208**		.183*		.436	18.778
Model 3	-.148	-.569***	-.211*		.155	-.037	.437	14.883
9.5-30ppm								
Model 1	-.085	-.553***		-.140			.390	21.297
Model 2	-.033	-.498***		-.198*	.247**		.445	19.855
Model 3	-.045	-.497***		-.201*	.203	-.049	.446	15.750

*p<.05, **p<.01, ***p<.001

In summary, the significance of the percentage of CO from 6.5-9ppm and 9.5-30ppm indicates that greater percentage of readings between these ranges is associated with higher WAIS-BD scores. Therefore, greater CO exposure was related to better performance in areas of visuospatial ability and problem solving (see Table 4.6 for summary model details and Table A1.2.1 for full Model details). Examination of the significant interaction between age and the percentage of CO readings at 0ppm revealed that the negative main effect of advancing age on WAIS-BD scores (r=-.24) is moderated by CO exposure. Lower percentage of CO readings at 0ppm, indicating greater exposure, strengthened the negative relationship between age and WAIS-BD scores (r=-.43), whereas low/no CO exposure weakened the relationship (r=-.11). Further examination of the

interaction, by age group, revealed that greater CO exposure was associated with increased performance scores in younger adults (*r*=.17) and decreased performance in old older adults (*r*=-.47).

Similar effects were observed when examining the significant interaction between age and the percentage of CO readings from 0.5-3ppm and 3.5-6ppm, with the negative relationship between age and WAIS-BD scores strengthened by greater exposure between these ranges (*r*=-.53; *r*=-.45) and weakened by lower exposure (*r*=-.11; *r*=-.06), respectively. Examination of the interaction effect by age group revealed that greater CO exposure from 0.5-3ppm and 3.5-6ppm was associated with increased performance scores in younger older adults (*r*=.23; *r*=.39 respectively), and increased CO from 0.5-3ppm was associated with decreased performance scores in old older adults (*r*=-.46). An effect of CO exposure from 3.5-6ppm on performance in old older adults was not present (*r*=-.08).

Therefore the negative main effect of age on visuospatial ability and problem solving changes as a function of CO exposure, with greater exposure strengthening the negative impact of advancing age on performance, and lower exposure weakening this relationship. Further examination of these interactions by age group also revealed that the effect of age (younger older adults versus old older adults) on performance changed as a function of CO exposure. That is, lower exposure showed little difference in effect on performance between the age groups whereas increasing exposure was associated with negative performance effects in old older adults and positive impacts, indicating better performance, in younger older adults. Interaction effects were plotted for interpretation purposes using bivariate models (not multivariate) and are displayed in Figures 4.1-4.6.

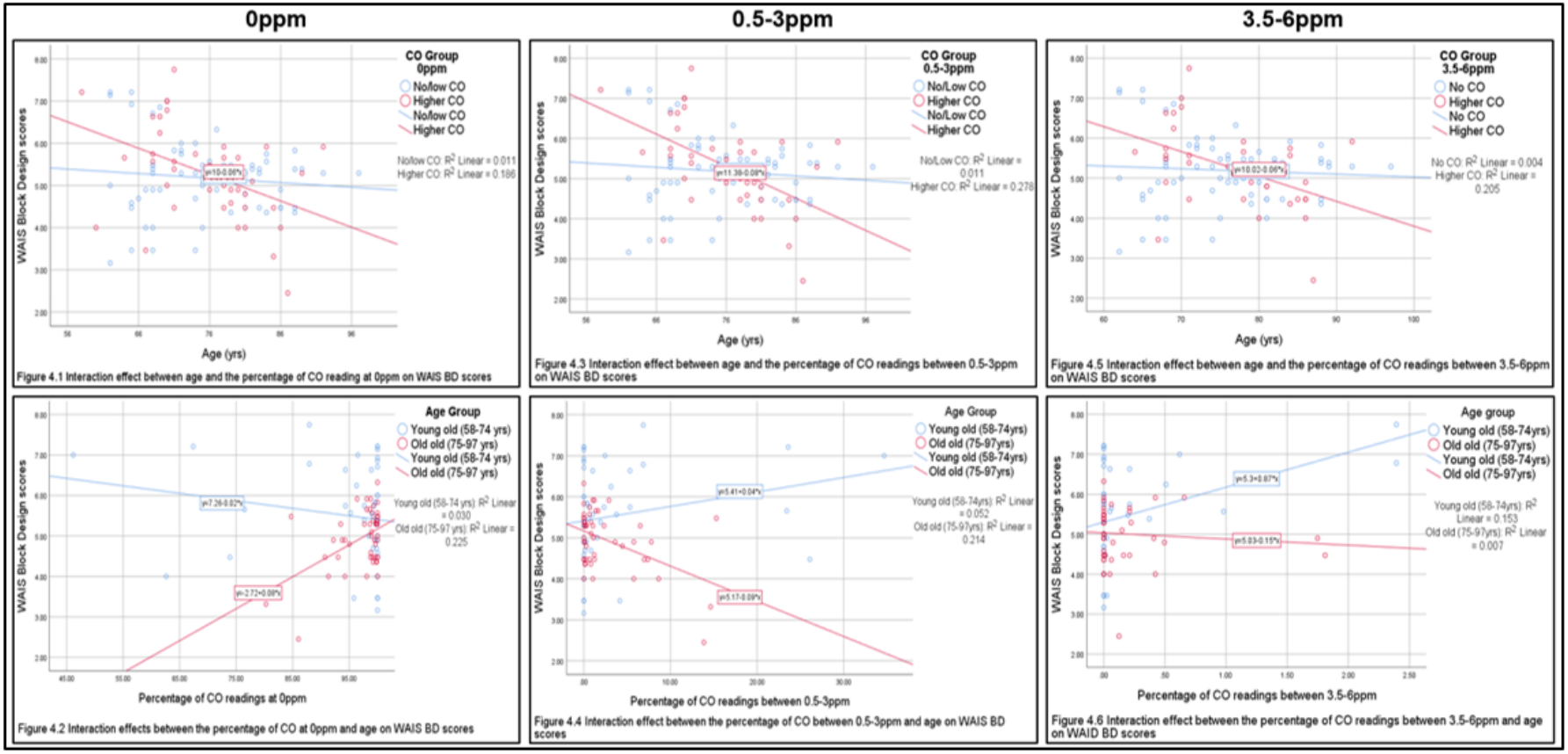


Figure 4.1 Interaction effect between age and the percentage of CO reading at 0ppm on WAIS BD scores

Figure 4.3 Interaction effect between age and the percentage of CO readings between 0.5-3ppm on WAIS BD scores

Figure 4.5 Interaction effect between age and the percentage of CO readings between 3.5-6ppm on WAIS BD scores

Figure 4.2 Interaction effects between the percentage of CO at 0ppm and age on WAIS BD scores

Figure 4.4 Interaction effect between the percentage of CO between 0.5-3ppm and age on WAIS BD scores

Figure 4.6 Interaction effect between the percentage of CO readings between 3.5-6ppm and age on WAID BD scores

Figures 4.1-4.6. Interaction effects between age and CO on WAIS-BD scores, with CO moderating the relationship between age and visuospatial ability (the graphs represent interaction effects generated using bivariate models, not multivariate models). The top row of Figures (4.1, 4.3 and 4.5) display the relationship between age (X) and performance (Y) by CO group (no/low CO; blue data points and regression line versus higher CO; red data points and regression line) for the percentage of readings at 0ppm and between 0.5-3ppm and 3.5-6ppm. Interpretation of these figures indicate that the overall negative main effect of advancing age on performance is moderated by CO exposure, in that scores change depending on the amount of CO exposure between these ranges. Greater CO exposure strengthened the negative relationship between age and performance, whereas low/no CO exposure weakened this relationship. Further examination of the interactions by age group (younger older adults; blue data points and regression line versus old older adults; red data points and regression line) plotted by CO (X) and performance scores (Y) are displayed in Figures 4.2, 4.4 and 4.6 in the bottom row. Interpretation indicates that greater CO exposure >0ppm and between 0.5-3ppm and 3.5-6ppm was associated with increased performance scores in younger older adults and increased CO >0ppm and between 0.5-3ppm was associated with decreased performance scores in old older adults. An effect of CO exposure between 3.5-6ppm on performance in old older adults was not present.

4.3.5.2 Regression on WMS Memory Recognition (WMS-R)

Model 1: Control variables

The first model was significant, R^2=.238, F(3,100)=10.387 p<.001; adjusted R^2=.215, explaining 23.8% of the variance in WMS-R scores. Age and NART errors were significant predictors within the model.

Model 2 & 3: Percentage of CO readings at 0ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a significant increase in explained variance (R^2 *change*=.036, F(1,99)=4.845, p=.030). Age, NART errors and the percentage of CO at 0ppm were significant predictors within the model. The interaction term included in Model 3 led to a significant increase in variance explained (R^2 *change*=.064, F(1,98)=9.399, p=.003). The final model was significant, R^2=.337, F(5,98)=9.952, p<.001; adjusted R^2=.303, explaining 33.7% of the variance in WMS-R scores. Age, NART errors and the interaction between age and the percentage of CO readings at 0ppm were significant predictors within the model.

Model 2 & 3: Percentage of CO readings from 0.5-3ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a significant increase in explained variance (R^2 *change*=.037, F(1,100)=5.070, p=.027). Age, NART errors and the percentage of CO from 0.5-3ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 led to a significant increase in variance explained (R^2 *change*=.053, F(1,99)=7.709, p=.007). The final model was significant, R^2=.318, F(4,99)=11.563, p<.001; adjusted R^2=.291, explaining 31.8% of the variance in WMS-R scores. Age, NART errors and the interaction between age and the percentage of CO readings from 0.5-3ppm were significant predictors within the model.

Model 2 & 3: Percentage of CO readings from 3.5-6ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a near significant increase in explained variance (R^2 *change*=.030, F(1,98)=3.868, p=.052). Age,

NART errors and the percentage of CO from 3.5-6ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 led to a significant increase in variance explained (R^2 *change*=.094, $F(1,97)=13.790$, $p<.001$). The final model was significant, $R^2=.336$, $F(4,97)=12.262$, $p<.001$; adjusted $R^2=.308$, explaining 33.6% of the variance in WMS-R scores. Age, NART errors and the interaction between age and the percentage of CO readings from 3.5-6ppm were significant predictors within the model.

Model 2 & 3: Percentage of CO readings from 6.5-9ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 did not lead to a significant increase in explained variance (R^2 *change*=.004, $F(1,98)=.527$, $p=.469$). The interaction term included in Model 3 led to a significant increase in variance explained (R^2 *change*=.115, $F(1,97)=16.733$, $p<.001$). The final model was significant, $R^2=.331$, $F(4,97)=12.003$, $p<.001$; adjusted $R^2=.304$, explaining 33.1% of the variance in WMS-R scores. Age, NART errors and the interaction between age and the percentage of CO from 6.5-9ppm were significant predictors within the model.

Model 2 & 3: Percentage of CO readings from 9.5-30ppm and interaction between age and CO

The addition of the percentage of CO readings in Model 2 did not lead to a significant increase in explained variance (R^2 *change*=.001, $F(1,100)=.114$, $p=.736$). The interaction term included in Model 3 led to a significant increase in variance explained (R^2 *change*=.101, $F(1,99)=14.565$, $p<.001$). The final model was significant, $R^2=.316$, $F(4,99)=11.422$, $p<.001$; adjusted $R^2=.288$, explaining 31.6% of the variance in WMS-R scores. Age, NART errors and the interaction between age and the percentage of CO from 9.5-30ppm were significant predictors within the model.

Table 4.7. Regression models with the percentage of CO readings between each range predicting variance in WMS recognition (WMS-R) scores and the interaction effect between age and CO at each level.

WMS-R	Variable (β)					R^2	F
	Age	NART	HSH	CO	Age*CO		
0ppm							
Model 1	-.263**	-.311**	-.109			.238	10.387
Model 2	-.203*	-.324***	-.146	-.198*		.273	9.301
Model 3	-.261**	-.330***	-.124	.216	.475**	.337	9.952
0.5-3ppm							
Model 1	-.304**	-.335***				.228	14.924
Model 2	-.257**	-.364***		.200*		.265	12.040
Model 3	-.308**	-.359***		-.202	-.456**	.318	11.563
3.5-6ppm							
Model 1	-.260**	-.357***				.211	13.276
Model 2	-.231*	-.357***		.175*		.241	10.396
Model 3	-.400***	-.413***		-.156	-.467***	.336	12.262
6.5-9ppm							
Model 1	-.260**	-.357***				.211	13.276
Model 2	-.253**	-.348***		.066		.216	8.984
Model 3	-.706***	-.369***		-.506**	-.764***	.331	12.003
9.5-30ppm							
Model 1	-.287**	-.336***				.214	13.766
Model 2	-.290**	-.341***		-.031		.215	9.135
Model 3	-.503***	-.336***		-.709**	-.754***	.316	11.422

*p<.05, **p<.01, ***p<.001

In summary, the significance of the percentage of CO readings at 0ppm and from 0.5-3ppm and 3.5-6ppm indicates that higher percentage of readings above 0ppm and between these ranges is associated with higher WMS-R scores. Therefore, greater CO exposure was related to better performance in memory recognition (see Table 4.7 for summary model details and Table A1.2.2 for full Model details). Examination of the significant interaction between age and the percentage of CO readings at 0ppm revealed that the overall negative main effect of advancing age on WMS-R scores (r=-.37) is moderated by CO exposure. Lower percentage of CO readings at 0ppm, indicating greater exposure, strengthened the negative relationship between age and WMS-R scores (r=-.57) compared to lower exposure whereby the relationship was weakened (r=-.17). Further examination of the interaction, by age group, revealed that greater CO exposure was associated with increased performance scores in younger old adults (r=.28) and decreased performance in old older adults (r=-.26).

Similar effects were observed when examining the significant interaction between age and the percentage of CO readings from 0.5-3ppm, 3.5-6ppm, 6.5-9ppm and 9.5-30ppm with the negative relationship between age and WMS-R

scores strengthened by greater exposure between these ranges (*r*=-.59; *r*=-.59; *r*=-.71; *r*=-.69) and weakened by lower exposure (*r*=-.16; *r*=-.11; *r*=-.16; *r*=-.24), respectively). Examination of the interaction effect by age group, revealed that greater CO exposure from 0.5-3ppm, 3.5-6ppm, 6.5-9ppm and 9.5-30ppm was associated with decreased performance scores in old older adults (*r*=-.24; *r*=-.20; *r*=-.31; *r*=-.37) and increased performance in young older adults (*r*=.29; *r*=.37; *r*=.23), respectively. An association between greater CO exposure from 9.5-30ppm on performance in younger older adults was not present (*r*=.09).

Therefore the negative effect of age on memory recognition changes as a function of CO exposure, with greater exposure strengthening the negative impact of advancing age on performance and lower exposure weakening this relationship. Further examination of these interactions by age group also revealed that the effect of age (younger older adults versus old older adults) on performance changed as a function of CO exposure. That is, lower exposure had little effect on the difference in performance between the age groups whereas increasing exposure was associated with negative performance effects in old older adults and either no effect or positive impacts, indicating better performance, in younger older adults. Interaction effects were plotted for interpretation purposes using bivariate models (not multivariate) and are displayed in Figures 4.7-4.16).

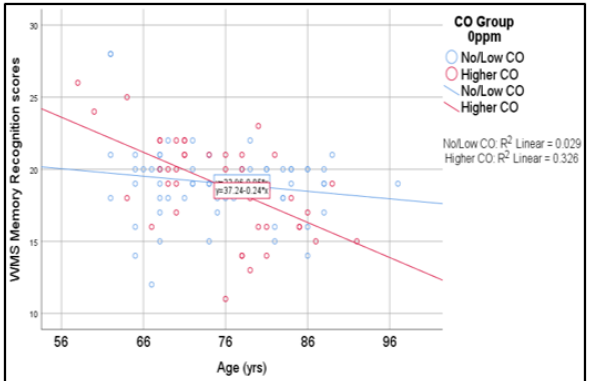


Figure 4.7 Interaction effect between age and the percentage of CO readings at 0ppm on WMS-R scores

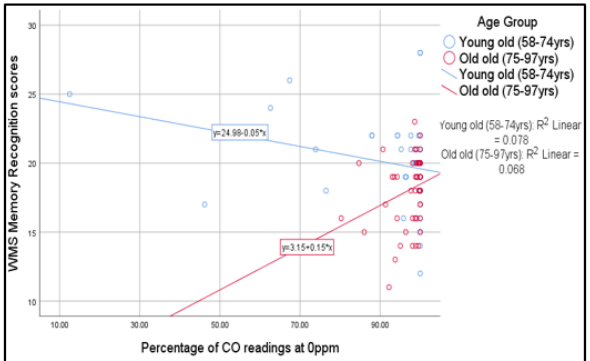


Figure 4.8 Interaction effect between the percentage of CO readings at 0ppm and age on WMS-R scores

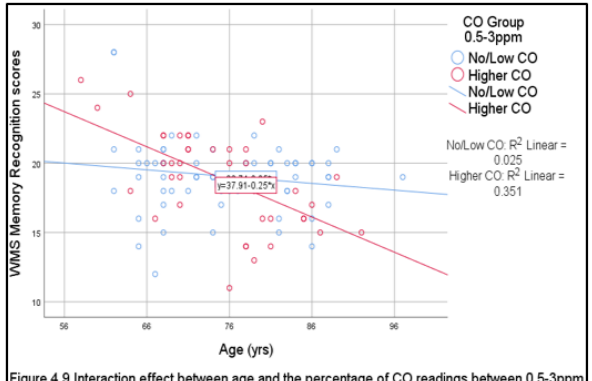


Figure 4.9 Interaction effect between age and the percentage of CO readings between 0.5-3ppm on WMS-R scores

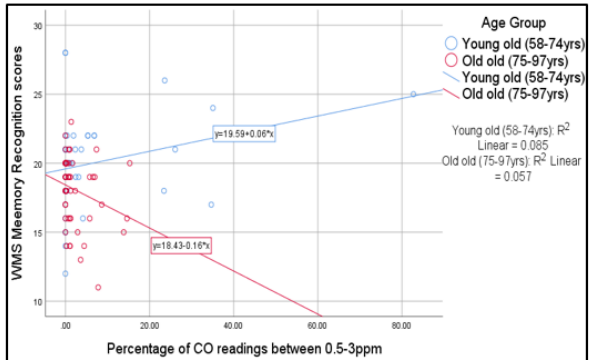


Figure 4.10 Interaction effect between the percentage of CO readings between 0.5-3ppm and age on WMS-R scores

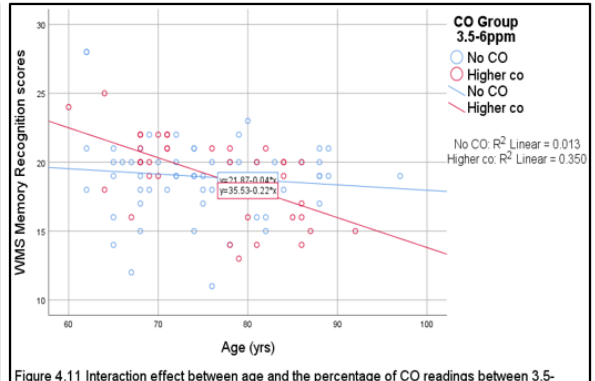


Figure 4.11 Interaction effect between age and the percentage of CO readings between 3.5-6ppm on WMS-R scores

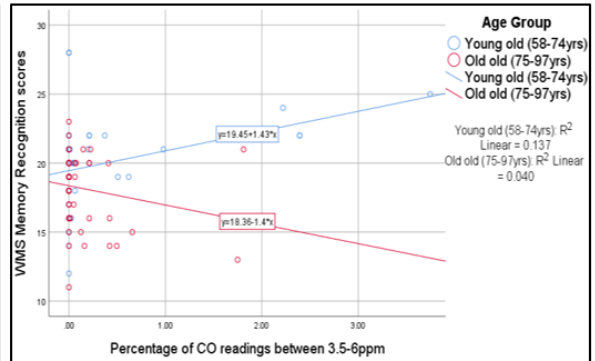


Figure 4.12 Interaction effect between the percentage of CO readings between 3.5-6ppm and age on WMS-R scores

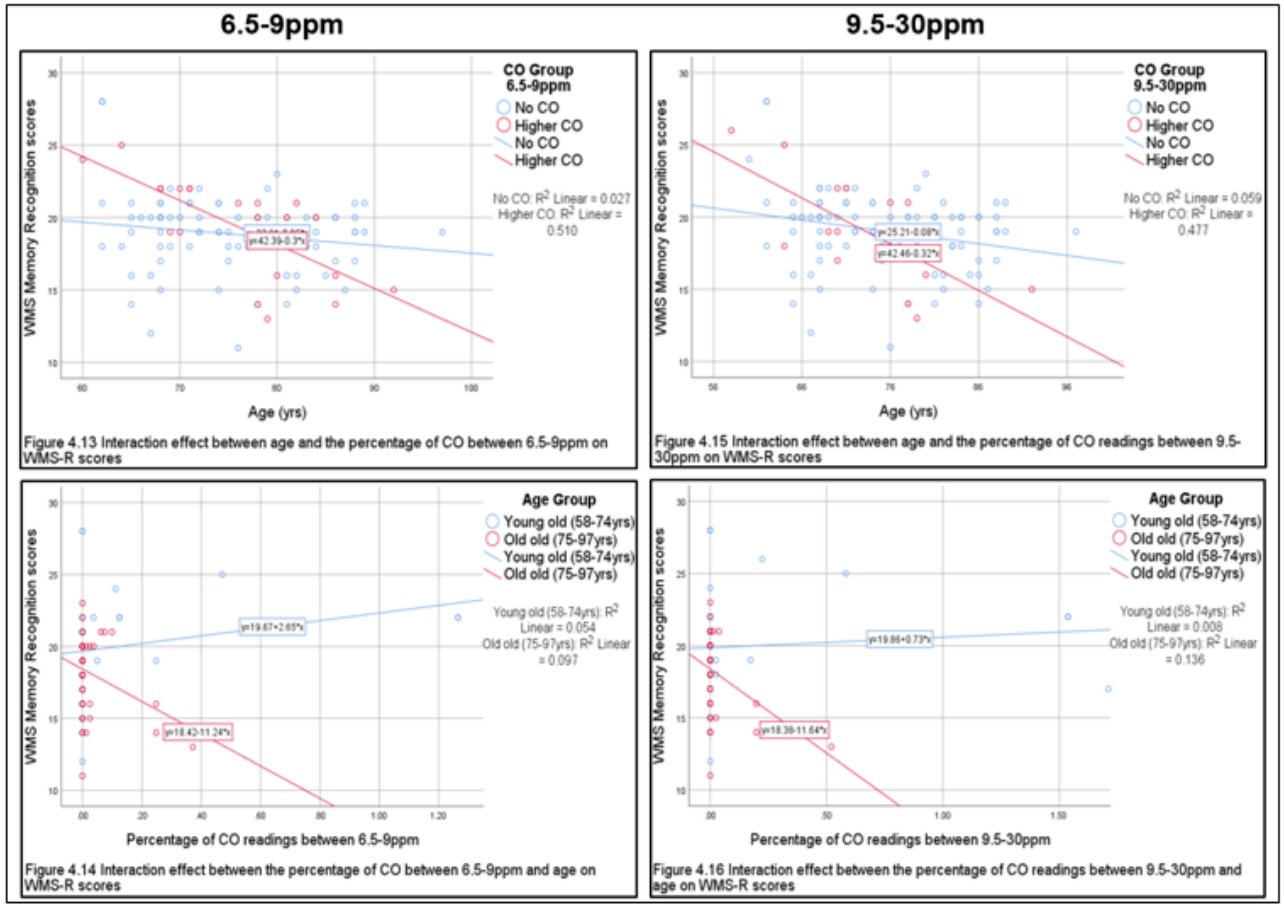


Figure 4.13 Interaction effect between age and the percentage of CO between 6.5-9ppm on WMS-R scores

Figure 4.15 Interaction effect between age and the percentage of CO readings between 9.5-30ppm on WMS-R scores

Figure 4.14 Interaction effect between the percentage of CO between 6.5-9ppm and age on WMS-R scores

Figure 4.16 Interaction effect between the percentage of CO readings between 9.5-30ppm and age on WMS-R scores

Figures 4.7-4.16. Interaction effects between age and CO on WMS-R scores, with CO moderating the relationship between age and memory recognition (the graphs represent interaction effects generated using bivariate models, not multivariate models). The top row of Figures (4.7, 4.9, 4.11, 4.13 and 4.15) display the relationship between age (X) and performance (Y) by CO group (no/low CO; blue data points and regression line versus higher CO; red data points and regression line) for the percentage of readings at 0ppm and between 0.5-3ppm, 3.5-6ppm, 6.5-9ppm and 9.5-30ppm. Interpretation of these figures indicate that the overall negative main effect of advancing age on performance is moderated by CO exposure, in that scores change depending on the amount of CO exposure between these ranges. Greater CO exposure strengthened the negative relationship between age and performance, whereas low/no CO exposure weakened this relationship. Further examination of the interactions by age group (younger older adults; blue data points and regression line versus old older adults; red data points and regression line) plotted by CO (X) and performance scores (Y) are displayed in Figures 4.8, 4.10, 4.12, 4.14 and 4.16 in the bottom rows. Interpretation indicates that greater CO exposure >0ppm and between each range is associated with increased performance scores in younger older adults, with the exception of CO between 9.5-30ppm where no effect was present. In relation to old older adults, increased CO exposure >0ppm and between all ranges was associated with decreased performance scores.

4.3.5.3 Regression on CORSI Block Span Total (CORSI-BST) (visual working memory)

Model 1: Control variables

The first model was significant, R^2=.152, F(2,98)=8.793 p<.001; adjusted R^2=.135, explaining 15.2% of the variance in CORSI-BST scores. NART errors was the only significant predictor within the model.

Model 2 & 3: Percentage of CO readings from 6.5-9ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a significant increase in explained variance (R^2 *change*=.044, F(1,98)=5.265, p=.024). Model 2 was significant, R^2=.183, F(3,98)=7.328, p<.001; adjusted R^2=.158, explaining 18.3% of the variance in CORSI-BST scores. NART errors and the percentage of CO readings from 6.5-9ppm were significant predictors within the model. The inclusion of the interaction in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.006, F(1,97)=.760, p=.385).

Model 2 & 3: Percentage of CO readings from 9.5-30ppm and interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a near significant increase in explained variance (R^2 *change*=.031, F(1,95)=3.486, p=.065). Model 2 was significant, R^2=.156, F(3,95)=5.843, p=.001; adjusted R^2=.129, explaining 15.6% of the variance in CORSI-BST scores. NART errors was the only significant predictor within the model. The percentage of CO readings from 6.5-9ppm reached near significance (p=.065). The inclusion of the interaction in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.003, F(1,94)=.346, p=.558).

Table 4.8. Regression models with the percentage of CO readings 6.5-9ppm and 9.5-30ppm predicting variance in CORSI Block Span Total (CORSI-BST) scores and the interaction effect between age and CO.

CORSI-BST	**Variable (β)**				**R^2**	**F**
	Age	**NART**	**CO**	**Age*CO**		
6.5-9ppm						
Model 1	-.081	-.355***			.139	8.015
Model 2	-.047	-.324**	.215*		.183	7.328
Model 3	-.054	-.324**	.123	-.121	.190	5.673

9.5-30ppm						
Model 1	-.052	-.345**			.125	6.845
Model 2	-.029	-.312**	.181[a]		.156	5.843
Model 3	-.065	-.310**	.062	-.131	.159	4.439

*p<.05, **p<.01, ***p<.001, [a] near significance

In summary, the significance of the percentage of CO readings from 6.5-9ppm and near significant from 9.5-30ppm indicates that greater exposure in these ranges is associated with higher CORSI-BST scores, and therefore better performance in visual WM (see Table 4.8 for summary model details and Table A1.2.3 for full model details).

4.3.5.4 Regression on Tower of London (TOL) (planning and problem solving)

Model 1: Control variables

The first model was not significant, R^2=.016, F(1,100)=1.603 p=.208; adjusted R^2=.006, explaining 1.6% of the variance in TOL scores. There were no significant predictors within the model.

Model 2 & 3: Percentage of CO readings from 3.5-6ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a significant increase in explained variance (R^2 *change*=.066, F(1,100)=7.196, p=.009). Model 2 was significant, R^2=.081, F(2,100)=4.401, p=.015; adjusted R^2=.063, explaining 8.1% of the variance in TOL scores. The percentage of CO readings from 3.5-6ppm was the only significant predictor within the model. The inclusion of the interaction in Model 3 did not lead to a significant increase in explained variance (R^2 *change*<.001, F(1,99)=.005, p=.942).

Model 2 & 3: Percentage of CO readings from 6.5-9ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a significant increase in explained variance (R^2 *change*=.046, F(1,101)=4.986, p=.028). Model 2 was significant, R^2=.062, F(2,101)=3.365, p=.038; adjusted R^2=.044, explaining 6.2% of the variance in TOL scores. The percentage of CO readings from 6.5-9ppm was the only significant predictor within the model. The inclusion

of the interaction in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.005, $F(1,100)$=.484, p=.488).

Table 4.9. Regression models with the percentage of CO readings between 3.5-6ppm and 6.5-9ppm predicting variance in Tower of London (TOL) scores and the interaction effect between age and CO.

TOL	Variable (β)			R^2	F
	Age	CO	Age*CO		
3.5-6ppm					
Model 1	-.121			.015	1.512
Model 2	-.063	.264**		.081	4.401
Model 3	-.062	.271	.010	.081	2.906
6.5-9ppm					
Model 1	-.127			.016	1.677
Model 2	-.090	.218*		.062	3.365
Model 3	-.096	.141	-.102	.067	2.393

*p<.05, **p<.01, ***p<.001

In summary, the significance of the percentage of CO readings from 3.5-6ppm and 6.5-9ppm indicates that greater exposure in these ranges was associated with higher TOL scores, and therefore better performance on planning and problem solving (see Table 4.9 for summary model details and Table A1.2.4 for full model details).

4.3.5.5 Regression on WAIS Digit Span Backward (DSB) (auditory working memory)

Model 1: Control variables

The first model was significant, R^2=.290, $F(2,101)$=20.601, p<.001; adjusted R^2=.276, explaining 29.0% of the variance in DSB scores. Age and NART errors were significant predictors within the model.

Model 2 & 3: Percentage of CO readings at 0ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a significant increase in explained variance (R^2 *change*=.044, $F(1,100)$=6.638, p=.011). Model 2 was significant, R^2=.334, $F(3,100)$=16.713, p<.001; adjusted R^2=.314, explaining 33.4% of the variance in DSB scores. NART errors and the percentage of CO readings at 0ppm were significant predictors within the model. The

inclusion of the interaction in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.002, *F*(1,99)=.317, *p*=.575).

Model 2 & 3: Percentage of CO readings from 0.5-3ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a significant increase in explained variance (R^2 *change*=.045, *F*(1,100)=6.840, *p*=.010). Model 2 was significant, R^2=.335, *F*(3,100)=16.808, *p*<.001; adjusted R^2=.315, explaining 33.5% of the variance in DSB scores. NART errors and the percentage of CO readings from 0.5-3ppm were significant predictors within the model. The inclusion of the interaction in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.002, *F*(1,99)=.257, *p*=.613).

Model 2 & 3: Percentage of CO readings from 3.5-6ppm and the interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a near significant increase in explained variance (R^2 *change*=.026, *F*(1,97)=3.586, *p*=.061). Model 2 was significant, R^2=.298, *F*(3,97)=13.711, *p*<.001; adjusted R^2=.276, explaining 29.8% of the variance in DSB scores. NART errors was the only significant predictor within the model. The percentage of CO readings from 3.5-6ppm reached near significance (*p*=.061). The inclusion of the interaction between age and the percentage of CO readings in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.001, *F*(1,96)=.190, *p*=.664).

Table 4.10. Regression models with the percentage of CO readings at 0ppm and between 0.5-3ppm and 3.5-6ppm predicting variance in WAIS Digit Span Backward (WAIS-DSB) scores and the interaction effect between age and CO at each level.

WAIS-DSB	**Variable (β)**				**R^2**	**F**
	Age	**NART**	**CO**	**Age*CO**		
0ppm						
Model 1	-.160	-.496***			.290	20.601
Model 2	-.116	-.521***	-.216*		.334	16.713
Model 3	-.126	-.522***	-.172	.063	.336	12.528
0.5-3ppm						
Model 1	-.160	-.496***			.290	20.601
Model 2	-.115	-.537***	.221*		.335	16.808
Model 3	-.124	-.537***	.183	-.056	.337	12.577
3.5-6ppm						
Model 1	-.099	-.499***			.272	18.290
Model 2	-.098	-.474***	.163[a]		.298	13.711

Model 3	-.049	-.477***	.177[a]	.063	.299	10.245

*p<.05, **p<.01, ***p<.001, [a] near significance

In summary, the significance of the percentage of CO readings above 0ppm and from 0.5-3ppm and near significant from 3.5-6ppm indicates that greater exposure was associated with higher DSB scores and therefore better performance on auditory WM (see Table 4.10 for summary model details and Table A1.2.5 for full model details).

4.3.5.6 UFOV-SA (selective attention and resistance to distractor interference)

Model 1: Control variables

The first model was statistically significant, R^2=.479, F(2,99)=45.464, p<.001; adjusted R^2=.468, explaining 47.9% of the variance in UFOV-SA scores. Age and NART errors were significant predictors within the model.

Model 2 & 3: Percentage of CO readings from 9.5-30ppm and interaction between age and CO

The addition of the percentage of CO readings in Model 2 led to a significant increase in explained variance (R^2 *change*=.021, F(1,98)=4.100, p=.046). Model 2 was significant, R^2=.490, F(3,98)=31.438, p<.001; adjusted R^2=.475, explaining 49% of the variance in UFOV-SA scores. Age, NART errors and the percentage of CO readings from 9.5-30ppm were significant predictors within the model. The inclusion of the interaction in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.001, F(1,97)=.154, p=.696).

Table 4.11. Regression models with the percentage of CO readings between 9.5-30ppm predicting variance in UFOV Selective Attention (UFOV-SA) scores and the interaction effect between age and CO.

UFOV-SA	**Variable (β)**				**R^2**	**F**
	Age	**NART**	**CO**	**Age*CO**		
9.5-30ppm						
Model 1	.574***	.338***			.469	43.737
Model 2	.555***	.312***	-.150*		.490	31.438
Model 3	.574***	.311***	-.089	.067	.491	23.413

*p<.05, **p<.01, ***p<.001

In summary, the significance of the percentage of CO readings from 9.5-30ppm indicates that increased exposure was associated with lower UFOV-SA scores, signifying greater ability to selectively attend to stimuli (see Table 4.11 for summary model details and Table A1.2.6 for full model details).

None of the CO ranges were significant predictors of scores on the TMTA, TMTAB, WMS immediate or delayed recall, SART-RTs, errors, RT-IIV, WAIS-DSF, UFOV-PS or DA; neither were there significant interactions between age and CO on these functions (p>.05).

4.3.6 Summary of CO-related Effects on Cognitive Function

In summary, lower percentage of CO readings at 0ppm, indicating greater exposure, was associated with positive effects on auditory WM and memory recognition. Significant positive CO-related effects were also found for increased exposure in the 0.5-3ppm and 3.5-6ppm ranges in areas of memory recognition and auditory WM (near significant for auditory WM from 3.5-6ppm). Similarly, greater CO exposure from 3.5-6ppm and 6.5-9ppm was associated with better planning and problem solving ability and from 6.5-9ppm and 9.5-30ppm with increased performance in areas of visuospatial ability, problem solving and visual WM (near significant from 9.5-30ppm for visual WM). Finally, greater CO exposure from 9.5-30ppm was associated with increased performance in selective attention and resistance to distractor interference. These findings provide contradicting evidence to the hypotheses that chronic low-level CO exposure would be associated with deficits in cognitive performance (H_1, H_2), which is possibly explained by the low-levels of CO observed. The findings, however, support H_4, with low-level exposure associated with positive cognitive effects, particularly in auditory WM, long-term memory, visuospatial ability and problem solving. The results also indicate that aspects of memory, including recognition and auditory WM, are positively affected by lower concentrations of CO (0.5-6ppm), whereas executive function, including selective attention, resistance to distractor interference, planning and problem solving, along with visual WM are positively affected by higher concentrations of CO (3.5-30ppm) (These findings are summarised in Table 4.12).

Table 4.12. Tasks, cognitive domains assessed and CO level where significant positive effects were observed in Model 2.

Task	Cognitive Domain	0ppm	0.5-3ppm	3.5-6ppm	6.5-9ppm	9.5-30ppm
WAIS-DSB	Auditory working memory	Y(+)	Y(+)	Y(+)*	N	N
WMS-R	Long-term memory	Y(+)	Y(+)	Y(+)	N	N
CORSI BS	Visual working memory	N	N	N	Y(+)	Y(+)*
TOL	Planning and problem solving	N	N	Y(+)	Y(+)	N
WAIS-BD	Problem solving and visuospatial	N	N	N	Y(+)	Y(+)
UFOV- SA	Selective attention, inhibition	N	N	N	N	Y(+)

Y= yes; N= no; += positive effect
* Effects were nearly significant

4.3.7 Summary of Interaction Effects between Age and CO on Cognitive Function

In summary, the significant interactions between all CO ranges and age on memory recognition, and the lowest three ranges and age on visuospatial ability and problem solving, revealed that the effect of age on these functions is moderated by CO exposure. Greater exposure strengthened the negative relationship between age and memory recognition, and age and visuospatial ability, compared to lower exposure whereby the relationship was weakened. It is important to note that greater exposure does not indicate higher CO levels, but greater percentage of CO readings within a given range indicating increased exposure at that level. Further examination of these interactions by age group revealed that the effect of age (younger older adults versus old older adults) on performance changed as a function of CO exposure. That is, lower exposure had little effect on performance differences between the age groups whereas increasing exposure was associated with negative performance effects in old older adults and either no effect or positive impacts, indicating better performance, in younger older adults. These results indicate the presence of a positive CO-related effect in younger older adults, with better performance observed with greater CO exposure; whereas negative exposure effects were observed in old older adults with scores decreasing with increasing CO (see Table 4.13). Examination of the coefficients in Table 4.13 supports this, with positive relationships observed in the younger older adult group and negative associations in the old older adult group. Furthermore, for memory recognition, where the interaction effect was present across all CO ranges, the positive CO-related effects observed in the younger older adult group generally decreased with increasing CO level. Conversely, the negative effect of CO observed in the

old older adult group increases in strength with increasing CO level, particularly in the two highest ranges. This suggests that the positive effect of CO on memory in younger older adults gradually diminishes with higher levels of CO, whereas the negative effects of CO on memory increases in the old older adult group (see Table 4.13). These findings provide support for H_3, in that the relationship between age and cognitive functioning would be strengthened by greater CO exposure.

Table 4.13 Task and cognitive domains assessed and CO level where significant interactions with age were observed in Model 3 and correlation coefficients by age group.

Task	Cognitive Domain	0ppm	0.5-3ppm	3.5-6ppm	6.5-9ppm	9.5-30ppm
WAIS-DSB	Auditory working memory	N	N	N	N	N
WMS-R	Memory recognition	Y	Y	Y	Y	Y
Young (*r*)		.28	.29	.37	.23	.09
Old (*r*)		-.26	-.24	-.20	-.31	-.37
CORSI BTS	Visual working memory	N	N	N	N	N
TOL	Planning and problem solving	N	N	N	N	N
WAIS-BD	Problem solving and visuospatial	Y	Y	Y	N	N
Young (*r*)		.17	.23	.39	-----	-----
Old (*r*)		-.47	-.46	-.08	-----	-----
UFOV- SA	Selective attention, inhibition	N	N	N	N	N

Y= yes; N= no
r= correlation coefficient

4.4 Discussion

4.4.1 Overview of Findings

The current study examined the relationship between chronic low-level CO exposure and cognitive function in older adults, who as a group may be specifically vulnerable to CO. Of interest was whether the addition of percentage of CO within specified ranges into regression models led to a significant increase in explained variance in levels of cognitive functioning, once common predictive factors had been controlled for. The aims were to examine whether chronic exposure to extremely low-level CO can result in positive or negative effects on cognitive function, and to contribute towards determining the thresholds at which these exposures may become harmful to older adults. Additionally, the relationship between age and CO exposure on cognitive function was explored.

The main study findings were that chronic exposure to low-level CO was associated with positive effects on auditory WM, memory recognition, visual WM, visuospatial ability, problem solving, planning, selective attention and resistance to distractor interference. Furthermore, a pattern of performance improvements relating to exposure level emerged, whereby aspects of memory including recognition and auditory WM were positively affected by lower concentrations (0.5-6ppm), whereas visual WM, visuospatial ability and EF, specifically planning, problem solving, selective attention and resistance to distractor interference were positively affected by higher concentrations (3.5-30ppm). Another key finding of the study was that the relationship between age and memory recognition, and age and visuospatial ability and problem solving was moderated by CO exposure. Results indicated that greater CO exposure at each level for memory recognition, and at the lowest three ranges for visuospatial ability and problem solving, had a negative impact in old older adults (≥75 years), and positive effects in younger older adults (58-74 years).

There was no evidence to suggest that CO within any of the specified ranges significantly contributed to the explained variance in measures of visuomotor speed, cognitive flexibility, resistance to pro-active interference, pre-potent response inhibition, sustained attention, auditory short-term memory, immediate or delayed memory recall, processing speed, or divided attention.

4.4.2 Discussion of findings

4.4.2.1 Potential beneficial CO-related effects and patterns of impairment

The positive CO-related effects reported here are perhaps not surprising, due to the extremely low-levels of CO recorded, with the highest peak in the data being 29ppm, which is also reflected in the low COHb range observed in the non-smoking participants (.20-1.40%). These low COHb levels are similar to those resulting from endogenously produced CO when combined with environmental exposure (<2% in non-smokers) (Harper & Croft-Baker, 2004; Raub & Benignus, 2002). Endogenous CO, predominantly resulting from the degeneration of haem, has known beneficial effects with therapeutic actions including vasodilation, proliferation, anti-apoptotic factors and anti-inflammatory properties (Prockop & Chichkova, 2007). Endogenous CO therefore plays a vital role in cellular

maintenance, protection, regeneration and survival (for reviews see Mahan, 2012; Queiroga, Vercelli & Vieira, 2015). If exogenous CO is associated with similar beneficial effects, this may explain the results reported here. In support of this, the results of Volans et al., (2007) study also indicated trends towards increased cognitive performance following chronic low-level home exposure. That study reported higher CO readings than those observed here, with CO levels in 14 homes found to exceed the 8-hour guideline of 8.6ppm, compared to none of the homes in the current study. However, the majority of homes in Volans et al (2007) study had mean 15-minute average CO concentrations ≤5ppm, with an overall mean of 1.89ppm. This is comparable to the mean CO level of .09ppm observed here, with exposure levels across studies representing low exposure. Moreover, the greatest performance increases (>.05 *SD*) in Volans et al (2007) study were observed in auditory WM, immediate and delayed visual memory recall, visuospatial ability and problem solving (although all were non-significant). It is acknowledged that these deviations are small, with the authors reporting no clear evidence of adverse neuropsychological effects following chronic low-level exposure. However, these findings are remarkably consistent with those reported here, specifically the beneficial effects on specific cognitive domains including auditory WM, aspects of long-term memory, visuospatial ability and problem solving.

However, there is evidence that detrimental neuropsychological effects follow both acute low-level exposure with deficits in inhibition, and potentially long-term memory and psychomotor speed (see Chapter 2), and case reports indicate deficits in learning ability, motor slowing and impaired memory following chronic low-level exposure (Ryan, 1990; Myers et al., 1998). Results from epidemiological studies also suggest associations between chronic exposure to air pollution and increased risk of stroke, MI, heart failure and dementia (Maheswaran et al., 2005; Shah et al., 2013; Mustafic et al., 2012; Chang et al., 2014).

The inconsistencies reported in the literature on the cognitive domains affected, and in the direction of effects, following low-level CO exposure are likely due to variations in the concentration and duration, population studied and potential

differences in the underlying physiological mechanisms. In acute studies, participants were typically exposed to around 100ppm for 1-4 hours with resulting COHb levels approximately between 5 and 12%. These exposures, although shorter in duration, are much higher than the exposure concentrations observed here and under chronic conditions would not represent low-level exposure, particularly in reference to the WHO indoor air guidelines (2010) and to concentrations previously reported in UK homes. The higher exposure concentrations observed in acute low-level studies may explain the absence of significant positive effects, but also the negative effects found on inhibition, long-term memory and psychomotor speed that were typically observed in the final hour of exposure (4^{th} hour). Acute low-level exposure conditions, where higher CO concentrations are administered, may therefore result in negative effects only, following sufficient exposure time (See review, Chapter 2). However, acute exposure studies have typically studied young healthy adults who, in addition to being least likely to show any adverse effects, are potentially least likely to benefit from any protective properties of exogenous CO due to maximal physiological reserve. Whether beneficial effects can present in older adults following acute low-level exposure is however, currently unknown.

Under chronic exposure conditions to low-level CO, adaptation, tolerance and compensatory mechanisms may play a protective role up to a certain CO dose and duration. Furthermore, if low doses of inhaled CO are associated with similar physiologic and cytoprotective properties to those resulting from endogenous CO, this may lead to a certain degree of neuroprotection potentially resulting in beneficial effects. For example, in resistance vessels, CO is involved in the regulation of vascular tone, acting as a vasodilator in cerebral and systemic circulations (Maines, 1997; Leffler et al., 1999). Vasodilation increases blood flow through relaxation of smooth muscle cells within the walls of blood vessels resulting in widening (Ramanlal & Gupta, 2022). Vascular structure and tone are maintained and regulated by the endothelium (Xu et al., 2017) and vascular dysfunction is a hallmark for cerebrovascular, cardiovascular and neurodegenerative diseases (Assar et al., 2012). Due to its vasoactive properties, low-level exposure to CO may play a protective role to cognitive function by temporarily increasing and maintaining CBF in individuals where this

is compromised, such as older adults. For example, endothelium-dependent vasodilatation and CBF are known to decline in healthy ageing (Belohlavek et al., 2009; Rodriguez-Manas et al., 2009). Furthermore, age-related vascular changes can lead to impaired vessel function resulting in vascular dysfunction, suboptimal CBF and hypo-perfusion (Xu et al., 2017). Moreover, cardiovascular risk factors are more common in older adults and can lead to greater decreases in CBF and chronic hypo-perfusion, further compromising the already reduced CBF that is present in ageing (de la Torre, 2012; Leenders et al., 1990; Zhao et al., 2007; Bentourkia et al., 2000; Parkes et al., 2004; Heo et al., 2010).

The joint effect of the structural and functional changes on blood flow observed in ageing and disease can result in a neuronal energy crisis, followed by neuronal dysfunction and death, contributing to, and increasing the risk of, cognitive decline and dementia (de la Torre, 2012; Mosconi et al., 2009). This process is initiated in ischaemic-sensitive zones such as the hippocampus, basal ganglia and the cerebral white matter (CWM) (Ruitenberg et al., 2005; Moody, Bell, & Challa, 1990; Pullicino, Caplan, & Hommel, 1993; Donnan, Norrving, Bamford, & Bogousslavsky, 1995). If low-level exogenous CO acts as a vasodilator, similar to endogenous CO, this may increase blood flow through dilation of the vessels. Chronic low-level CO exposure may therefore be associated with temporary increases in CBF, which would be particularly beneficial to older adults and to specific ischemic-sensitive brain areas.

In support of this, these ischaemic-sensitive brain regions are associated with cognitive functions similar to the pattern of performance improvements observed here in memory recognition, auditory and visual WM, visual spatial ability and aspects of EF including selective attention, resistance to distractor interference, planning and problem solving. Executive functioning relies heavily on complex CWM networks for connectivity between distributed neural systems (Andres, 2003; Morris, Craik & Gick, 1990). This connectivity between brain regions can be altered by damage to the CWM, resulting in disruptions in neurocognitive networks and subsequent EF deficits (Geschwind, 1965; Nickel & Gu, 2018; Gunning-Dixon & Raz, 2000). Historically, the prefrontal cortex (PFC) has been

associated with EF, with age-related cognitive decline and impaired EF related to atrophy in this region (Park, 2000; Park, Polk, Mikels, Taylor & Marshuetz, 2001; West, 1996; Cabeza, 2002; Logan, Sanders, Snyder, Morris, & Buckner, 2002; Rosen et al., 2002; Grady & Craik, 2000). Furthermore, white matter hyperintensities (WMH) may be particularly detrimental to the frontal areas of the brain compared to other regions (Schuff et al., 2003; Tullberg et al., 2004) with associations between WMH and impairments in executive control that potentially result from PFC dysfunction (Gunning-Dixon & Raz, 2000; DeCarli et al., 1995; Nordahl et al., 2013). The hippocampus is typically associated with long-term memory, with lesions in this area commonly associated with memory impairments (Zola-Morgan & Squire, 1993) and the basal ganglia (BG) has predominantly been linked to motor function (Siniscalchi et al., 2012; Netravathi, Pal, & Indira Devi, 2012). However, evidence is accumulating that indicates BG involvement in working memory (WM), with recent work focused upon the role of the BG and PFC in WM, and the interaction between them, building on the historical association between the PFC and WM (see Helie, Chakravarthy, & Moustafa, 2013 for a review). Low-level exogenous CO, may result in temporary increases in CBF playing a protective role particularly to ischaemic-sensitive brain regions resulting in slightly improved functioning in the cognitive areas they are associated with. However, vasodilation only represents one of many potential physiologic mechanisms that may underpin the observed positive effects (see Chapter 1 and 5).

It is also possible that the observed positive impacts in particular areas of functioning represent cognitive domains that are less susceptible to CO, and those functions where positive CO-related effects were not present represent areas more vulnerable. Therefore, the observed positive effects may not represent beneficial cognitive impacts that result from chronic exposure to low-level CO, but instead that particular areas may be more sensitive, and others more resilient, to the negative effects of CO. However, currently this is unknown. Studies examining the neuroprotective effects of the administration of low-level CO may provide evidence to support the physiologic and cytoprotective properties of exogenous CO (for reviews see Mahan, 2012; Queiroga, Vercelli & Vieira, 2015). However, whether these effects can result from chronic exposure

to low-level environmental CO is currently unclear, as are the potential underlying physiologic mechanisms, and are areas that warrant future research.

The protective properties of low-level exogenous CO, if present, are likely to be transient with COHb accumulation over time, and the stress this places on the body's physiological resources, reaching a point where the body can no longer compensate for the continuous uptake of CO. Subsequently, insufficient CBF and ischaemia may follow, resulting in a shift from positive to negative cognitive impacts. It is plausible that the brain regions that potentially benefit most from CO-related temporary increases in CBF, are also areas most susceptible to damage when levels exceed certain thresholds, with COHb accumulation over time accelerating the neuronal energy crisis-dysfunction-death cascade initiated in ischaemic-sensitive zones. Damage to areas including the hippocampus, BG and CWM is therefore likely, potentially resulting in deficits in similar cognitive areas to the beneficial effects observed here. The results indicate that auditory WM and memory recognition may be more sensitive to CO exposure, with the observed positive effects present in the lower ranges only. This may indicate that a potential shift from beneficial to negative effects occurs at lower concentrations in these functions compared to other areas of cognition. The results suggest that the effects related to chronic low-level CO exposure may be viewed on a continuum, with one end representing extremely low-level exposure and potential beneficial effects, that likely dissipate at slightly higher concentrations, prior to the transition into negative impacts that present at the opposite end of the spectrum with increasing exposure duration and concentration. Specific cognitive functions such as visual WM, planning, problem solving, selective attention and resistance to distractor interference may be more resilient to CO, with positive effects observed at higher exposure concentrations (3.5-30ppm). These positive effects likely decrease in strength with increasing CO level, reaching a point where no observable effects are present, prior to the shift to negative impacts at a certain unknown level, above those observed here.

Increased susceptibility to damage in older adults is again likely, due to age-related vascular changes that can lead to sub-optimal CBF and hypo-perfusion, which have been associated with the development of MCI and AD (David &

Taylor, 2004; Belohlavek et al., 2009; Jerskey et al., 2009; Jefferson et al., 2007; Forti et al., 2006; de la Torre, 2012; Mosconi et al., 2009). Cardiovascular risk factors further compromise CBF leading to chronic hypo-perfusion, increasing the risk of cognitive decline and dementia (de la Torre, 2012; Mosconi et al., 2009). Furthermore, the brain abnormalities observed in CO poisoned patients include ischaemic-sensitive areas, with lesions to the globus pallidus (O'Donnell et al., 2000; Porter et al., 2002; Varrassi et al., 2017) atrophy of the hippocampus (Gale et al., 1999; Gale & Hopkins, 2004) and WMH (Hou et al., 2013) commonly reported. WMH and atrophy of the hippocampus are also associated with ageing and have been identified as predictors of cognitive decline (Tondelli et al., 2012; Kloppenborg, Nederkoorn, Geerlings, & Van Den Berg, 2014), increased risk of early cognitive decline (den Heijer et al., 2006; Smith et al., 2008), AD and vascular dementia (Bigler, Kerr, Victoroff, Tate & Breitner, 2002). The possibility that chronic exposure to low-level CO adds to this burden presents significant concern, and may place an already susceptible group at an even greater risk of early cognitive decline and dementia development beyond that associated with ageing and disease.

4.4.2.2 Interactions between Age and CO Exposure on Cognitive Function

The relationships between age and memory recognition, visuospatial ability and problem solving, were found to be moderated by CO, with greater exposure associated with better performance in younger older adults and poorer performance in old older adults. This suggests that whilst CO exposure may be associated with beneficial effects in older adults, these may, to a certain degree, be dependent upon factors such as physiological and cognitive reserve capacity, intrinsic capacity and an individual's resilience, all of which would be expected to reduce with older age. Briefly, physiological reserve refers to the potential functional capacity of biological systems to respond to stress (Whitson et al., 2016; 2018), whereas cognitive reserve is the brain's capacity to minimise clinical symptoms by mitigating or buffering age-related changes and pathology (Kraal et al., 2021). Resilience is demonstrated by an individual's capacity to recover relatively well from stressful events (Rutter, 2006), and can be viewed on a continuum spread across the lifespan that can be measured at any point, with individuals demonstrating varying degrees of resilience throughout the lifespan

(Whitson et al., 2018; Kirkland, Stout, & Sierra, 2016). Physical resilience is defined as one's ability to maintain or recover physical health and resist functional decline during, and following, exposure to health stressors (Whitson et al., 2018; 2016; Hadley, Kuchel, & Newman, 2017; Cesari et al., 2018) and psychological resilience is the ability to adapt, respond and cope with difficult or stressful experiences such as trauma, tragedy and threats (Wagnild, 2009). The likelihood of compensating, or recovering from functional loss, depends upon an individual's level of physiological reserve and may also be influenced by environmental, social and psychological health factors (Whitson et al., 2018). Intrinsic capacity refers to all of the physical and mental capabilities of an individual that are underpinned by the amount of reserve and resources that can be drawn upon during the lifespan (WHO, 2015; Belloni & Cesari, 2019).

If the potential beneficial effects of exogenous CO are dependent upon these factors, in particular areas of functioning, then it is perhaps not surprising that positive CO-related effects were not observed in the old older adult group. For example, frail individuals have low resilience and are vulnerable to adverse events due to reduced reserve capacity, placing them at greater risk from minor external stressors resulting in disproportionate changes in health (Campbell & Buchner, 1997; Whitson et al., 2018; Clegg, Young Iliffe, Rikkert, & Rockwood., 2013). In these individuals, the ability to restore homeostasis following a stress is depleted, resulting from cumulative age-related declines in function across multiple physiological systems, that are close to, or beyond, the thresholds of failure (Campbell & Buchner, 1997; Xue, 2011). The gradual decline in physiological reserve associated with ageing is accelerated in frail individuals and systems begin to fail (Ferrucci et al., 2002). Frailty commonly develops close to the end of life and is observed in a small percentage of older adults (Whitson et al., 2018; Kirkland, Stout, & Sierra, 2016), with results of a systematic review indicating frailty prevalence rates of 4% in 65-69 year olds, 7% in 70-74 years, 9% in 80-84 years and 16% in those aged 85 and older (Collard, Boter, Schoevers, & Voshaar, 2012). However, these prevalence rates were limited to studies that used the phenotype model (Fried et al., 2001) to define frailty, which focuses on physical indicators only, without consideration of cognitive and psychosocial factors that are important indicators of frailty (Collard et al., 2012).

Prevalence figures therefore are higher when these factors are integrated as indicators of frailty (Collard et al., 2012).

The observed beneficial CO-related effects on memory recognition, visuospatial ability and problem solving observed in older adults may therefore be, to a certain degree, dependent upon factors such as physiological and cognitive reserve capacity, intrinsic capacity and an individual's resilience. In younger older adults, where CBF is reduced or restricted due to age and disease-related pathology, physiological mechanisms such as vasodilation may be beneficial to these areas of cognition up to a certain dose and duration. However, in old older adults, particularly those who are frail, negative impacts in these domains appear to follow CO exposure, that likely arise from increased vulnerability to minor stressors resulting from extremely limited physiological reserve and resilience. In these individuals, exposure to CO, and the additional burden this potentially places on biological systems that are potentially close to, or already failing, is likely to be detrimental. The results from the current study support this in areas of memory recognition, visuospatial ability and problem solving. However, the remaining results suggest an overall positive effect of CO exposure across a range of cognitive functions in older adults, irrespective of age. Why particular functions appear to be potentially more dependent upon additional health indicators such as resilience and reserve capacity, rather than age alone, is currently unknown.

It is also noteworthy that the results of the systematic review in Chapter 2 indicated that impaired inhibition, long-term memory and psychomotor speed may follow acute low-level exposure, yet these areas, with the exception of long-term memory, were not affected by chronic exposure to low-level CO in this study. As mentioned previously, acute exposure studies have typically used higher CO concentrations and groups of healthy young adults, which may explain the absence of significant positive effects in these studies. It is plausible that these functions are positively affected by higher concentrations, above 29ppm, but at levels that are still significantly lower than the exposure concentrations used in acute studies. However, it is possible that particular areas of cognition, including

psychomotor speed and pre-potent response inhibition, are not associated with potential beneficial exposure effects. Instead, these areas of cognition may be associated with negative CO-related effects only that present at a certain unknown level, above those reported here.

It is also unclear why performance effects were observed on particular tasks and not others that assess similar areas of cognitive functioning. For example, performance on the UFOV selective attention task was affected yet no CO-related performance effects were found on the TMTAB or SART task, when all assess inhibition. The lack of consistency in findings across these tasks suggests that they may reflect different aspects of inhibition, supporting the viewpoint that inhibitory control is multifaceted (Hung et al., 2018). Inhibitory constructs consist of pre-potent response inhibition, resistance to distractor interference and resistance to proactive interference (Friedman and Miyake, 2004; Nigg, 2000). Pre-potent or response inhibition involves the suppression of a dominant response in order to execute a task appropriate response (e.g. SART), resistance to distractor interference requires the ability to supress irrelevant distractors (i.e. UFOV SA), and resistance to pro-active interference is the suppression of previously relevant information from working memory (i.e. TMTBA) (Bissett, Nee, & Jonides, 2009). Historically, these components of inhibition, and the tasks used to assess them, have been used interchangeably. However, results from these studies indicate the presence of distinct aspects of inhibitory control as opposed to a single underpinning mechanism (Noreen & Macleod, 2015). It may be that aspects of cognition including pre-potent response inhibition and resistance to pro-active interference, cognitive flexibility and psychomotor speed do not follow the same exposure effect trajectory of *positive-zero-negative* or *positive-negative effects* that may be present in other areas of functioning including working memory, memory recognition, selective attention, resistance to distractor interference, planning and problem solving. Instead, they are perhaps negatively affected by CO only, following longer exposure durations or higher concentrations suggested not only by the absence of positive effects found here but also results from the review indicating negative effects in these areas (see Chapter 2). However, further research is needed in order to examine this.

4.4.3 Future Implications and Research

CO exposure ultimately results in damage. The behavioural literature on chronic CO exposure is extremely limited with evidence from sources other than anecdotal reports sparse. Furthermore, experimental exposure studies have focused on the short-term effects only, without longitudinal follow up. Future research should be directed to further ascertain the level and duration at which the body's protective, and potentially beneficial, physiological responses become ineffective and harm is initiated across multiple cognitive domains. This would assist in answering questions such as whether the beneficial cognitive effects reported here are short lasting, and whether they subsequently result in impairments given sufficient exposure time. Furthermore, whether potential negative effects are short lasting or result in long-term negative impacts is also unknown. Longitudinal studies are needed to assist in answering these important questions.

The negative effects that chronic low-level CO exposure may pose on cognition are well documented in case reports (Myers et al., 1998; Ryan, 1990; Nakamura et al., 2016) and epidemiological studies (Chang et al., 2014). These findings, along with the inference of a *positive-negative* exposure trajectory, present significant public health concern particularly to the older adult population, not only due to increased susceptibility, but also the increased risk of home exposure from domestic appliances. The time point at which the potential shift from protective effects to toxicity occurs will be largely dependent upon the dose and duration alongside other factors such as age and pre-existing disease. Identifying the levels at which chronic exposures become harmful would be invaluable in informing policy, guidelines and safety technology in order to keep those most vulnerable safe. Further research on the cognitive effects associated with chronic low-level CO exposure is needed, with a particular focus upon the time point and thresholds at which the potential shift from protective effects to toxicity occurs in vulnerable populations. The thresholds at which the potential shift from positive to negative impacts occurs across multiple cognitive domains is currently unknown and therefore requires further investigation with a greater range of levels of exposure than available in this study.

Research focused upon the specific cognitive areas that are affected by chronic low-level CO exposure is also needed. This would provide information on possible patterns of impairment that would be invaluable in clinical settings to aid in the diagnosis of low-level CO exposure. The results reported here provide preliminary evidence that chronic exposure, for at least one month, may be positively associated with auditory WM and memory recognition up to levels of 6ppm, and visual WM, visuospatial ability, planning, problem solving, selective attention and resistance to distractor interference are positively affected by concentrations in the 3.5-30ppm range. This may indicate that auditory WM and memory recognition are more vulnerable to CO exposure, compared to visual WM, planning, problem solving and selective attention that are potentially more resilient to CO, with positive effects observed at higher exposure concentrations. Whether a shift to negative effects is observed in these areas of cognition at levels higher than 29ppm is unknown. Further research is warranted in order to understand whether negative effects do follow in these areas of cognition. An identifiable pattern of effects may also exist whereby the potential beneficial effects of CO may be associated with certain cognitive functions and not others. Areas of cognition including inhibition and psychomotor speed may be associated with negative CO-related effects only, that present at a certain unknown level. Further research on the levels at which specific cognitive functions are affected and the direction of effects is clearly needed along with longitudinal studies examining any long-term effects. Whilst overall positive main effects of CO exposure were observed in the older adult sample studied here, some of these effects specifically in areas of memory recognition, visuospatial ability and problem solving, were more dependent upon age, and potentially other indicators of health such as frailty. Research on the effects of exposure in vulnerable groups should therefore focus not only on these groups collectively, but also subgroups within these populations, with the results presented here indicating that age differences within a group of older adults can lead to substantial differences in the strength and direction of observed effects.

4.4.4 Limitations

The current study has some limitations. The first relates to the positioning of the CO data loggers. As the study aimed to examine individual exposure, loggers

were placed in the room that the participants indicated they spent the most time in, which in all cases except one, was the living room. This location was considered to be the most accurate representation of individual exposure. However, in terms of reflecting ambient CO levels within the home more generally, measurements may be best taken in rooms containing the main sources of CO, such as the kitchen where boilers and gas cookers are typically located. Moving forward, the monitoring of CO in several locations would be invaluable, particularly when the research aim is to ascertain not only ambient home CO levels but also the associated exposure effects. The monitoring of CO in various rooms would also provide crucial information relating to the contribution of different appliances to raised CO levels, highlighting those that are potentially more dangerous, and whether CO travels through the home to other locations such as upstairs bedrooms. The next limitation relates to the layout, size and ventilation of the home and room where the data logger is situated. These factors can all modify CO levels disparately across monitored homes, however this problem is associated with indoor exposure studies in general, and thus is more of an observation. The final limitation relates to the observational design of the study and resulting small range of CO observed within the monitored homes. Subsequently, analyses of the higher CO ranges were based only on a small number of observations resulting in increased risk of type II errors and reduced power. Monitoring a greater number of homes may have potentially led to a wider range of CO measurements, but this would not necessarily result from simply increasing the sample size. Other factors that may increase the likelihood of observing greater variance in CO concentrations include monitoring homes in several geographical locations, including both urban and rural areas, potentially capturing differences in, for example, the fuels used to heat the home. The finding that the CO levels within the monitored homes were relatively low is reassuring; however, if we are to identify the levels at which exposures become harmful then the analysis of a greater CO range is required.

The remaining limitations relate to the neuropsychological testing. The duration of the assessments were particularly long, typically 3-4 hours, which was quite demanding on the participants. To alleviate any fatigue and boredom, regular breaks were taken as and when required. Due to the number of tasks included,

the assessments were also carried out in a fixed order, rather than counterbalanced, thus resulting in the possibility of order effects. In order to reduce the likelihood of this, the more repetitive tasks were carried out towards the end of testing. A comprehensive cognitive battery was considered necessary, due to the lack of existing evidence, in order to ascertain which areas of functioning, if any, were associated with chronic exposures. However, this led to a large number of measures, subsequently increasing the number of statistical tests required and therefore the risk of Type 1 errors. Additionally, analysing the CO data between specified ranges also increased the number of statistical tests and thus risk of Type 1 errors. Alternative approaches to analysing the CO data in order to lower this risk have been previously suggested (see Chapter 3). In relation to the number of cognitive tasks, an alternative approach would have been to reduce the measures into a smaller number of variables using, for example factor analysis, prior to running the main analyses. This would have reduced the number of cognitive tasks into a smaller number of cognitive domains and therefore the number of significance tests required would have decreased. Another potential way to decrease the risk of Type 1 errors would have been to lower the alpha value to 0.01.

A further limitation relates to the sample size. This was calculated using G power, with an effect size of .25, alpha of .05 and power of .80, with results indicating that the largest sample sized required would be 130 participants. However, the resulting sample size was lower at 106 participants. Although this sample is larger than many previous studies in the CO behavioural literature, the study still may have been underpowered for definitive hypothesis testing. Sample size, alpha values, power and effect sizes are all closely related. Estimated sample sizes increase with decreasing effect size, and power decreases with decreasing effect size. Therefore, the low effect size used in the current study (.25) and the relatively small sample size (106) may have led to the study being underpowered. Future research examining the effects of low-level CO exposure, where small effect sizes are anticipated, should aim to increase the sample size, in turn, increasing the power of future studies.

4.4.5 Conclusion

The research presented here provides a foundation for future research in the behavioural chronic CO exposure literature, an area in which there is a significant knowledge gap. Results indicated that at least four weeks CO exposure ≤29ppm is associated with beneficial cognitive effects in visual and auditory WM, memory recognition, visuospatial ability and areas of EF including planning, problem solving, selective attention and resistance to distractor interference. Furthermore, the positive effects observed in auditory WM and memory recognition were associated with lower concentrations (≤6ppm), indicating greater exposure vulnerability in these functions, whereas visual WM, planning and problem solving and selective attention were positively affected by higher concentrations (≥3.5ppm). These cognitive functions are associated with ischaemic-sensitive areas including the hippocampus, basal ganglia and white matter. Physiological mechanisms, such as vasodilation, may temporarily maintain CBF to these high oxygen dependent regions in older adults where this is compromised. Likewise, damage may be initiated in these regions when the protective-harm threshold is reached, resulting in impairments in similar areas of cognition. The results also revealed that the beneficial effects on memory recognition, visuospatial ability and problem solving were, to a degree, dependent upon age with positive effects observed in younger older adults (58-74 years) and negative impacts in old older adults (75-97 years). This suggests that whilst CO exposure may be associated with beneficial effects in these areas of cognition in younger older adults they may, to a certain degree, be dependent upon factors such as physiological and cognitive reserve capacity, intrinsic capacity and an individual's resilience. These results therefore highlight the vulnerability of old older adults to CO exposure.

Study 4 examines the longer-term effects of chronic low-level exposure in older adults with longitudinal follow up of the same participants, with a particular focus upon the time point and thresholds at which the potential shift from protective effects to toxicity occurs in particular cognitive functions. Specifically, whether the positive effects reported here are short lasting and ultimately result in negative impacts was examined. Additionally, the particular cognitive domains affected and the direction of effects at various CO levels and durations was investigated

in order to identify not only thresholds of harm but also patterns of impairment for use in clinical settings.

Chapter 5: Study 4

A Longitudinal Study of the Cognitive Effects of Chronic Low-level CO Exposure in Older Adults.

5.1 Introduction

The literature on the neuropsychological effects of low-level carbon monoxide (CO) exposure is both limited and inconsistent. Evidence indicates that detrimental effects, including impaired inhibition (pre-potent response), long-term memory and psychomotor speed may follow acute exposures (Horvath et al., 1971; Ramsey, 1972; Putz, 1979; Gliner et al., 1983; see Chapter 2), and deficits in learning ability, motor slowing and memory follow chronic exposure (Ryan, 1990; Myers et al., 1998). Epidemiological studies further support the detrimental impact of chronic low-level exposure on health and cognitive function, with reported associations between air pollution and increased risk of stroke (Maheswaran et al., 2005), myocardial infarction (MI) (Shah et al., 2013), heart failure (Mustafic et al., 2012) and dementia (Chang et al., 2014). However, other studies have found no evidence of CO-related neuropsychological effects following acute exposure (Roche et al., 1981; Wright & Shephard, 1978; Benignus et al., 1977). Furthermore, results from the observational study in this thesis (see Study 3, Chapter 4) indicate potential *beneficial* effects in auditory and visual working memory (WM), visuospatial ability, planning, problem solving, selective attention, resistance to distractor interference and memory recognition following chronic exposure. Similarly, Volans et al., (2007) found trends towards *increased* performance following chronic exposure, the largest of which were observed in auditory WM, immediate and delayed visual memory recall, visuospatial ability and problem solving. The observed performance improvements were small, none of which reached significance. However, they are remarkably consistent with the positive effects reported in Chapter 4, specifically in auditory WM, aspects of long-term memory, visuospatial ability and problem solving. These beneficial effects are likely to be short lasting, potentially observed in older adult populations only, and ultimately result in damage given sufficient exposure time. However, currently this is unknown. The study presented in this Chapter, examined the longer-term impact of chronic low-level

CO exposure on cognitive function, building on the results from the cross-sectional study (Chapter 4).

The extremely low-levels of CO observed in Study 3 and Volans et al., (2007) study may explain the resulting positive effects, with overall means of .09ppm (COHb .20-1.40%) and 1.89ppm, respectively. At these low levels, endogenous CO has known physiologic and cytoprotective properties (for reviews see Mahan, 2012; Queiroga, Vercelli & Vieira, 2015), exposure to extremely low-level exogenous CO may therefore result in similar protective effects (see Chapter 4). The differences in the direction of CO-related effects following low-level CO exposure reported in the literature are likely to be due to variation in the concentration and duration, population studied and potential differences in the underlying physiological mechanisms. For example, in acute exposure studies, participants are typically exposed to higher CO concentrations and samples have generally included young healthy adults. This potentially explains the absence of positive effects and observed negative effects in pre-potent response inhibition, long-term memory and psychomotor speed (see Chapter 2 and 4).

Adaptation, tolerance and compensatory mechanisms, and the potential physiological properties of exogenous CO, may minimise risk to the central nervous system (CNS) under chronic exposure conditions, playing a protective and even beneficial role up to a certain dose and duration. For example, due to its vasoactive properties, low-level CO may be beneficial to cognitive functioning by temporarily increasing and maintaining cerebral blood flow (CBF) in individuals where this is compromised such as older adults (see Chapter 4). Age-related vascular changes can lead to suboptimal CBF and hypo-perfusion which have been identified as precursors for mild cognitive impairment (MCI) and reported to accurately predict the development of Alzheimer's disease (AD) (David & Taylor, 2004; Belohlavek et al., 2009; Jerskey et al., 2009; Jefferson et al., 2007; Forti et al., 2006). In addition, cardiovascular risk factors are more common in older adults and lead to greater decreases in CBF and chronic hypo-perfusion (de la Torre, 2012; Leenders et al., 1990; Zhao et al., 2007; Bentourkia et al., 2000; Parkes et al., 2004; Heo et al., 2010). The effect of these structural and functional alterations on blood flow can result in a neuronal energy crisis,

followed by neuronal dysfunction and death, contributing to, and increasing the risk of, cognitive decline and dementia (de la Torre, 2012; Mosconi et al., 2009). This process is initiated in ischaemic-sensitive zones such as the hippocampus, basal ganglia and the cerebral white matter (CWM) (Ruitenberg et al., 2005; Moody, Bell, & Challa, 1990; Pullicino, Caplan, & Hommel, 1993; Donnan et al., 1995). If low-level chronic exposure to CO is associated with temporary increases in CBF in older adults, this may be particularly beneficial to ischaemic-sensitive brain regions. In support of this, the performance increases observed in Study 3 were found in areas of cognition that are associated with these regions (see Chapter 4).

The relationship between age and memory recognition, visuospatial ability and problem solving was also found to be moderated by CO exposure, in that, greater exposure was associated with increased performance in younger older adults (58-75 years) and decreased performance in old older adults (75-97 years). This suggests that whilst CO exposure may be associated with beneficial effects in older adults, these effects in particular areas of functioning may be more dependent upon factors such as physiological and cognitive reserve capacity, intrinsic capacity and resilience (see Chapter 4). For example, frail individuals are more likely to have low resilience and reduced reserve capacity to deal with stressful events and restore homeostasis. This places them at greater risk from minor external stressors that results in disproportionate changes in health (Campbell & Buchner, 1997; Whitson et al., 2018; Clegg et al, 2013). This increased vulnerability results from cumulative age-related declines in function across multiple physiological systems, that are close to, or beyond, the threshold of failure (Campbell & Buchner, 1997; Xue, 2011). The finding of negative exposure effects in old older adults is therefore not surprising, particularly if a number of the individuals in this group were frail. Therefore, in younger older adults, where CBF is reduced or restricted due to age and disease-related pathology, physiological mechanisms such as vasodilation may be beneficial to cognition up to a certain dose and duration. However, in old older adults, particularly those who are frail, the additional burden CO exposure potentially places on biological systems that are potentially close to, or already failing appears to be detrimental for particular areas of functioning.

5.1.1 Continuum of Exposure from Positive to Negative Effects

The protective properties of low-level exogenous CO if present, are likely transient, with carboxyhaemoglobin (COHb) accumulation over time, and the stress this places on the body's physiological resources, reaching a point where the body can no longer compensate for the continuous uptake of CO. Subsequently, insufficient CBF and ischaemia may follow, resulting in a shift from positive to negative cognitive impacts. The brain regions that potentially benefit most from CO-related temporary increases in CBF, may also be areas most susceptible to damage when levels exceed certain thresholds with COHb accumulation over time, potentially accelerating the neuronal energy crisis-dysfunction-death cascade. Damage to ischaemic-sensitive zones is therefore likely, potentially resulting in deficits in similar cognitive areas to the beneficial effects observed in Chapter 4. The effects related to chronic low-level CO exposure may therefore be viewed on a continuum; with one end representing low-level exposure and potential beneficial effects followed by a transition into negative effects at the opposite end of the spectrum, observed with increasing exposure duration and concentration. The results from the cross-sectional study (Chapter 4) revealed a pattern of performance improvements related to exposure level, with aspects of memory including recognition and auditory WM positively affected by lower concentrations (≤6ppm), and visual WM, visuospatial ability, planning, problem solving, selective attention, and resistance to distractor interference positively affected by higher concentrations (3.5-30ppm). This may indicate that auditory WM and memory recognition are more sensitive to exposure, with positive effects present at lower levels only, and that a shift to negative impacts occurs at lower concentrations in these functions compared to other areas of cognition. This suggests that a transition period of no effects may be present, prior to the shift to negative impacts at a certain unknown level. Visual WM, planning, problem solving, selective attention and resistance to distractor interference however, appear to be more resilient to CO, with positive effects present at higher exposure concentrations (3.5-30ppm). Whether these effects are followed by a transient period of no effects, prior to a shift to negative impacts at a certain unknown level, is currently unknown.

Other areas of cognitive functioning may be associated with negative CO-related effects only. Support for this inference is provided by results from acute exposure studies indicating that impaired long-term memory, pre-potent response inhibition, cognitive flexibility and psychomotor speed follow low-level exposure to higher concentrations (see Chapter 2 and 4). As mentioned above, the higher CO concentrations used in acute studies (100ppm) and the samples of young healthy adults studied, potentially explain the absence of significant positive effects. However, it is also possible that these areas are not associated with beneficial exposure effects. Further support for this is provided by the results from Study 3 (see Chapter 4), wherein with the exception of long-term memory, positive CO-related effects were not observed in these areas or in the additional domain of resistance to proactive interference. These areas of functioning may therefore not follow an exposure effect trajectory of *positive-zero-negative or positive-negative effects* that is potentially present in other areas of functioning. Instead, they are perhaps associated with negative CO-related effects only, following longer exposure durations or higher concentrations. However, it is possible that positive effects do follow chronic exposure in these cognitive areas but at higher concentrations than those observed in Chapter 4.

Older adults are also likely more susceptible to exposure, with shifts to negative effects potentially occurring at lower concentrations and durations than in young healthy adults, due to the already sub-optimal CBF and hypo-perfusion associated with the vasculature changes present in ageing and possible cardiovascular disease. These alterations, along with age-related cerebral changes such as atrophy of the hippocampus and white matter hyperintensities (WMH) have all been associated with greater risk of early cognitive decline and dementia development (David & Taylor, 2004; Belohlavek et al., 2009; Jerskey et al., 2009; Jefferson et al., 2007; Forti et al., 2006; den Heijer et al., 2006; Smith et al., 2008; Bigler et al., 2002). Moreover, the brain abnormalities observed in CO poisoned patients include ischaemic-sensitive areas, with lesions to the globus pallidus (O'Donnell et al., 2000; Porter et al., 2002; Varrassi et al., 2017) atrophy of the hippocampus (Gale et al., 1999; Gale & Hopkins, 2004) and WMH (Hou et al., 2013) commonly reported. COHb accumulation over time may add to this burden, potentially accelerating the neuronal energy crisis-dysfunction-death

cascade. Older adults who are exposed to CO, may therefore be at an even greater risk of early cognitive decline and dementia development beyond that associated with ageing and disease.

Evidence from case reports indicate the longer term impacts of chronic low-level exposures with deficits in learning ability, memory and motor slowing reported to persist once exposure had ceased, suggesting they are persistent in nature (Ryan, 1990; Myers et al., 1998). In some cases, complete recovery is achieved. However, symptoms and neuropsychological impairments can remain, ranging in severity from mild to severe. These impairments can prevent individuals from making a full recovery and contribute to significant morbidity, and therefore should not be overlooked as this often leads to inappropriate and incomplete treatment which can significantly impact upon the lives of patients and families longer term (Myers et al., 1998).

5.1.2 The Current Study

Whether the beneficial cognitive effects reported in Chapter 4 are short lasting, potentially observed in older adult populations only, and ultimately result in damage given sufficient exposure time is unknown. Additionally, if negative impacts do follow, whether these can result in long-term cognitive impacts is unclear. The current study therefore examined the longer-term impact of chronic low-level CO exposure on cognitive function, through longitudinal follow up of the same participants, building on the results from the cross-sectional study (Chapter 4). Increased understanding of the long-term neuropsychological effects associated with chronic CO exposure, the direction of effects at various concentrations, differences across various age subgroups within older adult populations and patterns of impairment is needed, if we are to advance knowledge of the levels at which these exposures present risk to neuropsychological function. This would assist in answering important questions such as whether the observed beneficial cognitive effects are short-lasting and subsequently result in impairments given sufficient time post-exposure (if the exposure has ceased), but also the level and durations at which these exposures become harmful under conditions of continuous exposure. The potential shift from protective effects to toxicity will be largely dependent upon the dose and

duration alongside other factors such as age and pre-existing disease. For example, results from the cross-sectional chapter indicated positive effects of CO exposure in older adults across a range of cognitive domains. However, in particular areas of functioning these effects were dependent upon age, with positive effects present in younger older adults and negative impacts in old older adults. Therefore, the impact of CO exposure on particular areas of cognition may be more dependent upon an individual's reserve capacity and resilience, rather than age alone.

Identifying the thresholds at which the body's protective, and potentially beneficial, physiological responses become ineffective, and harm initiated, is vital in order to keep the public safe. Identification of the cognitive areas affected by chronic low-level CO exposure is also crucial in order to highlight potential patterns of impairment. Preliminary results suggest that chronic exposure to CO for at least four weeks may be positively associated with auditory working memory and memory recognition, visual WM, planning, problem solving, selective attention and resistance to distractor interference (see Chapter 4). Auditory WM and memory recognition may be more vulnerable to CO exposure with positive effects observed at lower exposure levels (≤6ppm), whereas visual WM, planning, problem solving, selective attention and resistance to distractor interference are potentially more resilient, with positive effects observed at higher concentrations (3.5-30ppm). However, these cognitive functions, and their associated brain regions, potentially benefit most from CO-related temporary increases in CBF, but are also likely to be areas that are most susceptible to damage when physiological responses can no longer compensate for the continuous accumulation of COHb. Cognitive deficits would therefore follow in similar areas to the reported beneficial effects due to the vulnerability of the hippocampus, basal ganglia and CWM to ischaemia insult. However, whether there is a shift from positive to negative effects across multiple cognitive domains, and if negative effects do follow, whether these are short lasting or result in long-term negative impacts is currently unknown. The current study aimed to examine these important questions.

5.1.4 Aims and Objectives

The main aim of the study was to examine the longer-term impact of chronic low-level CO exposure on cognitive function in older adults through longitudinal follow up of the same participants seven months after the first assessment. Specifically, the study aims were to examine any potential lasting effects associated with the exposure at Time 1 (T1; cross-sectional study; Chapter 4) and to determine the impact of a second 1-month exposure period (Time 2; T2) on cognitive functioning at seven month follow-up. The exposure at T1 therefore reflects the longer-term impact CO exposure may pose on cognitive function, and the exposure at T2 reflects effects in the short-term following exposure. Based on the literature presented above and earlier findings, it is hypothesised that the longer-term impact of the exposure at T1 will be related to negative cognitive effects, particularly in areas of memory recognition, auditory WM, and potentially pre-potent response inhibition, resistance to pro-active interference, psychomotor speed and cognitive flexibility. The impact of the exposure at T2 in the short-term on these functions is also hypothesised to be negative or not present. These areas include those where positive effects were observed in the short-term at lower CO levels only (memory recognition and auditory WM) in Study 3 (see Chapter 4), and those highlighted to be associated with negative effects in acute exposure studies (see Chapter 2) with no positive effects observed in the short-term in Study 3 (pre-potent response inhibition, resistance to pro-active interference, psychomotor speed and cognitive flexibility). The latter is therefore also a test of replication of the findings from Study 3 (see Chapter 4).

In relation to the areas of functioning where positive effects were observed at higher concentrations in Chapter 4, the exposure at T2 is predicted to have similar positive effects in the short-term, these areas included visual WM, visuospatial ability, planning, problem solving, selective attention and resistance to distractor interference, and is therefore also a test of replication. Finally, due to the biological changes associated with ageing and disease, it is predicted that the relationship between advancing age and cognitive decline will increase with greater CO exposure, specifically in memory recognition, visuospatial ability and problem solving.

Hypotheses:

H_1 CO exposure at T1 will be associated with longer-term negative effects on cognitive function seven months later, particularly in areas of memory recognition, auditory WM, and potentially pre-potent response inhibition, resistance to pro-active interference, psychomotor speed and cognitive flexibility.

H_2 If exposure effects are present at T2 in the short-term in areas of memory recognition, auditory WM, pre-potent response inhibition, resistance to pro-active interference, psychomotor speed and cognitive flexibility, only negative effects will be observed.

H_3 The exposure at T2 will be associated with positive effects in the short-term on cognitive function, with the exception of those mentioned above, and particularly in areas of visual WM, visuospatial ability, planning, problem solving, selective attention and resistance to distractor interference.

H_4 The total CO summated over both time periods will be associated with overall negative effects on cognitive function and the relationship between advancing age and cognitive decline will increase with greater CO exposure. Additionally, the moderating effect of greater CO exposure on the relationship between age and cognition, particularly in memory recognition, visual spatial ability and problem solving, is predicted to be more dependent upon an individual's reserve capacity and resilience, with positive performance effects predicted in younger older adults and negative effects in old older adults.

5.2 Method

5.2.1 Study Design

The study was a longitudinal observational study that incorporates a correlational design.

5.2.2 Participants

Of the 106 participants recruited onto the study (see Chapter 4), 78 were followed up at seven months. A total of 28 participants were lost at follow up; nine due to ill health, five due to illness of partner, one passed away, nine due to withdrawal

of participation and four could not be followed up due to the COVID-19 government restrictions. The sample of 78 older adults continuing participation were aged 59 to 93 years (*M*=75.15, *SD*= 7.626). The inclusion criteria were individuals residing in Coventry, ≥58 years of age and fluent in the English language. The exclusion criteria were individuals who had experienced an acute CO poisoning episode and those lacking mental capacity according to the Mental Capacity Act (MCA; 2005) (see Chapters 3 and 4 for full details on recruitment and the inclusion and exclusion criteria).

5.2.3 Measures

5.2.3.1 Neuropsychological Measures

Global cognitive function was assessed using the Addenbrooke's Cognitive Examination III (ACE-III; Noone, 2015). The National Adult Reading Test (NART; Nelson, 1982) was used as a measure of pre-morbid IQ. Selective attention and resistance to distractor interference, divided attention and processing speed were assessed using the Useful Field of View test (UFOV; Ball et al., 1988). Psychomotor speed was assessed using the Trail Making Test part A (TMTA) and executive functioning, specifically cognitive flexibility and inhibition (resistance to pro-active interference), using part B (Reitan & Wolfson, 1985). Immediate and delayed recall and recognition were assessed using the logical memory subtest of the Wechsler Memory Scale (WMS-IV; Wechsler, 2010). The block design task from the WAIS-III (WAIS-BD) was used as a measure of visuospatial ability and problem solving. The Sustained Attention to Response Task was used to assess sustained attention, intra-individual variability and inhibition (pre-potent response) (SART; Robertson et al., 1997). Auditory short-term memory was assessed using the forward digit span and auditory working memory using the backwards digit span from the Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV; Wechsler, 2010). Visual working memory was assessed using The Corsi block test (Corsi, 1972). Executive functioning, specifically planning and problem solving was assessed using The Tower of London task (TOL; Shallice, 1982). The Hospital anxiety and depression scale (HADS; Zigmond & Snaith, 1983) was used as a measure of anxiety and depression. A questionnaire including demographic, medical (such as pre-existing physical and psychiatric diagnoses, health care use and symptoms) and

property information (such as home appliances) was included. For information relating to the reliability of the included measures, task instructions, administration and scoring see Chapter 4.

A breathalyser was used as a physiological measure of CO levels in exhaled breath (ppm) in order to determine the degree of exposure. Participants were required to inhale and hold their breath for 15 seconds prior to exhaling into the monitor. Blood pressure was measured using a digital monitor with recordings used as a physiological marker of health. A personal CO monitor was used in order to keep the researcher safe when entering properties from potential CO in the ambient air and to record the CO level during the assessment. Data loggers were used to continuously measure to ambient CO levels for one month.

5.2.3.2 Equipment

CO alarms, data loggers, breathalyser and blood pressure monitor

The equipment used in the cross-sectional study (Chapter 4) was employed in the current study and included FireAngel CO-9X Wireless Carbon Monoxide Alarms, Lascar electronics easy log carbon monoxide data loggers (EL-USB-CO300), a Honeywell ToxiRAE 3 (PGM-1700) personal CO monitor, a Bedfont Micro-Smokerlyzer (AWR-BM+01) and a BDFA electronic LCD digital display blood pressure monitor. For information relating to use of equipment, specification, accuracy, placement and alarm activation thresholds and CO data preparation see Chapters 3 and 4.

5.2.4 Informed Consent and Ethical Approval

During the initial consent process for Study 3, participants were informed by the fire service and researcher that there would be two testing points with approximately seven months between them. This information was also provided on the information sheet left with participants. All participants gave consent to be contacted again for the follow up Study, and informed written consent for continued participation was obtained by the researcher. The study received ethical approval by the Faculty of Health and Medicine research ethics committee, Lancaster University. Reference number: FHMREC17082.

5.2.5 Procedure

Participants were recruited via liaison with West Midlands Fire Service. Fire officers re-visited the properties approximately seven months after the initial visit to re-deploy the data loggers, check the CO alarms and provide health and safety information to the participants regarding CO sources, safety and prevention, and the associated health risks. Following the Fire Service visit, appointments with the researcher were scheduled at a time during the four weeks that the data loggers were in place. Health and mental health screening questionnaires and repeated neuropsychological testing were carried out along with breath CO levels (ppm and COHb) and blood pressure monitoring. The tasks were carried out in the same fixed order as at Time 1: General information questionnaire, HADS, ACE-III, WMS, NART, TMTAB, WAIS-BD, WMS, CORSI, WAIS-DSF DSB, TOL, SART and UFOV. Due to the number of measures the order of assessments were not counterbalanced (see Chapter 4 for rationale). Participants were given a detailed debrief following participation. The CO data loggers were collected from the properties after they had been in place for a total of one month. The data were downloaded and initially checked for safety purposes by the Fire Service prior to being shared with the researcher. The study was double blind with both the researcher and participants unaware of exposure status at the time of assessment (see Chapters 3 & 4 for full procedure details).

5.2.6 Statistical Analysis

In order to examine $H_{1,}$ that the longer-term impact of chronic CO exposure at T1 would be associated with impaired cognitive function at T2, particularly in areas of memory recognition and auditory WM, and potentially pre-potent response inhibition, resistance to pro-active interference, psychomotor speed and cognitive flexibility, correlation analyses were initially carried out. Correlation analyses were also carried out between the CO exposure at T2 and cognitive measures at T2 in order to examine $H_{2,}$ that if CO-related effects in the short-term present, these will be negative in memory recognition, auditory working memory, and potentially pre-potent response inhibition, resistance to pro-active interference, psychomotor speed and cognitive flexibility. These areas include those where positive effects were observed in the short-term at lower CO levels only (memory recognition and auditory WM) in Study 3 (see Chapter 4), and those highlighted

to be associated with negative effects in acute exposure studies (see Chapter 2) with no positive effects observed in the short-term in Study 3 (pre-potent response inhibition, resistance to pro-active interference, psychomotor speed and cognitive flexibility). H_3 was also examined, with positive effects on cognition predicted to be associated with the exposure at T2 in the short-term (with the exceptions of those functions mentioned in H_2) and particularly in areas of visual working memory, visuospatial ability, planning, problem solving, selective attention and resistance to distractor interference as a test of replication of earlier findings (see Chapter 4). Additionally, correlation analyses between T1 and T2 exposure were conducted in order to investigate any potential relationships between the exposures. Correlations between the cognitive measures and age, hours spent within the home, pre-morbid IQ, anxiety, depression, physical and psychiatric diagnoses and the cognitive scores at T1 were carried out to determine the variables that were associated with the cognitive measures at T2 so that their variance could be controlled for in further analyses, in order to control for potential confounders. Smoking status was not controlled for due to the low number of smokers within the sample (six). Finally, correlation analysis between all of the control variables and the percentages of CO readings in each range at T1 and T2 were examined in order to assess the relationships, and any Multicollinearity, between the variables prior to further analysis.

Regression models were then developed from the results of the correlation analyses with control variables entered into Block 1 of the model when they were significantly correlated with the cognitive measures. These were subsequently dropped from the model when their contribution was not significant, with the exception of the cognitive scores at T1 and the main effects of interest, in order to increase the degrees of freedom due to the lower number of observations at T2 (78). The main effects of interest, the percentage of CO readings between each range at T1 and T2 (See Chapter 3 for details on CO measures) were entered into Block 2 to examine $H_{1\text{-}3.}$ Carbon monoxide data were separated into specified ranges (0ppm, 0.5-3ppm, 3.5-6ppm, 6.5-9pmm and 9.5-30ppm) with the percentage of readings in each used in the analysis. However, due to the lower number of observations at T2, the two highest CO ranges (6.5-9ppm and 9.5-30ppm) were combined into one range. The exposure at T1 and T2 for each

of the ranges were entered into separate regression models due to Multicollinearity (for details on CO data preparation and rationale see Chapters 3 & 4).

In order to answer H_4 that the total CO over both time periods would be associated with overall negative effects on cognitive function and that the association between advancing age and cognitive decline will increase with greater CO exposure, similar regression models were developed in terms of the selection and inclusion of control variables in Block 1 of the models. However, the CO exposure at T1 and T2 were summated and converted into overall percentages to provide a measure of the total exposure within each range. This enabled the investigation as to whether the overall total CO exposure is associated with detrimental effects on cognition, and whether the relationship between advancing age and cognition increases with greater overall exposure. The total CO exposure in each range was entered into Block 2 and the interaction term between the total exposure and age was entered into Block 3. In cases where the interaction was significant, graphs were plotted by age group, with two groups created (younger older adults: 59-74 years (*n*=39); old older adults: 75-93 years (*n*=39) in order to further examine the interaction effect. The age groups were determined by median split.

5.2.7 Data Processing

The raw data were entered into IBM SPSS Statistics 26 (2019) for analysis.

5.2.7.1 Missing Data

There was an extremely small amount of missing data, only 2 cases were missing across the UFOV tasks. Analyses were run without these cases.

5.2.7.2 Data Transformations

Prior to correlation analysis, variables were assessed for normality by inspection of histograms, Q-Q plots, skewness and kurtosis values and tests of normality (Kolmogorov-Smirnov test). Data transforms were used when required on the cognitive variables with transformation chosen based on Field, (2013). Transformed variables were used in correlation analyses for normality and in

regression analyses to correct for linearity and homoscedasticity problems. The interpretation of the direction of effect for reflected variables, are reversed and are presented as such (i.e. positive correlations for reflected variables are interpreted as negative) (Field, 2013).

5.2.7.3 Mean Centring

All of the variables except the cognitive measures were mean centred for regression analysis, by subtracting the mean from all observations for each variable, in order to reduce multicollinearity. This included the percentage of CO readings across all ranges at both T1 and T2 and all of the control variables. This enabled the examination of interaction effects between the total CO exposure over both time periods and age on cognitive function.

5.2.7.4 Assumption Testing and Bias from Outliers and Influential Cases

Outliers greater than ±3 SDs were removed from the correlation and regression analyses. In the regression models, the influence of a case on the ability of the model to predict that case was also assessed using studentized deleted residual (difference between adjusted predicted value and observed value divided by the standard error). Residuals ±3.29 were removed from the analysis (see Field, 2013). Additionally, the influence of a case on the model's ability to predict all cases (the full model) was assessed using Cook's and leverage values. Leverage cut off points of >0.5 were used with values exceeding this removed from the analyses (see Huber, 1981). Cooks distance values above 1 indicate potentially large influence and represent cause for concern and so were removed from the regression analysis (Cook and Weisberg, 1982). Independence of observations (residuals) were assessed by the Durbin Watson statistic which was approximately 2 for each regression indicating no correlation between the residuals. Linearity and homoscedasticity were assessed by visual inspection of the studentized residuals and unstandardized predicted values plot and partial regression plots. There was no evidence of multicollinearity, as assessed by correlations <.80, VIF values >4.0 and tolerance >0.2 (Field, 2013; Hair et al., 2010). The assumption of normality of the residuals was assessed by a histogram of the standardized residuals and a normal P-P plot. The removal of influential

cases from the analyses did not lead to a large number of omitted cases, with all analyses run with ≥70 observations, with the exception of one (*N*=68).

5.3 Results

5.3.1 Descriptive Statistics

Descriptive statistics are provided in Table 5.1. It can be seen that the mean age for male participants (*M*=74.5 years) was slightly lower than for female participants (*M*=75.5 years). Years in education ranged from 9-21, with a mean of 11.77 years, and NART errors between 1 and 46, with higher scores indicating lower pre-morbid IQ.

Table 5.1. Mean, standard deviation and range for age, education level, NART errors, gender and age by gender

	Age (yrs)	**Education (yrs)**	**NART errors**	**Age by gender**	
				M	**F**
N	78	78	78	26	52
Range	59-93	9-21	1-46	59-93	61-90
M	75.15	11.77	20.79	74.50	75.48
SD	7.63	2.31	10.10	8.733	7.078

5.3.2 Mean, Standard Deviation and Range for Ambient, Breath and COHb Levels

Descriptive statistics are presented in Table 5.2. Smoking status, breath CO (ppm) and COHb levels are reported as an indication of exposure severity for descriptive purposes and were not controlled for in the analysis. It can be seen that smokers had a higher level of CO in their breath at both times points, as would be expected. The mean ambient CO level was higher in the homes of smokers (*M*=.16ppm) compared to those of non-smokers (*M*=.09ppm) at T1. However at T2, the mean ambient CO levels were higher in the homes of non-smokers (*M*=.08) compared to those of smokers (*M*=.05).

Table 5.2. Mean, SD and range of CO measures by smoking status.

T1	**Ambient CO (ppm)**	**Breath CO (ppm)**	**COHb (%)**	**T2**	**Ambient CO (ppm)**	**Breath CO (ppm)**	**COHb (%)**
Smoker				*Smoker*			
N	6			*N*	6		
Range	.00-11.50	4.00-22.00	.80-4.20	*Range*	.00-6.00	4.00-18.00	.80-3.40
M	.16	13.50	2.58	*M*	.05	14.00	2.67
SD	.33	7.37	1.37	*SD*	.07	5.18	.96

Non-smoker				*Non-smoker*			
N	72			*N*	72		
Range	.00-29.00	1.00-7.00	.20-1.40	*Range*	.00-25.50	1.00-6.00	.20-1.20
M	.09	2.46	.50	*M*	.08	2.69	.54
SD	.24	1.01	.20	*SD*	.28	.90	.18

5.3.3 Mean and Standard Deviation for Independent and Dependent Variables

Means and standard deviations for all variables at T2 are displayed in Table 5.3. As the effect of T1 CO exposure on the cognitive scores at T2 was of interest, details are also provided for T1 CO levels (for the 78 participants that completed the follow up at T2). Means are presented for the untransformed variables with outliers and therefore trimmed means (5%) are also reported (the highest and lowest 5% of the data were excluded and means calculated from the remaining 90% of data points). These were included in order to examine the influence of the outliers on the mean. Comparison between the two measures revealed only small differences indicating that the outliers did not have a large influence on the overall mean.

Table 5.3. Mean and standard deviation for control, predictor and dependent variables at T2 and for CO ranges at T1.

Variable T2	**Mean (SD)**	**5% trimmed mean**
Age (yrs)	75.15 (7.63)	75.05
Hours spent in the home	21.22 (1.94)	21.30
NART Errors	20.79 (10.10)	20.56
Depression	4.12 (3.14)	3.92
Anxiety	4.90 (3.57)	4.62
Physical diagnoses (N)	1.88 (1.42)	1.80
Psychiatric diagnoses (N)	.29 (.76)	.17
% of CO readings at 0ppm T1	94.54 (14.07)	97.05
% of CO readings between 0.5-3ppm T1	4.78 (13.01)	2.59
% of CO readings between 3.5-6ppm T1	.48 (1.81)	.17
% of CO readings between 6.5-30ppm T1	.20 (.74)	.05
% of CO readings at 0ppm T2	95.74 (13.32)	98.02
% of CO readings between 0.5-3ppm T2	3.74 (12.09)	1.77
% of CO readings between 3.5-6ppm T2	.35 (1.93)	.09
% of CO readings between 6.5-30ppm T2	.16 (.88)	.027
TMTA	52.36 (21.23)	50.24
TMTB	139.06 (72.81)	132.83
TMTBA	86.71 (61.58)	81.41
ACE-III Total	87.41 (8.37)	87.92
WAIS-BD	29.09 (10.64)	28.65
WMS-IR	32.51 (7.17)	32.81
WMS-DR	19.74 (6.54)	19.91
WMS-R	19.13 (2.39)	19.20
SART-RT	497.87 (94.04)	496.20
SART Errors	9.77 (5.32)	9.60
SART RTIIV	.30 (.08)	.30
CORSI-BS	4.81 (.76)	4.83

CORSI-BSTS	32.59 (11.15)	32.33
TOL	30.26 (3.26)	30.38
WAIS-DSF	5.78 (1.08)	5.76
WAIS-DSB	4.22 (1.07)	4.20
UFOV-PS	34.74 (35.90)	28.72
UFOV-DA	151.08 (113.69)	143.92
UFOV-SA	277.29 (135.42)	276.25

PPM= parts per million; TMT= trail making task; ACE-III= Addenbrookes cognitive examination-III; WAIS-BD=Welschler adult intelligence scale block design; WMS-IR=Welschler memory scale immediate recall; WMS-DR= delayed recall; WMS-R= recognition; SART-RT= Sustained attention response time mean reaction time; IIV= Intraindividual variability; CORSI BS= CORSI block span; BSTS= block span total score; TOL= tower of London task; WAIS DSF= digit span forward; WAIS-DSB= digit span backwards; UFOV-PS= useful field of view processing speed; DA= divided attention; SA= selective attention.

5.3.4 Bivariate Pearson Correlations

Correlations between the control variables and predictor variables (CO ranges) are presented in Table 5.4, between the control variables and cognitive scores at T2 in Table 5.5 and between the CO ranges and the cognitive measures in Table 5.6.

5.3.4.1 Correlation Analyses between Control Variables and CO Ranges

Interpretation of Table 5.4. indicates no significant correlations between the percentage of CO readings within any range and the control variables. Significant relationships were observed between the number of hours spent in the home per day and age (p<.01) and depression (p<.05), with more hours spent in the home per day associated with greater levels of depression and older age. Depression was also significantly correlated with NART errors (p<.01), anxiety (p<.01) and physical diagnoses (p<.05), with higher levels of depression associated with greater NART errors (indicating lower pre-morbid IQ) and physical diagnoses. Total psychiatric diagnoses were significantly correlated with anxiety (p<.05) with greater number of diagnoses associated with higher levels of anxiety. The percentages of CO in each range at T1 and T2 were significantly correlated with each other at the .001, .01 and .05 level.

Table 5.4. Correlations between control variables and CO ranges at T1 and T2.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
(1) % CO 0ppm T1														
(2) % CO 0.5-3ppm T1	-.986***													
(3) % CO 3.5-6ppm T1	-.504***	.353**												
(4) % CO 6.5-30ppm T1	-.447***	.297**	.931***											
(5) % CO 0ppm T2	.891***	-.868***	-.500***	-.446***										
(6) % CO 0.5-3ppm T2	-.890***	.897***	.350**	.303**	-.980***									
(7) % CO 3.5-6ppm T2	-.396***	.262*	.869***	.809***	-.526***	.347**								
(8) % CO 6.5-30ppm T2	-.381**	.247*	.854***	.808***	-.512***	.333**	.991***							
(9) Age	-.017	.045	-.154	-.095	-.108	.133	-.061	-.051						
(10) Hours in the home	-.031	.042	-.044	-.032	-.101	.097	.053	.073	.330**					
(11) NART	-.073	.101	-.103	-.139	.079	-.047	-.174	-.172	.036	.001				
(12) Depression	-.016	.020	-.031	.019	.028	-.007	-.109	-.095	.197	.247*	.311**			
(13) Anxiety	-.062	.064	.018	-.003	-.075	.064	.073	.096	-.193	.123	.116	.362**		
(14) Physical Diagnoses	-.142	.148	.028	.021	-.055	.066	-.026	-.018	-.117	-.040	.346**	.287*	.209	
(15) Psychiatric Diagnoses	.035	-.032	-.032	-.035	.060	-.059	-.043	.000	-.146	.075	.148	.177	.244*	.210

N= 78, *p<.05, **p<.01, ***p<.001

5.3.4.2 Correlation Analyses between Control and Cognitive Variables

Interpretation of Table 5.5. indicates that correlations between age and the majority of the cognitive variables were significant at varying levels (p<.001-p<.05), with advancing age associated with poorer performance. These findings reveal cognitive decline across a range of domains with increasing age including psychomotor and processing speed, cognitive flexibility, divided and selective attention, visual spatial ability, auditory and visual WM, planning and problem solving and immediate and delayed recall and recognition. A larger number of NART errors were also significantly associated with decreased performance across the majority of cognitive variables at varying levels (p<.001-p<.05). Additionally, greater number of hours spent within the home per day and depression were significantly correlated with worse performance across approximately half of the cognitive domains (p<.001-p<.05). There were no significant correlations between the number of physical diagnoses and the cognitive measures. The number of psychiatric diagnoses was associated with the performance on the sustained attention response task (p<.05) only, with lower number of psychiatric diagnoses associated with greater errors (indicating poorer sustained attention and inhibitory control).

Table 5.5. Correlations between the control variables and the cognitive measures at T2.

Scores T2	Age	HSH	NART	Depression	Anxiety	Physical diagnoses	Psychiatric diagnoses	Scores T1
TMTA	**.448*** **	**.239***	**.369****	**.370****	.031	.153	.035	.694***
TMTB	**.492*** **	**.431*** **	**.458*** **	**.344****	.046	.080	.060	.816***
TMTBA	**.441*** **	**.423*** **	**.428*** **	**.253***	.013	.037	.068	.711***
ACE-III Total	**-.314****	**-.244***	**-.697*** **	**-.315****	.035	-.179	-.051	.870***
WAIS-BD	**-.327****	-.098	**-.582*** **	**-.324****	-.020	-.088	-.149	.820***
WMS-IR	**-.316****	**-.240***	**-.553*** **	**-.378****	-.061	-.103	.011	.806***
WMS-DR	**-.328****	**-.244***	**-.495*** **	**-.283***	.028	-.079	.008	.768***
WMS-R	**-.287***	-.175	**-.443*** **	**-.279***	-.049	-.143	-.018	.605***
SART-RT	**.293****	**.243***	**.265***	.145	-.040	.123	.199	.812***
SART Errors	-.024	.018	.066	.130	-.005	.175	**-.288***	.566***
SART RTIIV	.143	.017	.186	.206	-.124	.208	-.171	.507***
CORSI-BS	**-.333****	**-.342****	-.154	-.209	.026	-.106	.035	.315**
CORSI-BSTS	**-.227***	-.171	-.156	-.126	-.087	-.034	-.020	.454***
TOL	-.119	-.183	**-.260***	.075	-.002	.086	-.023	.296**
WAIS-DSF	-.013	.154	**-.428*** **	-.133	-.094	-.194	.006	.482***
WAIS-DSB	**-.295****	-.218	**-.479*** **	**-.301****	-.057	-.097	-.076	.512***
UFOV-PS	.109	.057	.078	-.034	-.023	.042	-.076	.453***
UFOV-DA	**.426*** **	.222	**.340****	.158	-.173	.053	-.128	.701***
UFOV-SA	**.581*** **	**.263***	**.267***	.150	-.140	.061	-.076	.855***

N= 78, *p<.05, **p<.01, ***p<.001

HsH= hours spent in the home; TMT= trail making task; ACE-III= Addenbrookes cognitive examination-III; WAIS-BD=Welschler adult intelligence scale block design; WMS-IR=Welschler memory scale immediate recall; WMS-DR= delayed recall; WMS-R= recognition; SART-RT= Sustained attention response time mean reaction time; IIV= Intraindividual variability; CORSI-BS= CORSI block span; BSTS= block span total score; TOL= tower of London task; WAIS-DSF= digit span forward; WAIS-DSB= digit span backwards; UFOV-PS= useful field of view processing speed; DA= divided attention; SA= selective attention.

5.3.4.3 Correlation Analyses between CO Ranges and Cognitive Variables

Examination of Table 5.6. revealed significant correlations between the percentage of CO readings at 0ppm at T2 (short-term effect) and TOL scores, with lower percentage of CO readings at 0ppm, indicating greater exposure, associated with better performance (p<.05). These results indicate a positive CO-related effect on planning and problem solving. The percentage of CO readings from 0.5-3ppm at T2 were also found to be significantly correlated with scores on the TOL task (p<.05), with greater number of CO readings in these ranges, and therefore higher exposure, related to better performance scores. Significant positive correlations between the percentage of CO readings from 3.5-6ppm and 6.5-30ppm at T2 and WAIS-BD scores (p<.01-p<.05) were also found, with greater CO exposure in these ranges associated with better performance on visuospatial and problem solving ability. Finally, significant correlations were found between the percentage of CO readings at T2 from 3.5-6ppm and 6.5-30ppm and UFOV-SA scores (p<.05), with greater CO exposure related to better performance in selective attention and resistance to distractor interference. These findings support H_3 with positive effects associated with the CO exposure in the short-term at T2 in areas of planning, visuospatial ability, problem solving, selective attention and resistance to distractor inference.

Significant correlations between the percentage of CO readings at 0ppm at T1 (longer-term effect) and TOL scores were found, with lower percentage of CO readings at 0ppm, indicating greater exposure, associated with better performance at T2 (p<.05). The percentage of CO readings from 3.5-6ppm at T1 were also found to be significantly correlated with scores on the TOL task at T2, (p<.05), with greater number of CO readings in these ranges, and therefore higher exposure, related to better performance scores. Significant positive correlations between the percentage of CO readings from 3.5-6ppm and 6.5-30ppm at T1 and T2 WAIS-BD scores (p<.01-p<.05) were also found, with greater CO exposure in these ranges associated with better performance on visuospatial and problem solving ability. The percentage of CO readings from 6.5-30ppm at T1 and T2 CORSI-BST scores were significantly associated (p<.05), with greater exposure in this range related to better visual WM performance. Finally, significant correlations were found between the percentage

of CO readings at T1 from 3.5-6ppm and 6.5-30ppm and T2 UFOV-SA scores (p<.05), with greater CO exposure related to better performance in selective attention and resistance to distractor interference. These positive longer-term effects associated with the exposure at T1 in areas of planning, problem solving, visuospatial ability, visual WM, selective attention and resistance to distractor interference at 7 months are inconsistent with H_1 with negative longer-term cognitive impacts predicted.

There was some support for H_1 in that greater percentage of CO readings from 6.5-30ppm at T1 were significantly associated with increased number of T2 SART errors (p<.05). The percentage of CO readings from 3.5-6ppm and 6.5-30ppm at T1 were also significantly related to intra-individual variability in responding on this task (p<.05). These results suggest that increased CO exposure at T1 between these ranges were associated with greater intra-individual variability and errors (pre-potent response inhibition) at 7 months. This provides support for the longer-term negative CO-related effects of T1 exposure in areas of sustained attention, pre-potent response inhibition and variability in responding (H_1).

Finally, negative CO-related effects were also associated with the exposure at T2 (short-term) from 3.5-6ppm and 6.5-30ppm and SART errors and intra-individual variability in responding (p<.05), with increased CO exposure associated with greater number of errors and variability. These results provide support for H_2, in that if exposure effects do present in the short-term at T2 these would be negative in particular areas of cognition, including pre-potent response inhibition.

Table 5.6. Correlations between the CO ranges T1 and T2 and the cognitive measures at T2

Time 2 measures	% CO T1 0ppm	% CO T1 0.5-3ppm	% CO T1 3.5-6ppm	% CO T1 6.5-30ppm	% CO T2 0ppm	% CO T2 0.5-3ppm	% CO T2 3.5-6ppm	% CO T2 6.5-30ppm
TMTA	.047	-.012	-.209	-.178	.042	-.002	-.195	-.184
TMTB	.002	.014	-.092	-.075	.016	-.003	-.069	-.049
TMTBA	-.037	.044	-.023	-.015	-.011	.012	-.007	.013
ACE-III Total	-.069	.041	.170	.178	-.125	.096	.186	.176
WAIS-BD	-.055	.007	**.251***	**.300****	-.115	.072	**.242***	**.225***
WMS-IR	.069	-.067	-.043	-.030	.057	-.059	-.017	-.015
WMS-DR	-.044	.042	-.046	.000	-.046	.051	.004	-.009
WMS-R	.088	-.080	-.112	-.007	.087	-.089	-.043	-.006
SART-RT	.030	-.005	-.132	-.165	.082	-.053	-.164	-.154
SART Errors	.044	-.091	.291	**.230***	-.010	-.049	**.258***	**.251***
SART RTIIV	-.072	.023	**.282***	**.278***	-.038	-.014	**.242***	**.237***
CORSI-BS	-.099	.078	.144	.158	-.093	.093	.047	.025
CORSI-BSTS	-.121	.090	.196	**.228***	-.143	.136	.105	.070
TOL	**-.235***	.211	**.248***	.162	**-.240***	**.226***	.172	.149
WAIS-DSF	.049	-.069	.073	.104	-.102	.096	.071	.068
WAIS-DSB	-.024	.007	.089	.112	-.017	-.001	.096	.066
UFOV-PS	.139	-.125	-.115	-.168	.159	-.150	-.109	-.106
UFOV-DA	.012	.026	-.200	-.203	.075	-.037	-.198	-.203
UFOV-SA	-.003	.055	**-.273***	**-.238***	.041	.012	**-.252***	**-.246***

N= 78, *p<.05, **p<.01, ***p<.001

ppm= parts per million; HsH= hours spent in the home; TMT= trail making task; ACE-III= Addenbrookes cognitive examination-III; WAIS-BD=Welschler adult intelligence scale block design; WMS-IR=Welschler memory scale immediate recall; WMS-DR= delayed recall; WMS-R= recognition; SART-RT= Sustained attention response time mean reaction time; IIV= Intraindividual variability; CORSI-BS= CORSI block span; BSTS= block span total score; TOL= tower of London task; WAIS-DSF= digit span; WAIS-DSB= digit span backwards; UFOV-PS= useful field of view processing speed; DA= divided attention; SA= selective attention.

5.3.5 Regression Models

Regression model analyses are reported in two sections. Firstly, the hypotheses that the longer-term impact of chronic exposure to CO from T1 will be associated with cognitive impairments, particularly in memory recognition, auditory WM, psychomotor speed, cognitive flexibility, pre-potent response inhibition and resistance to pro-active interference and that the exposure at T2 would also be associated with negative effects in these areas were examined (H_1 & H_2). Hypothesis 3 was also examined in this section, with the exposure at T2 predicted to be associated with positive effects in the short-term on cognition (with the exception of those functions mentioned in H_2), particularly in areas of visual WM, visuospatial ability, planning, problem solving, selective attention and resistance to distractor interference (H_3).

The second investigates the total CO exposure (summated across both time points) on cognitive function, with a specific focus on the interaction between CO exposure and age on cognition. The hypotheses that the total CO over both time periods would be associated with overall negative effects on cognitive function and that the association between advancing age and cognitive decline will increase with greater CO exposure were explored (H_4).

5.3.5.1 CO Exposure at T1 and T2 on Cognitive Function

In order to examine $H_{1\text{-}3}$, hierarchical multiple regression models were developed. The models included the control variables that significantly correlated with the neuropsychological assessment scores, permitting investigation of any CO-related effects at T1 and T2, whilst controlling for the variance accounted for by these factors. Age, hours spent within the home, NART errors and depression were significantly correlated with the majority of the cognitive variables and were therefore controlled for in Block 1. The cognitive scores at T1 were also regressed on T2 scores to control for baseline performance. Variables were dropped from the regression models when their contribution was not significant to increase the degrees of freedom, with the exception of the cognitive scores at T1 and the main effects of interest (CO exposure at T1 and T2).

The contribution of each CO range was examined in separate models and entered into Block 2. These were entered for T1, to examine the longer-term effects of the previous exposure, and T2 to examine any short-term effects resulting from the second exposure. Due to the large number of cognitive variables assessed, regression models are reported only when the CO exposure significantly contributed to the variance explained by the model and for the specific significant ranges only.

5.3.5.2 Regression on WAIS Digit Span Forward (DSF): Short-term memory

Model 1: Control variables

The first model was significant, R^2=.386, F(3,69)=14.466, p<.001; adjusted R^2=.359, explaining 38.6% of the variance in DSF scores. Hours spent in the home, NART errors and DFS T1 scores were significant predictors within the model.

Model 2: Percentage of CO readings at 0ppm

The addition of the percentage of CO readings at T1 and T2 in Model 2 led to a significant increase in explained variance (R^2 *change*=.119, F(2,67)=8.026, p=.001). Model 2 was significant, R^2=.505, F(5,67)=13.657 p<.001; adjusted R^2=.468, explaining 50.5% of the variance in DSF scores. NART errors, DSF T1 scores and the percentage of CO readings at 0ppm T2 were significant predictors within the model.

Model 2: Percentage of CO readings from 0.5-3ppm

The addition of the percentage of CO readings at T1 and T2 in Model 2 also led to a significant increase in explained variance (R^2 *change*=.117, F(2,67)=7.929, p=.001). Model 2 was significant, R^2=.504, F(5,67)=13.594, p<.001; adjusted R^2=.467, explaining 50.4% of the variance in DSF scores. NART errors, DSF T1 scores and the percentage of CO readings from 0.5-3ppm T2 were significant predictors within the model.

Model 2: Percentage of CO readings from 3.5-6ppm

The addition of the percentage of CO readings at T1 and T2 in Model 2 also led to a significant increase in explained variance (R^2 *change*=.061, F(2,68)=3.935,

p=.024). Model 2 was significant, R^2=.477, *F*(5,68)=12.391, *p*<.001; adjusted R^2=.438, explaining 47.7% of the variance in DSF scores. NART errors, hours spent within the home, DSF T1 scores and the percentage of CO readings from 3.5-6ppm T2 were significant predictors within the model.

Table 5.7. Regression models with the percentage of CO readings at 0ppm and between 0.5-3ppm and 3.5-6ppm at T1 and T2 predicting variance in WAIS Digit Span Forward (WAIS-DSF) scores.

WAIS-DSF	**Variable (β)**					**R^2**	**F**
	HSH	**NART**	**DSF T1**	**CO T1**	**CO T2**		
0ppm							
Model 1	.203*	-.339**	.396***			.386	14.466
Model 2	.155	-.273**	.402***	.143	-.338***	.505	13.657
0.5-3ppm							
Model 1	.203*	-.339**	.396***			.386	14.466
Model 2	.160	-.280**	.399***	-.144	.329***	.504	13.594
3.5-6ppm							
Model 1	.221*	-.365**	.379***			.416	16.634
Model 2	.189*	-.294**	.399***	-.172	.296**	.477	12.391

*p<.05, **p<.01, ***p<.001

The significance of the percentage of readings at T2 indicates that decreased percentage of CO readings at 0ppm, signifying greater exposure, and increased exposure from 0.5-3ppm and 3.5-6ppm, were associated with higher DSF scores, indicating that greater exposure is related to better short-term memory performance (see Table 5.7 for summary model details and Table A1.3.1 for full details on each model).

5.3.5.3 Regression on UFOV Processing Speed (UFOV-PS)

Model 1: Control variables

The first model was significant, R^2=.296, *F*(2,71)=14.951, *p*<.001; adjusted R^2=.277, explaining 29.6% of the variance in UFOV-PS scores. UFOV-PS T1 scores was the only significant predictor within the model.

Model 2: Percentage of CO readings from 3.5-6ppm

The addition of the percentage of CO readings at T1 and T2 in Model 2 led to a significant increase in explained variance (R^2 *change*=.081, *F*(2,69)=4.498, *p*=.015). Model 2 was significant, R^2=.378, *F*(4,69)=10.461, *p*<.001; adjusted R^2=.341, explaining 37.8% of the variance in UFOV-PS scores. UFOV-PS T1

scores, the percentage of CO readings from 3.5-6ppm T1 and T2 were significant predictors within the model.

Table 5.8. Regression models with the percentage of CO readings between 3.5-6ppm at T1 and T2 predicting variance in UFOV Processing Speed (UFOV-PS) scores.

UFOV-PS	Variable (β)				R^2	F
	NART	UFOV-PS T1	CO T1	CO T2		
3.5-6ppm						
Model 1	-.077	.560***			.296	14.951
Model 2	-.156	.557***	.280*	-.250*	.378	10.461

*p<.05, **p<.01, ***p<.001

The significance of the percentage of readings at T2 indicates that greater percentage of CO readings from 3.5-6ppm were associated with lower UFOV-PS scores indicating better performance. In contrast, the significance of the percentage of readings at T1 from 3.5-6ppm indicates that greater percentage of CO readings were related to higher UFOV-PS scores and therefore slower processing speed at 7 months (see Table 5.8 for summary Model details and Table A1.3.2. for full details on each Model).

5.3.5.4 Regression on WAIS Block Design (WAIS-BD): Visuospatial ability and problem solving

Model 1: Control variables

The first model was significant, R^2=.734, F(2,70)=96.473, p<.001; adjusted R^2=.726, explaining 73.4% of the variance in WAIS-BD scores. WAIS-BD T1 scores was the only significant predictor within the model.

Model 2: Percentage of CO readings from 3.5-6ppm

The addition of the percentage of CO readings at T1 and T2 in Model 2 did not lead to a significant increase in explained variance (R^2 *change*=.017, F(2,68)=2.375, p>.05). Model 2 was significant, R^2=.751, F(4,68)=51.319, p<.001; adjusted R^2=.737, explaining 75.1% of the variance in WAIS-BD scores. WAIS-BD T1 scores and the percentage of CO readings from 3.5-6ppm T2 were significant predictors within the model. Age reached near significance (p=.051).

Model 2: Percentage of CO readings from 6.5-30ppm

The addition of the percentage of CO readings at T1 and T2 in Model 2 did not lead to a significant increase in explained variance (R^2 *change*=.018, $F(2,66)=2.112$, $p>.05$). Model 2 was significant, $R^2=.724$, $F(4,66)=43.228$, $p<.001$; adjusted $R^2=.707$, explaining 72.4% of the variance in WAIS-BD scores. WAIS-BD T1 score was the only significant predictor within the model. The percentage of CO readings from 6.5-30ppm T2 reached near significance ($p=.062$).

Table 5.9. Regression models with the percentage of CO readings between 3.5-6ppm and 6.5-30ppm at T1 and T2 predicting variance in WAIS Block Design (WAIS-BD) scores.

WAIS-BD	**Variable (β)**				**R^2**	**F**
	Age	**WAIS-BD T1**	**CO T1**	**CO T2**		
3.5-6ppm						
Model 1	-.089	.837***			.734	96.473
Model 2	-.127[a]	.812***	-.129	.161*	.751	51.319
6.5-30ppm						
Model 1	-.093	.821***			.706	81.672
Model 2	-.122	.815***	-.065	.171[a]	.724	43.228

*$p<.05$, **$p<.01$, ***$p<.001$, [a] near significance

The significance of the percentage of readings at T2 from 3.5-6ppm, and near significance from 6.5-30ppm, indicates that greater percentage of CO readings were associated with higher WAIS-BD scores, and therefore better performance in areas of visuospatial ability and problem solving (see Table 5.9 for summary Model details and Table A1.3.3 for full details on each model).

5.3.5.5 Regression on TMTA (Psychomotor/ Visuomotor function and speed)

Model 1: Control variables

The first model was significant, $R^2=.512$, $F(2,68)=35.704$, $p<.001$; adjusted $R^2=.498$ explaining 51.2% of the variance in TMTA scores. NART errors and TMTA T1 scores were significant predictors within the model.

Model 2: Percentage of CO readings from 6.5-30ppm

The addition of the percentage of CO readings at T1 and T2 in Model 2 led to a near significant increase in explained variance (R^2 *change*=.039, $F(2,66)=2.880$, $p=.063$). Model 2 was significant, $R^2=.551$, $F(4,66)=20.279$, $p<.001$; adjusted $R^2=.524$, explaining 55.1% of the variance in TMTA scores. NART errors, TMTA

T1 scores and the percentage of CO readings from 6.5-30ppm T2 were significant predictors within the model.

Table 5.10. Regression models with the percentage of CO readings between 6.5-30ppm at T1 and T2 predicting variance in TMTA scores.

TMT-A	Variable (β)				R^2	F
	NART	TMTA T1	CO T1	CO T2		
6.5-30ppm						
Model 1	.178*	.655***			.512	35.704
Model 2	.230*	.673***	-.141	.274*	.551	20.279

*p<.05, **p<.01, ***p<.001

The significance of CO readings at T2 indicates that greater exposure from 6.5-30ppm is associated with higher TMTA scores and therefore poorer cognitive flexibility and inhibition performance (see Table 5.10 for summary Model details and Table A1.3.4 for full Model details).

5.3.5.6 Regression on SART: intra-individual variability (RT-IIV)

Model 1: Control variables

The first model was significant, R^2=.315, F(2,73)=16.804, p<.001; adjusted R^2=.296, explaining 31.5% of the variance in RT-IIV scores. NART errors and RT-IIV T1 scores were significant predictor within the model.

Model 2: Percentage of CO readings from 3.5-6ppm

The addition of the percentage of CO readings at T1 and T2 in Model 2 did not lead to a significant increase in explained variance (R^2 *change*=.048, F(2,71)=2.669, p=.076). Model 2 was significant, R^2=.363, F(4,71)=10.120, p<.001; adjusted R^2=.327, explaining 36.3% of the variance in SART-IIV scores. RT-IIV T1 scores and the percentage of CO readings from 3.5-6ppm T1 were significant predictors in the model.

Table 5.11. Regression models with the percentage of CO readings between 3.5-6ppm at T1 and T2 predicting variance in SART intra-individual variability (SART-IIV) scores.

SART-IIV	Variable (β)				R^2	F
	NART	SART-IIV T1	CO T1	CO T2		
3.5-6ppm						
Model 1	.204*	.512***			.315	16.804
Model 2	.156	.528***	.242*	-.109	.363	10.120

*p<.05, **p<.01, ***p<.001

The significance of the percentage of readings at T1 indicates that greater percentage of CO readings from 3.5-6ppm were associated with higher RT-IIV, and therefore, greater variability in responding at 7 months (see Table 5.11 for summary Model details and Table A1.3.5 for full Model details).

5.3.5.7 Regression on UFOV-SA (Selective attention and resistance to distractor interference)

Model 1: Control variables

The first model was significant, R^2=.778, F(3,70)=81.705, p<.001; adjusted R^2=.768, explaining 77.8% of the variance in UFOV-SA scores. Hours spent in the home and UFOV-SA T1 scores were significant predictors within the model.

Model 2: Percentage of CO readings from 6.5-30ppm

The addition of the percentage of CO readings at T2 and T2 in Model 2 did not lead to a significant increase in variance explained (R^2 *change*=.015, F(2,68)=2.496 p>.05). Model 2 was significant, R^2=.793, F(5,68)=52.116, p<.001; adjusted R^2=.778 explaining 79.3% of the variance in UFOV-SA scores. Hours spent in the home, depression, UFOV-SA T1 scores and the percentage of CO readings from 6.5-30ppm T1 were significant predictors in the model.

Table 5.12. Regression models with the percentage of CO readings between 6.5-30ppm at T1 and T2 predicting variance in UFOV Selective Attention (UFOV-SA) scores.

UFOV-SA			**Variable (β)**			**R^2**	**F**
	HSH	**Depression**	**UFOVSA T1**	**CO T1**	**CO T2**		
6.5-30ppm							
Model 1	.183**	-.113[a]	.846***			.778	81.705
Model 2	.216**	-.142*	.863***	.131*	-.084	.793	52.116

*p<.05, **p<.01, ***p<.001, [a] near significance

The significance of the percentage of CO readings at T1 indicates that greater readings from 6.5-30ppm were related to higher UFOV-SA scores at 7 months and therefore reduced ability to selectively attend to stimuli and resist distractor interference (see Table 5.12 for summary Model details and Table A1.3.6 for full model details).

None of the CO ranges at either T1 or T2 were significant predictors of scores on the ACE-III, WMS immediate and delayed recall and recognition, DSB, TMTAB, UFOV-DA, TOL, CORSI, SART RT or errors (p>.05).

5.3.6 Summary of CO-related Effects at T1 and T2 on Cognition

5.3.6.1 Short-term Effects of CO Exposure at T2 on Performance at T2.

In summary, lower percentage of T2 CO readings at 0ppm, indicating increased exposure, and greater exposure from 0.5-3ppm were associated with positive effects on short-term memory. Significant positive effects of T2 exposure from 3.5-6ppm were also found in areas of short-term memory, processing speed, visuospatial ability and problem solving. A near significant positive effect of T2 exposure from 6.5-30ppm on visuospatial ability and problem solving was also observed. These findings provide support for Hypothesis 3, in that the CO exposure at T2 would be associated with short-term positive effects on cognition, particularly in visuospatial ability and problem solving. These results also replicate the findings reported in Chapter 4. However, short-term positive effects were not found in visual WM, planning, selective attention and resistance to distractor interference as predicted.

5.3.6.2 Longer-term Effects of CO Exposure at T1 on Performance at T2

Negative CO-related effects of T1 exposure from 3.5-6ppm were found in intra-individual variability in RTs and processing speed at seven months. Significant negative effects of CO were also found for the impact of T1 exposure from 6.5-30ppm on selective attention and resistance to distractor interference at seven months. These findings support Hypotheses 1, in that the longer-term impact of exposure from T1 would be associated with negative effects on cognition at seven months. There appears to be a relatively consistent pattern of results, with longer-term negative cognitive effects associated with T1 exposure at seven months, whereas the exposure at T2 was related to positive, and potentially short-term, effects.

As predicted, some of the observed findings were inconsistent with the predicted pattern of results. Significant negative effects of T2 exposure from 6.5-30ppm were found in psychomotor speed. Additionally, short-term positive effects of the

exposure at T2 were not present in areas of memory recognition, auditory WM, pre-potent response inhibition, resistance to pro-active interference and cognitive flexibility. These results provide support for Hypothesis 2, that the impact of the exposure at T2 in the short-term would be negative or not present in these areas of functioning.

Table 5.13 Tasks, cognitive domains assessed and CO level where significant effects were observed at T1 and T2

Task	**Cognitive Domain**	**Time 2 (short-term exposure)**				**Time 1 (long-term exposure)**			
		0 ppm	0.5-3 ppm	3.5-6 ppm	6.5-30 ppm	0 ppm	0.5-3 ppm	3.5-6 ppm	6.5-30 ppm
WAIS-DSF	Short-term memory	Y(+)	Y(+)	Y(+)					
UFOV-PS	Processing speed			Y(+)				Y(-)	
WAIS-BD	Visual spatial, problem solving			Y(+)	Y*(+)				
TMTA	Psychomotor speed				Y(-)				
SART-IIV	Sustained attention, IIV							Y(-)	
UFOV-SA	Selective attention, RDI								Y(-)

Y= effect present; *=nearly significant; -/+; direction of effect
RDI: resistance to distractor interference; IIV: intra-individual variability

5.3.7 Total CO Exposure and the Interaction between the Total Exposure and Age on Cognitive Function

This section examines the hypotheses that the total CO summated over both time periods would be associated with overall negative effects on cognitive function and that the relationship between advancing age and cognitive decline will increase with greater CO exposure (H_4). Regression models were developed, with the percentage of total CO exposure in each range (T1+T2) examined in separate models. Age, hours spent within the home, NART errors and depression were significantly correlated with the majority of the cognitive variables and were therefore controlled for in Block 1. The cognitive scores at T1 were also regressed on T2 scores to control for baseline performance. Variables were dropped from the regression models when their contribution was not significant, to increase the degrees of freedom, with the exception of the cognitive scores at T1 and the main effects of the total CO exposure and age. The contribution of the total CO exposure within each range was examined in separate models and entered into Block 2. Finally, an interaction term was included and entered into Block 3 to examine the relationship between the total CO exposure and age on cognitive function. Significant results are reported only.

5.3.7.1 Regression on WMS-R (memory recognition)

Model 1: Control variables

The first model was significant, R^2=.474, F(3,71)=21.313, p<.001; adjusted R^2=.452, explaining 47.4% of the variance in WMS-R scores. NART errors and WMS-R T1 scores were significant predictors within the model.

Model 2 & 3: Percentage of total CO readings at 0ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 did not lead to a significant increase in variance explained (R^2 *change*=.004, F(1,70)=.570, p>.05). The inclusion of the interaction term in Model 3 led to a significant increase in explained variance (R^2 *change*=.030, F(1,69)=4.234, p=.043). The final model was significant, R^2=.508, F(5,69)=14.264, p<.001; adjusted R^2=.473, explaining 50.8% of the variance in WMS-R scores. NART errors, WMS-R T1

scores and the interaction term age*total CO exposure at 0ppm were significant predictors in the model.

Model 2 & 3: Percentage of total CO readings from 0.5-3ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 did not lead to a significant increase in variance explained (R^2 *change*=.006, $F(1,71)=.804$, $p>.05$). The inclusion of the interaction term in Model 3 reached near significance (R^2 *change*=.026, $F(1,70)=3.698$, $p=.059$). The final model was significant, $R^2=.506$, $F(5,70)=14.338$, $p<.001$; adjusted $R^2=.471$, explaining 50.6% of the variance in WMS-R scores. NART errors and WMS-R T1 scores were significant predictors in the model. The interaction term age*total CO exposure from 0.5-3ppm reached near significance ($p=.059$).

Model 2 & 3: Percentage of total CO readings from 3.5-6ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 did not lead to a significant increase in variance explained (R^2 *change*=.010, $F(1,68)=1.277$, $p>.05$). The inclusion of the interaction effect in Model 3 led to a significant increase in explained variance (R^2 *change*=.045, $F(1,67)=5.913$, $p=.018$). The final model was significant, $R^2=.486$, $F(5,67)=12.685$, $p<.001$; adjusted $R^2=.448$, explaining 48.6% of the variance in WMS-R scores. NART errors, WMS-R T1 scores and the interaction term age*total CO exposure from 3.5-6ppm were significant predictors in the model.

Model 2 & 3: Percentage of total CO readings from 6.5-30ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a significant increase in variance explained (R^2 *change*=.050, $F(1,70)=6.841$, $p=.011$). NART errors, WMS-R T1 scores and the percentage of total CO readings from 6.5-30ppm were significant predictors in the model. The inclusion of the interaction effect in Model 3 did not lead to a significant increase in explained variance (R^2 *change*<.001, $F(1,69)=.022$, $p>.05$). The final model was significant, $R^2=.493$,

$F(5,69)=13.402$, $p<.001$; adjusted $R^2=.456$, explaining 49.3% of the variance in WMS-R scores.

Table 5.14. Regression models with the percentage of total CO readings in each range predicting variance in WMS Recognition (WMS-R) scores and the interaction effect between age and CO.

WMS-R	Variable (β)					R^2	F
	Age	NART	WMS-R T1	CO T	Age*CO		
0ppm							
Model 1	-.103	-.300**	.479***			.474	21.313
Model 2	-.095	-.324**	.460***	-.071		.478	16.030
Model 3	-.163	-.366***	.360**	.107	.275*	.508	14.264
0.5-3ppm							
Model 1	-.107	-.309**	.474***			.474	21.625
Model 2	-.093	-.319**	.469***	.079		.480	16.376
Model 3	-.152	-.376***	.367**	-.098	-.259[a]	.506	14.338
3.5-6ppm							
Model 1	-.043	-.339**	.418***			.430	17.383
Model 2	-.044	-.364**	.401***	-.105		.441	13.409
Model 3	.315	-.343**	.529***	-.090	.408*	.486	12.685
6.5-30ppm							
Model 1	-.081	-.321**	.451***			.443	18.817
Model 2	-.077	-.350***	.418***	-.226*		.493	16.984
Model 3	-.069	-.352***	.421***	-.227*	.149	.493	13.402

*$p<.05$, **$p<.01$, ***$p<.001$, [a] near significance

The significance of the total percentage of readings from 6.5-30ppm indicates that greater exposure in this range was associated with lower WMS-R scores and therefore poorer performance. Examination of the significant interaction between the total CO exposure at 0ppm and age revealed that CO moderates the relationship between age and memory recognition, with advancing age associated with negative effects on performance but only during conditions of greater CO exposure ($r=-.62$) whereas no age-related performance effects were present during lower exposure conditions ($r=.00$). Similar effects were observed when examining the significant interaction between the total CO exposure from 3.5-6ppm (and near significant from 0.5-3ppm), with a negative effect of age on memory recognition present under greater exposure conditions only ($r=-.60$; $r=-.50$). Further examination of the interactions, by age group, revealed positive relationships between increasing CO exposure and memory recognition scores in the younger older adult group throughout the CO levels ($r=.51$; $r=.20$; $r=.29$) and negative relationships in the old older adult group ($r=-.33$; $r=-.30$; $r=-.30$).

Therefore, the negative effect of advancing age on memory recognition was present only when CO exposure is greater. Examination of these interactions by age group also revealed that the effect of age (younger older adult versus old older adult) on performance changed as a function of CO exposure. Lower exposure had little effect on performance differences between the age groups whereas increasing exposure was associated with decreased performance in old older adults and increased performance in younger older adults (see Table 5.14 for summary Model details and Table A1.3.7 for full model details. Interaction effects were plotted for interpretation purposes using bivariate models (not multivariate) and are displayed in Figures 5.1-5.6).

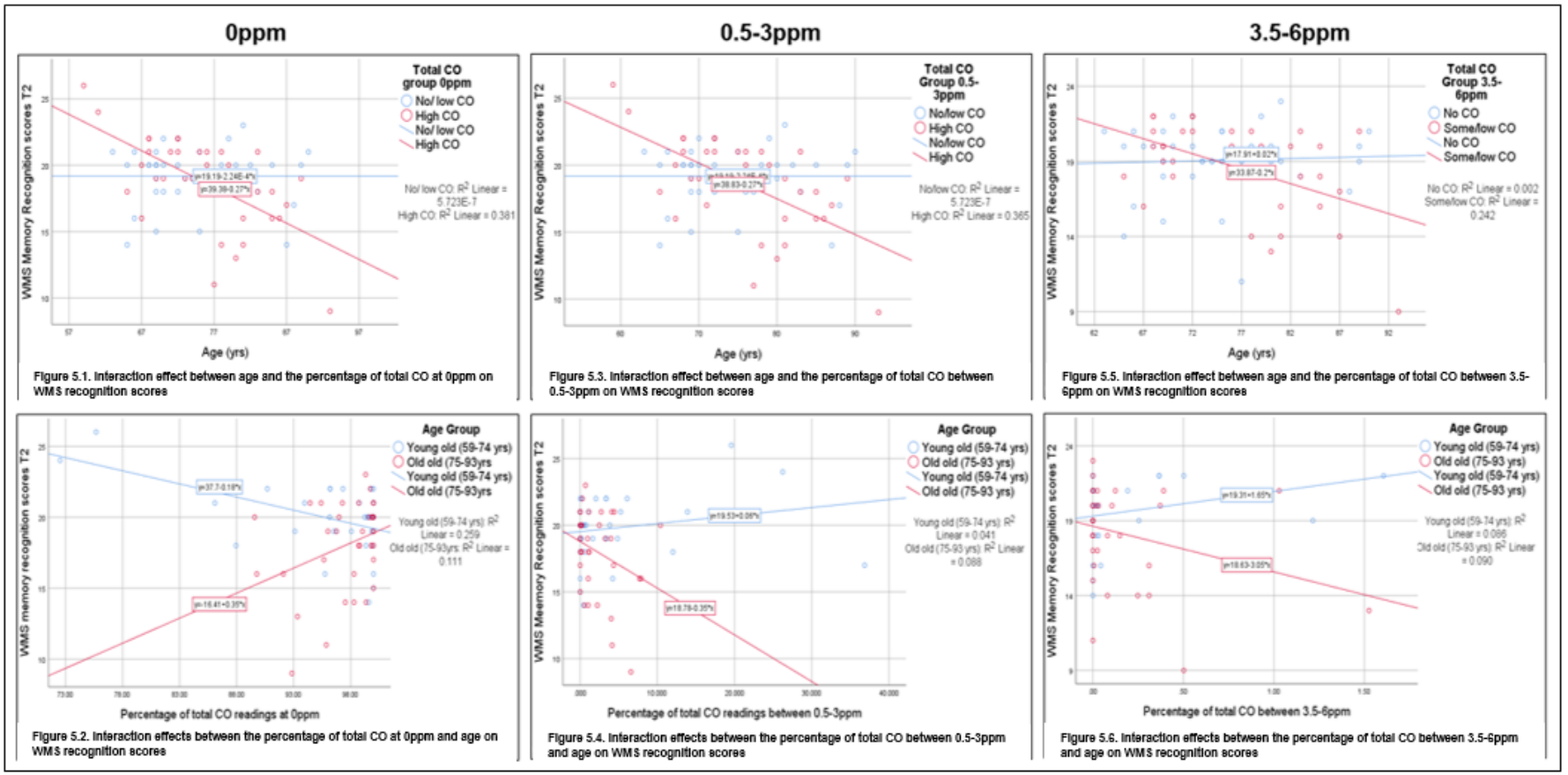


Figure 5.1. Interaction effect between age and the percentage of total CO at 0ppm on WMS recognition scores

Figure 5.3. Interaction effect between age and the percentage of total CO between 0.5-3ppm on WMS recognition scores

Figure 5.5. Interaction effect between age and the percentage of total CO between 3.5-6ppm on WMS recognition scores

Figure 5.2. Interaction effects between the percentage of total CO at 0ppm and age on WMS recognition scores

Figure 5.4. Interaction effects between the percentage of total CO between 0.5-3ppm and age on WMS recognition scores

Figure 5.6. Interaction effects between the percentage of total CO between 3.5-6ppm and age on WMS recognition scores

Figures 5.1-5.6. Interaction effects between age and total CO on WMS-R scores, with CO moderating the relationship between age and memory recognition (the graphs represent interaction effects generated using bivariate models, not multivariate models). The top row of Figures (5.1, 5.3 & 5.5) display the relationship between age (X) and performance (Y) by CO group (no/low CO; blue data points and regression line versus higher CO; red data points and regression line) for the percentage of readings at 0ppm and between 0.5-3ppm and 3.5-6ppm. Interpretation of these figures indicate that neither main effect of CO or age has a direct relationship with memory performance. The significant interaction indicates that CO moderates the relationship between age and memory recognition, in that advancing age is associated with negative effects on performance but only during conditions of greater CO exposure, whereas no age-related performance effects are present during lower exposure conditions. Further examination of the interactions by age group (younger older adults; blue data points and regression line versus old older adults; red data points and regression line) plotted by CO (X) and performance scores (Y) are displayed in Figures 5.2, 5.4 & 5.6 in the bottom row. Interpretation indicates that greater CO exposure >0ppm and between 0.5-3ppm and 3.5-6ppm is associated with increased performance scores in younger older adults and decreased performance scores in old older adults.

5.3.7.2 Regression on Digit Span Backward (DSB) (auditory working memory)

Model 1: Control variables

The first model was significant, R^2=.370, F(3,69)=13.483, p<.001; adjusted R^2=.342, explaining 37% of the variance in DSB scores. Age, NART errors and DSB T1 scores were significant predictors within the model.

Model 2 & 3: Percentage of total CO readings from 3.5-6ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a significant increase in variance explained (R^2 *change*=.038, F(1,68)=4.346, p=.041). Age, NART errors, DSB T1 scores and the percentage of total CO readings from 3.5-6ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.015, F(1,67)=1.697, p>.05). The final model was significant, R^2=.422, F(5,67)=9.786, p<.001; adjusted R^2=.379, explaining 42.2% of the variance in DSB scores.

Table 5.15. Regression models with the percentage of total CO readings between 3.5-6ppm predicting variance in WAIS Digit Span Backward (WAIS-DSB) scores and the interaction effect between age and CO.

WAIS-DSB	**Variable (β)**					**R^2**	**F**
	Age	**NART**	**DBS T1**	**CO T**	**Age*CO**		
3.5-6ppm							
Model 1	-.229*	-.336**	.305**			.370	13.483
Model 2	-.219*	-.339**	.372**	-.206*		.407	11.689
Model 3	-.387*	-.318**	.379**	-.207*	-.208	.422	9.786

*p<.05, **p<.01, ***p<.001

The significance of the total CO from 3.5-6ppm indicates that increased levels of exposure in this range were associated with lower DSB scores, signifying poorer performance in auditory WM (see Table 5.15 for summary Model details and Table A1.2.8 for full model details).

5.3.7.3 Regression on WAIS Block Design (WAIS-BD) (visuospatial ability and problem solving)

Model 1: Control variables

The first model was significant, R^2=.716, F(2,70)=88.185, p<.001; adjusted R^2=.708, explaining 71.6% of the variance in WAIS-BD scores. Age and WAIS-BD T1 scores were significant predictors within the model.

Model 2 & 3: Percentage of total CO readings from 3.5-6ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 did not lead to a significant increase in variance explained (R^2 *change*=<.001, F(1,69)=.011, p>.05). The inclusion of the interaction effect in Model 3 led to a significant increase in explained variance (R^2 *change*=.032, F(1,68)=8.625, p=.005). The final model was significant, R^2=.748, F(4,68)=50.433, p<.001; adjusted R^2=.733, explaining 74.8% of the variance in WAIS-BD scores. WAIS-BD T1 scores and the interaction term age*total CO exposure from 3.5-6ppm were significant predictors in the model.

Table 5.16. Regression models with the percentage of total CO readings between 3.5-6ppm predicting variance in WAIS Block Design (WAIS-BD) scores and the interaction effect between age and CO.

WAIS-BD	**Variable (β)**				**R^2**	**F**
	Age	**BD T1**	**CO T**	**Age*CO**		
3.5-6ppm						
Model 1	-.115	.812***			.716	88.185
Model 2	-.116	.810***	.007		.716	57.964
Model 3	.143	.863***	-.003	.309**	.748	50.433

*p<.05, **p<.01, ***p<.001

Examination of the significant interaction between CO exposure from 3.5-6ppm and age on WAIS-BD scores changes as a function of CO exposure, with no effects associated with lower exposure but greater exposure was related to better performance scores in younger older adults only (r=.32) with no effect observed in old older adults (r=.09). Therefore, increasing exposure is positively related to performance in younger older adults only (see Table 5.16 for summary Model details and Table A1.3.9 for full model details). Interaction effects were plotted for interpretation purposes using bivariate models (not multivariate) and are displayed in Figures 5.7-5.8).

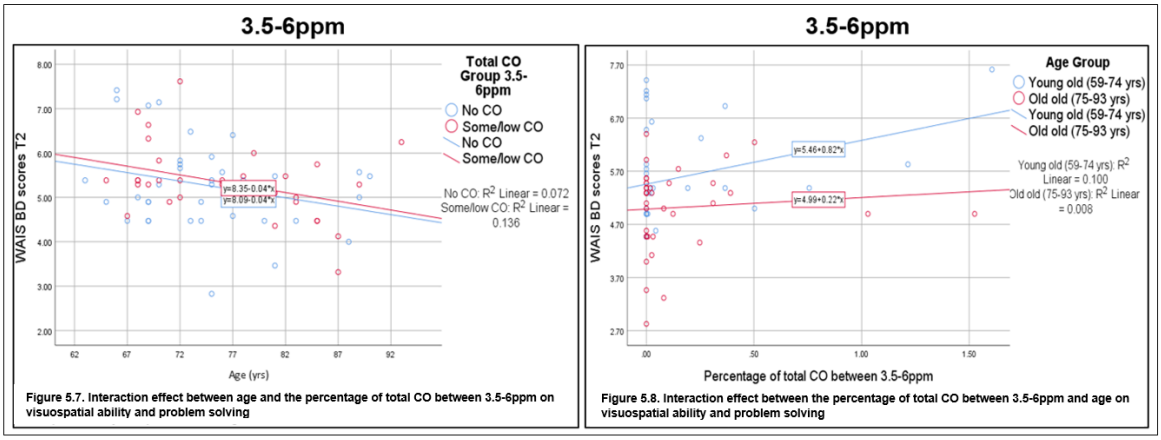


Figure 5.7. Interaction effect between age and the percentage of total CO between 3.5-6ppm on visuospatial ability and problem solving

Figure 5.8. Interaction effect between the percentage of total CO between 3.5-6ppm and age on visuospatial ability and problem solving

Figures 5.7 and 5.8. Interaction effect between age and total CO on WAIS-BD scores, with CO moderating the relationship between age and visuospatial ability and problem solving (the graphs represent interaction effects generated using bivariate models, not multivariate models). Figures 5.7 displays the relationship between age (X) and performance (Y) by CO group (no/low CO; blue data points and regression line versus higher CO; red data points and regression line) for the percentage of readings between 3.5-6ppm. Interpretation of figure 5.7 indicates that neither main effect of CO or age has a direct relationship with visuospatial ability and problem solving. Although there is a gradual decline in performance scores with advancing age this effect was not significant, and CO exposure condition had no effect on performance scores. However, examination of the interactions by age group (younger older adults; blue data points and regression line versus old older adults; red data points and regression line) plotted by CO (X) and performance scores (Y) displayed in Figure 5.8. indicates that greater CO exposure between 3.5-6ppm is associated with increased performance scores in younger older adults only with no effect observed in old older adults.

5.3.7.4 Regression on CORSI Block Span (CORSI-BS): Visual working memory

Model 1: Control variables

The first model was significant, R^2=.350 F(3,70)=12.549, p<.001; adjusted R^2=.322, explaining 35% of the variance in CORSI-BS scores. Hours spent in the home and CORSI-BS T1 scores were significant predictors within the model.

Model 2 & 3: Percentage of total CO readings at 0ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a significant increase in variance explained (R^2 *change*=.037, F(1,69)=4.121, p=.046. Hours spent in the home, CORSI-BS T1 scores and the percentage of total CO readings at 0ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.010, F(1,68)=1.162, p>.05). The final model was significant, R^2=.397, F(5,68)=8.942, p<.001; adjusted R^2=.352, explaining 39.7% of the variance in CORSI-BS scores.

Model 2 & 3: Percentage of total CO readings from 0.5-3ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a significant increase in variance explained (R^2 *change*=.035, $F(1,68)=4.045$, $p=.048$). Hours spent in the home, CORSI-BS T1 scores and the percentage of total CO readings from 0.5-3ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.015, $F(1,67)=1.822$, $p>.05$). The final model was significant, $R^2=.435$, $F(5,67)=10.310$, $p<.001$; adjusted $R^2=.393$, explaining 43.5% of the variance in CORSI-BS scores.

Table 5.17. Regression models with the percentage of total CO readings at 0ppm and between 0.5-3ppm predicting variance in CORSI Block Span (CORSI-BS) scores and the interaction effect between age and CO.

CORSI-BS	**Variable (β)**					**R^2**	**F**
	Age	**HSH**	**CORSI T1**	**CO T**	**Age*CO**		
0ppm							
Model 1	-.166	-.210*	.459***			.350	12.549
Model 2	-.111	-.200*	.484***	-.200*		.386	10.861
Model 3	-.076	-.206*	.495***	-.318*	-.152	.397	8.942
0.5-3ppm							
Model 1	-.153	-.206*	.501***			.385	14.395
Model 2	-.097	-.198*	.534***	.195*		.419	12.284
Model 3	-.053	-.209*	.549***	.345*	.190	.435	10.310

*$p<.05$, **$p<.01$, ***$p<.001$

The significance of the total percentage of readings at 0ppm and from 0.5-3ppm indicates that greater exposure was associated with higher CORSI-BS scores and therefore better performance (see Table 5.17 for summary Model details and Table A1.3.10 for full model details).

5.3.7.5 Regression on TMTAB (Cognitive flexibility and resistance to pro-active interference)

Model 1: Control variables

The first model was significant, $R^2=.601$ $F(4,71)=26.743$, $p<.001$; adjusted $R^2=.579$, explaining 60.1% of the variance in TMTAB scores. Age, hours spent in the home, NART errors and TMTAB T1 scores were significant predictors within the model.

Model 2 & 3: Percentage of total CO readings from 3.5-6ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a significant increase in variance explained (R^2 *change*=.021, $F(1,70)=3.958$, $p=.051$). Hours spent in the home, NART errors, TMTAB T1 scores and the percentage of total CO readings from 3.5-6ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in explained variance (R^2 *change*<.001, $F(1,69)=.079$, $p>.05$). The final model was significant, $R^2=.623$, $F(6,69)=18.991$, $p<.001$; adjusted $R^2=.590$, explaining 62.3% of the variance in TMTAB scores.

Table 5.18. Regression models with the percentage of total CO readings between 3.5-6ppm predicting variance in TMTAB scores and the interaction effect between age and CO.

TMTAB	Variable (β)						R^2	F
	Age	HSH	NART	TMTAB T1	CO T	Age*CO		
3.5-6ppm								
Model 1	.169*	.224**	.200*	.492***			.601	26.743
Model 2	.157[a]	.240**	.193*	.505***	.148*		.622	23.077
Model 3	.169	.238**	.193*	.508***	.146[a]	.024	.623	18.991

*$p<.05$, **$p<.01$, ***$p<.001$, [a] near significance

The significance of the total percentage of readings from 3.5-6ppm indicates that greater exposure was associated with higher TMTAB scores and therefore poorer performance (see Table 5.18 for summary Model details and Table A1.3.11 for full model details).

5.3.7.6 Regression on SART-IIV (Intra-individual variability in RTs)

Model 1: Control variables

The first model was significant, $R^2=.354$, $F(2,72)=19.705$, $p<.001$; adjusted $R^2=.336$, explaining 35.4% of the variance in SART-IIV scores. Age and RT-IIV T1 scores were significant predictors within the model.

Model 2 & 3: Percentage of total CO readings at 0ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a significant increase in variance explained (R^2 *change*=.078, $F(1,71)=9.781$, $p<.01$). Age, RT-IIV T1 scores and the percentage of total CO readings at 0ppm were

significant predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in explained variance (R^2 *change*<.001, $F(1,70)=.009$, $p>.05$). The final model was significant, $R^2=.432$, $F(4,70)=13.313$, $p<.001$; adjusted $R^2=.400$, explaining 43.2% of the variance in RT-IIV scores.

Model 2 & 3: Percentage of total CO readings from 0.5-3ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a significant increase in variance explained (R^2 *change*=.098, $F(1,73)=11.163$, $p=.001$). RT-IIV T1 scores and the percentage of total CO readings from 0.5-3ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.007, $F(1,72)=.776$, $p>.05$). The final model was significant, $R^2=.365$, $F(4,72)=10.344$, $p<.001$; adjusted $R^2=.330$, explaining 36.5% of the variance in RT-IIV scores.

Model 2 & 3: Percentage of total CO readings from 3.5-6ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a significant increase in variance explained (R^2 *change*=.044, $F(1,67)=5.423$, $p=.023$). Age, NART errors, RT-IIV T1 scores and the percentage of total CO readings from 3.5-6ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in explained variance (R^2 *change*<.001, $F(1,66)=.006$, $p>.05$). The final model was significant, $R^2=.451$, $F(5,66)=10.839$, $p<.001$; adjusted $R^2=.409$, explaining 45.1% of the variance in RT-IIV scores.

Model 2 & 3: Percentage of total CO readings from 6.5-30ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a near significant increase in variance explained (R^2 *change*=.033, $F(1,71)=3.730$, $p=.057$). NART errors and RT-IIV T1 scores were significant predictors within the model. The percentage of total CO readings from 6.5-30ppm reached near

significance (p=.057). The inclusion of the interaction term in Model 3 did not lead to a significant increase in explained variance (R^2 *change*=.029, F(1,70)=3.395, p=.070). The final model was significant, R^2=.394, F(5,70)=9.116, p<.001; adjusted R^2=.351, explaining 39.4% of the variance in RT-IIV scores. NART errors, RT-IIV T1 scores and the percentage of total CO readings from 6.5-30ppm were significant predictors within the model.

Table 5.19. Regression models with the percentage of total CO readings in each range predicting variance in SART intra-individual variability (SART-IIV) scores and the interaction effect between age and CO.

SART-IIV	**Variable (β)**					**R^2**	**F**
	Age	**NART**	**SART-IIV T1**	**CO T**	**Age*CO**		
0ppm							
Model 1	.197*		.552***			.354	19.705
Model 2	.268**		.569***	-.289**		.432	17.999
Model 3	.265**		.569***	-.279*	.013	.432	13.313
0.5-3ppm							
Model 1	.112		.482***			.260	12.996
Model 2	.177		.465***	.320**		.358	13.575
Model 3	.165		.475***	.237	-.117	.365	10.344
3.5-6ppm							
Model 1	.221*	.155	.559***			.406	15.518
Model 2	.233*	.207*	.567***	.218*		.451	13.751
Model 3	.213	.207*	.568***	.213[a]	-.021	.451	10.839
6.5-30ppm							
Model 1	.128	.202*	.501***			.332	11.908
Model 2	.115	.214*	.527***	.185[a]		.365	10.202
Model 3	.013	.253*	.522***	.213*	-.204	.394	9.116

*p<.05, **p<.01, ***p<.001, [a] near significance

The significance of the total percentage of readings at 0ppm and from 0.5-3ppm, 3.5-6ppm and 6.5-30ppm (near significance) indicates that greater exposure was associated with higher RT-IIV scores and therefore poorer performance (see Table 5.19 for summary Model details and Table A1.3.12 for full model details).

5.3.7.7 Regression on UFOV-SA (selective attention and resistance to distractor interference)

Model 1: Control variables

The first model was significant, R^2=.803, F(4,67)=68.423, p<.001; adjusted R^2=.792, explaining 80.3% of the variance in UFOV-SA scores. Hours spent in

the home, depression and UFOV-SA T1 scores were significant predictors within the model.

Model 2 & 3: Percentage of total CO readings at 0ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a significant increase in variance explained (R^2 *change*=.014, $F(1,66)=4.970$, $p=.029$). Hours spent in the home, depression, UFOV-SA T1 scores and the total percentage of CO readings at 0ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in explained variance (R^2 *change*<.001, $F(1,65)=.055$, $p>.05$). The final model was significant, $R^2=.817$, $F(6,65)=48.452$, $p<.001$; adjusted $R^2=.800$, explaining 81.7% of the variance in UFOV-SA scores.

Model 2 & 3: Percentage of total CO readings from 0.5-3ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 led to a significant increase in variance explained (R^2 *change*=.014, $F(1,66)=5.111$, $p=.027$). Hours spent in the home, depression, UFOV-SA T1 scores and the percentage of total CO readings from 0.5-3ppm were significant predictors within the model. The inclusion of the interaction term in Model 3 did not lead to a significant increase in explained variance (R^2 *change*<.001, $F(1,65)=.010$, $p>.05$). The final model was significant, $R^2=.818$, $F(6,65)=48.529$, $p<.001$; adjusted $R^2=.801$, explaining 81.8% of the variance in UFOV-SA scores.

Table 5.20. Regression models with the percentage of total CO readings at 0ppm and between 0.5-3ppm predicting variance in UFOV Selective Attention (UFOV-SA) scores and the interaction effect between age and CO.

UFOV-SA	**Variable (β)**						**R^2**	**F**
	Age	**HSH**	**Depression**	**UFOV-SA T1**	**CO T**	**Age*CO**		
0ppm								
Model 1	-.003	.168**	-.136*	.873***			.803	68.423
Model 2	.045	.180**	-.152**	.841***	-.125*		.817	58.976
Model 3	.047	.178**	-.150*	.841***	-.137	-.018	.817	48.452
0.5-3ppm								
Model 1	-.003	.168**	-.136*	.873***			.803	68.423
Model 2	.051	.179**	-.149*	.833***	.127*		.817	59.119
Model 3	.052	.177**	-.148*	.833***	.133	.008	.818	48.529

*$p<.05$, **$p<.01$, ***$p<.001$

The significance of the total percentage of readings at 0ppm and from 0.5-3ppm indicates that greater exposure was associated with higher UFOV-SA scores and therefore poorer performance (see Table 5.20 for summary Model details and Table A1.3.13 for full model details).

5.3.7.8 Regression on WMS-IR (immediate memory recall)

Model 1: Control variables

The first model was significant, R^2=.676, F(3,73)=50.879, p<.001; adjusted R^2=.663, explaining 67.6% of the variance in WMS-IR scores. NART errors and WMS-IR T1 scores were significant predictors within the model.

Model 2 & 3: Percentage of total CO readings from 0.5-3ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 did not lead to a significant increase in variance explained (R^2 *change*=.002, F(1,72)=.336, p>.05). The inclusion of the interaction term in Model 3 led to a significant increase in explained variance (R^2 *change*=.018, F(1,71)=4.277, p=.042). The final model was significant, R^2=.696, F(5,71)=32.552, p<.001; adjusted R^2=.675, explaining 69.6% of the variance in WMS-IR scores. NART errors, WMS-IR T1 scores and the interaction term age*total CO exposure from 0.5-3ppm were significant predictors in the model.

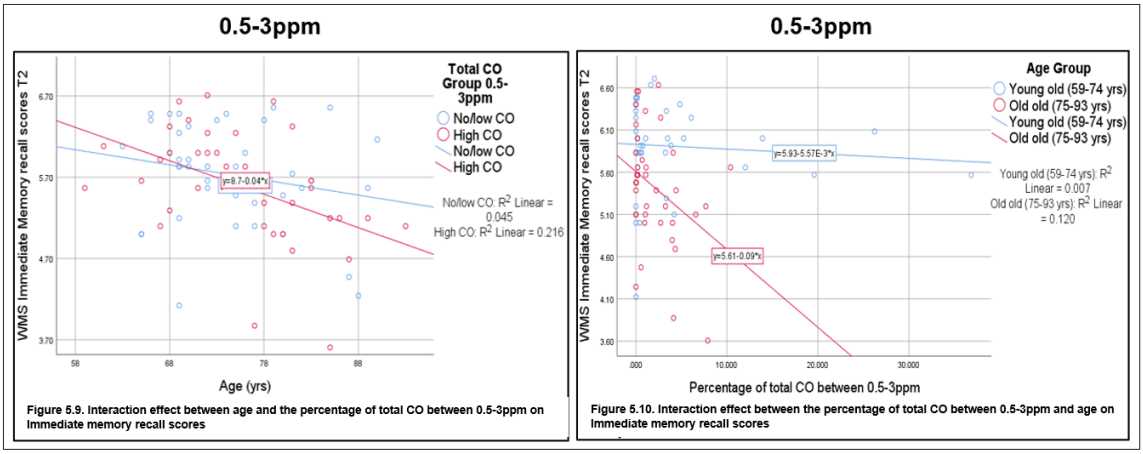
Table 5.21. Regression models with the percentage of total CO readings between 0.5-3ppm predicting variance in WMS Immediate Recall (WMS-IR) scores and the interaction effect between age and CO.

WMS-IR	**Variable (β)**					**R^2**	**F**
	Age	**NART**	**WMS-IR T1**	**CO T**	**Age*CO**		
0.5-3ppm							
Model 1	-.068	-.186*	.684***			.676	50.879
Model 2	-.078	-.184*	.678***	-.040		.678	37.896
Model 3	-.097	-.204*	.673	-.174	-.191*	.696	32.552

*p<.05, **p<.01, ***p<.001

Examination of the significant interaction between the total CO exposure from 0.5-3ppm and age revealed a gradual decline in performance scores with advancing age, an effect that was moderated by CO exposure with a stronger

relationship observed when the CO exposure was greater (*r*=-.47) compared to lower (*r*=-.21). Further examination by age group revealed that the relationship between age and performance changed as a function of CO, with lower exposure having no effect on performance scores, whereas increasing exposure was negatively related to performance in old older adults (*r*=-.35), but not in younger older adults (*r*=-.08). Therefore, increasing exposure is negatively related to performance in old older adults only (see Table 5.21 for summary Model details and Table A1.3.14 for full model details). Interaction effects were plotted for interpretation purposes using bivariate models (not multivariate) and are displayed in Figures 5.9-5.10).



Figures 5.9 and 5.10. Interaction effect between age and total CO on WMS-IR scores, with CO moderating the relationship between age and immediate memory recall (the graphs represent interaction effects generated using bivariate models, not multivariate models). Figure 5.9 displays the relationship between age (X) and performance (Y) by CO group (no/low CO; blue data points and regression line versus higher CO; red data points and regression line) for the percentage of readings between 0.5-3ppm. Interpretation of figure 5.9 indicates that neither main effect of CO or age has a direct relationship with immediate memory recall performance. There is a gradual decline in performance scores with advancing age, an effect that was stronger when the CO exposure was greater compared to lower, however neither effect was significant. Examination of the interactions by age group (younger older adults; blue data points and regression line versus old older adults; red data points and regression line) plotted by CO (X) and performance scores (Y) displayed in Figure 5.10. revealed that greater CO exposure between 0.5-3ppm is associated with decreased

5.3.7.9 Regression on WMS-DR (delayed memory recall)

Model 1: Control variables

The first model was significant, R^2=.654, F(3,68)=42.836, p<.001; adjusted R^2=.639, explaining 65.4% of the variance in WMS-DR scores. NART errors and WMS-DR T1 scores were significant predictors within the model.

Model 2 & 3: Percentage of total CO readings at 0ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 did not lead to a significant increase in variance explained (R^2 *change*<.001, F(1,67)=.002,

p>.05). The inclusion of the interaction term in Model 3 led to a significant increase in explained variance (R^2 *change*=.020, *F*(1,66)=4.085, *p*=.047). The final model was significant, R^2=.674, *F*(5,66)=27.308, *p*<.001; adjusted R^2=.649, explaining 67.4% of the variance in WMS-DR scores. NART errors, WMS-DR T1 scores and the interaction term age*total CO exposure at 0ppm were significant predictors in the model.

Model 2 & 3: Percentage of total CO readings from 0.5-3ppm and the interaction between age and CO

The addition of the percentage of total CO readings in Model 2 did not lead to a significant increase in variance explained (R^2 *change*=.001, *F*(1,71)=.139, *p*>.05). The inclusion of the interaction term in Model 3 led to a significant increase in explained variance (R^2 *change*=.020, *F*(1,70)=4.248, *p*=.043). The final model was significant, R^2=.677, *F*(5,70)=29.361, *p*<.001; adjusted R^2=.654, explaining 67.7% of the variance in WMS-DR scores. NART errors, WMS-DR T1 scores and the interaction term age*total CO exposure from 0.5-3ppm were significant predictors in the model.

Table 5.22. Regression models with the percentage of total CO readings at 0ppm and between 0.5-3ppm predicting variance in WMS Delayed Recall (WMS-DR) scores and the interaction effect between age and CO.

WMS-DR	**Variable (β)**					**R^2**	**F**
	Age	**NART**	**WMS-DR T1**	**CO T**	**Age*CO**		
0ppm							
Model 1	.034	-.230**	.686***			.654	42.836
Model 2	.034	-.230**	.686***	-.003		.654	31.656
Model 3	-.109	-.229**	.653***	-.021	.193*	.674	27.308
0.5-3ppm							
Model 1	025	-.183*	.724***			.657	45.943
Model 2	.031	-.186*	.725***	.027		.658	34.080
Model 3	-.008	-.224	.677	-.116	-.204*	.677	29.361

*p<.05, **p<.01, ***p<.001

Examination of the significant interaction between the total CO exposure at 0ppm and from 0.5-3ppm and age revealed that CO moderates the relationship between age and delayed memory recall, with advancing age related to negative effects on performance but only during conditions of greater CO exposure (*r*=-.62; *r*=-.59), whereas no age-related performance effects are present during

lower exposure conditions (*r*=-.06; *r*=-.06). Further examination by age group revealed that the relationship between age and performance changes as a function of CO, in that increasing CO exposure above 0ppm and from 0.5-3ppm was associated with slightly positive performance effects in the younger older adult group (*r*=.16; *r*=.08) and negative effects in the old older adult group (*r*=-.31; *r*=-.30). Therefore, the negative effect of advancing age on memory recognition is present only when CO exposure is greater and is related to decreased performance in old older adults and slightly increased performance in younger older adults (see Table 5.22 for summary Model details and Table A1.3.22 for full model details). Interaction effects were plotted for interpretation purposes using bivariate models (not multivariate) and are displayed in Figures 5.11-5.14).

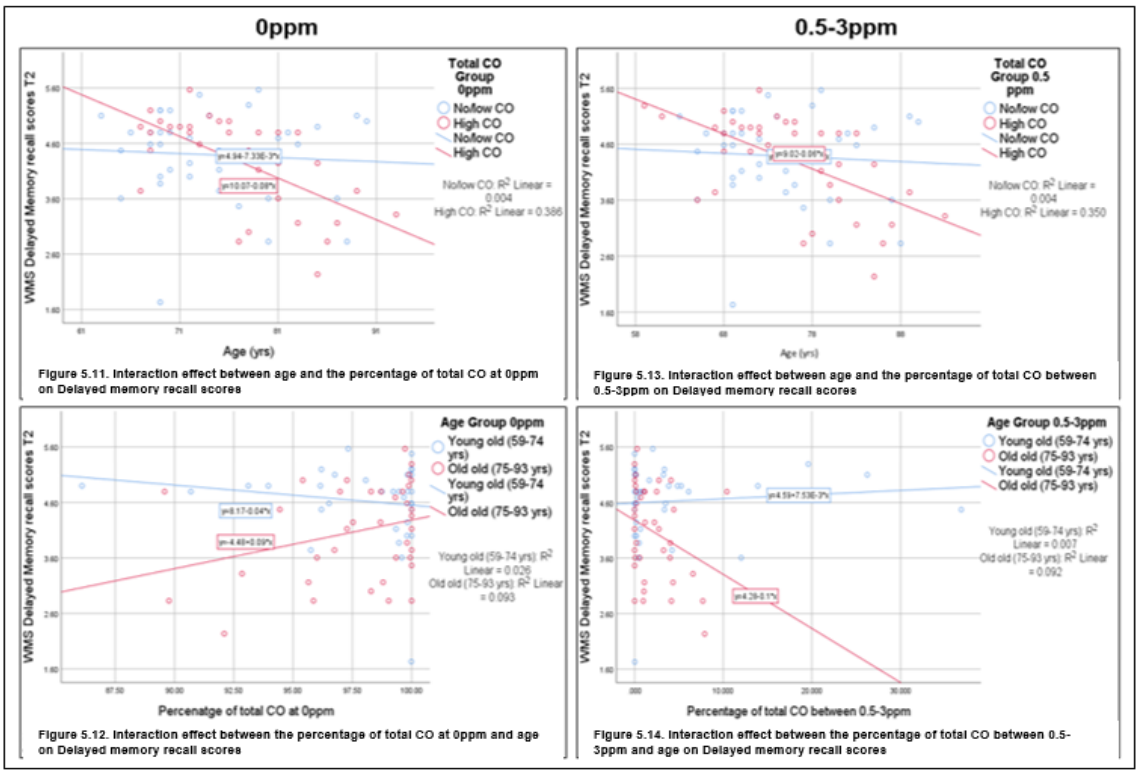


Figure 5.11. Interaction effect between age and the percentage of total CO at 0ppm on Delayed memory recall scores

Figure 5.13. Interaction effect between age and the percentage of total CO between 0.5-3ppm on Delayed memory recall scores

Figure 5.12. Interaction effect between the percentage of total CO at 0ppm and age on Delayed memory recall scores

Figure 5.14. Interaction effect between the percentage of total CO between 0.5-3ppm and age on Delayed memory recall scores

Figures 5.11-5.14. Interaction effects between age and total CO on WMS-DR scores, with CO moderating the relationship between age and delayed memory recall (the graphs represent interaction effects generated using bivariate models, not multivariate models). The top row of Figures (5.11 and 5.13) display the relationship between age (X) and performance (Y) by CO group (no/low CO; blue data points and regression line versus higher CO; red data points and regression line) for the percentage of readings at 0ppm and between 0.5-3ppm and 3.5-6ppm. Interpretation of these figures indicate that neither main effect of CO or age has a direct relationship with memory performance. The significant interaction indicates that CO moderates the relationship between age and delayed memory recall, in that advancing age is associated with negative effects on performance but only during conditions of greater CO exposure, whereas no age-related performance effects are present during lower exposure conditions. Further examination of the interactions by age group (younger older adults; blue data points and regression line versus old older adults; red data points and regression line) plotted by CO (X) and performance scores (Y) are displayed in Figures 5.12 & 5.14 in the bottom row. Interpretation indicates that greater CO exposure >0ppm and between 0.5-3ppm is associated with slightly increasing performance

The interaction between total CO exposure, across all ranges, and age was not significant in predicting levels of variance in neuropsychological scores on the TMTA, TMTAB, ACE-III, SART-RTs, intra-individual variability and errors, CORSI-BS, TOL, WAIS-DSF and DSB, UFOV-PS, DA and SA (p>.05). The total exposure across all CO ranges was not significant in predicting levels of variance in neuropsychological scores on the TMTA, ACE-III, WMS immediate and delayed recall, TOL, WAIS-BD, SART-RTs and errors, DSF, UFOV-PS or DA (p>.05).

5.3.8 Summary of the Relationship between Total CO Exposure (T1 and T2) and Cognitive Function and the Interaction between the Total CO Exposure and Age on Cognition

The results of the total CO exposure on cognition and the interaction effects between the total CO and age are presented in Table 5.23. In summary, the interaction between the total CO exposure and age on cognitive function revealed that the effect of age on cognition is moderated by CO exposure wherein the negative relationship between age and cognition was only present when the total CO exposure was greater. This was the case in areas of visuospatial ability and problem solving (3.5-6ppm), immediate memory recall (0.5-3ppm), delayed memory recall (0ppm and 0.5-3ppm) and memory recognition (0ppm, 3.5-6ppm and near significant from 0.5-3ppm). These findings provide support for Hypothesis 4, in that the relationship between age and cognitive functioning would be strengthened by greater CO exposure. Furthermore, when the interactions were examined by age group, greater CO exposure was related to increased performance in younger older adults and decreased performance in old older adults in memory recognition. This effect was also observed in delayed memory recall, with increasing CO exposure related to decreased performance in old older adults and slightly increased performance in younger older adults. In relation to immediate memory recall however, increased exposure was negatively related to performance in old older adults only, with no effects observed in younger older adults. Conversely, increased CO exposure was related to positive performance effects on visuospatial ability and problem solving in younger older adults only, with no effects observed in old older adults. Overall, greater CO exposure negatively affected aspects of both short and long-term

memory (immediate and delayed memory recall and recognition) performance in old older adults, and positively affected long-term memory performance (delayed memory recall and recognition) in younger older adults. Additionally, increased exposure positively affected visuospatial ability and problem solving performance in younger but not old older adults. The results therefore support the hypothesis that the moderating effect of greater CO exposure on the relationship between age and cognition in these areas of functioning is more dependent upon an individual's reserve capacity and resilience.

In relation to the total CO exposure, negative effects were observed in areas of cognitive flexibility and resistance to pro-active interference (3.5-6ppm), memory recognition (6.5-30ppm), selective attention and resistance to distractor interference (0ppm and 0.5-3ppm), intra-individual variability in responding (0ppm and 0.5-3ppm, 3.5-6ppm, 6.5-30ppm) and auditory WM (3.5-6ppm). These results also support Hypothesis 4, in that the total exposure would be associated with overall negative effects on cognitive function. However, the total exposure was found to be associated with positive CO-related effects on visual WM (>0ppm and 0.5-3ppm). The results from the regression models in section 2 above are summarised in Table 5.23.

Table 5.23. Tasks, cognitive domains assessed and CO level where significant effects were observed with the total exposure (Model 2) and the interaction effect between the total exposure and age (Model 3).

Task	**Cognitive domain**	**Total Exposure**				**Interaction Age* Total CO**			
		0 ppm	0.5-3 ppm	3.5-6 ppm	6.5-30 ppm	0 ppm	0.5-3 ppm	3.5-6 ppm	6.5-30 ppm
WAIS-DSB	Auditory working memory			Y(-)					
WMS-IR	Short-term memory						Y		
WMS-DR	Long-term memory					Y	Y		
WMS-R	Long-term memory				Y(-)	Y	Y*	Y	
CORSI BTS	Visual working memory	Y(+)	Y(+)						
WAIS-BD	Visual spatial ability, problem solving							Y	
TMTAB	Cognitive flexibility, inhibition (RPI)			Y(-)					
SART-IIV	Sustained attention (IIV)	Y(-)	Y(-)	Y(-)	Y(-)*				
UFOV- SA	Selective attention (RDI)	Y(-)	Y(-)						

Y= effect present; *=nearly significant; -/+; direction of effect

RPI: resistance to pro-active interference; IIV: intra-individual variability; RDI: resistance to distractor interference

5.4 Discussion

The study investigated the longer-term impact of chronic low-level CO exposure on cognitive function at seven months in an older adult sample, who as a group, are identified as particularly vulnerable to CO. Specifically, whether the observed positive effects in areas of auditory WM and memory recognition up to levels of 6ppm, and visual WM, planning, problem solving, selective attention and resistance to distractor interference from 3.5-30ppm (see Chapter 4) are short-lasting and ultimately result in impairments given sufficient exposure time was explored. Additionally, the levels at which a potential shift from beneficial effects to toxicity occurs in various aspects of cognition was examined. The research therefore aimed to increase understanding of the long-term cognitive impacts associated with chronic CO exposure including the identification of effect directions at various concentrations and patterns of impairment, with a specific focus on the impact of CO in ageing. The study aimed to contribute towards identifying thresholds of harm, which in addition to environmental factors, are likely largely dependent upon an individual's age and health status, and therefore likely underpinned by ones' reserve capacity and resilience. For example, the effects of CO exposure on the relationship between age and memory recognition, visuospatial ability and problem solving were more dependent upon these factors with positive effects present in younger older adults only. Furthermore, in some cases negative impacts were observed in old older adults (see Chapter 4). The impact of CO on functioning in the short-term following an additional months' exposure (Time 2) was also examined, thus providing a test of replication.

5.4.1 Discussion of Findings

5.4.1.1 Short-term Effects of T2 Exposure and Longer-term Impacts of T1 Exposure at seven months on Cognitive Function.

It was predicted that the beneficial cognitive effects reported in Chapter 4 would be short-lasting and ultimately result in impairments given sufficient exposure time. Long-term negative effects of the exposure from T1 were therefore predicted, particularly in areas of auditory WM, memory recognition. These cognitive domains are associated with ischaemia-sensitive brain regions, and therefore may be areas that benefit most from temporary CO-related increases in CBF. However, they are also likely to be areas most susceptible to damage when exposures exceed certain thresholds or durations. Therefore, cognitive

deficits may result in similar areas to those where beneficial effects were observed, due to the vulnerability of the hippocampus, basal ganglia and CWM to ischaemia insult, and the reliance of these functions on these regions. The positive effects on auditory WM and memory recognition observed in Chapter 4 were also present at lower levels (≤6ppm), when compared to other areas of functioning. This suggests that auditory WM and memory recognition may be more vulnerable to CO exposure and that a shift to negative impacts may occur at lower levels or shorter exposure durations in these areas. Additionally, negative longer-term effects from the exposure at T1 were also predicted in pre-potent response inhibition, resistance to pro-active interference, psychomotor speed and cognitive flexibility. These are areas where no positive effects in the short-term were observed in Study 3 and areas highlighted to be associated with negative CO-related effects in acute exposure studies in Study 1 (see Chapter 2). These aspects of cognition may therefore not follow an exposure effect trajectory of *positive-zero-negative or positive-negative effects* that may be present in other areas of functioning, but instead may be associated with negative CO-related effects only, following longer exposure durations or higher concentrations. In support of this, the longer-term impact of the exposure from T1 was associated with detrimental effects across a range of cognitive functions including processing speed, intra-individual variability, selective attention and resistance to distractor interference at seven months. However, longer-term negative impacts were not present in the specific areas predicted. Nevertheless, the longer-term impact of CO exposure on cognitive performance at 7 months appears to be negative.

It was also predicted that if exposure effects were present at T2 in the short-term in the same areas of memory recognition, auditory WM, pre-potent response inhibition, resistance to pro-active interference, psychomotor speed and cognitive flexibility, only negative impacts would be observed. The results were consistent with this *domain-specific* hypothesis, with negative effects present in the short-term following the exposure at T2 in psychomotor speed and no positive effects observed in any of the remaining areas. This supports the inference that particular areas of cognition may be more vulnerable to CO exposure, and that

specific areas may be associated with negative effects only, that present at particular doses and durations.

Positive effects on cognition were predicted to be associated with the exposure at T2 in the short-term, with the exception of the areas mentioned above, and particularly in visual WM, visuospatial ability, planning, problem solving, selective attention and resistance to distractor interference. This was based on previous findings that these specific areas of cognition appear to be more resilient to CO exposure, with positive effects observed at higher concentrations (3.5-30ppm) (see Chapter 4). In support of this, the exposure at T2 was associated with positive CO-related effects across a range of functions including processing speed, short-term memory, visuospatial ability and problem solving. The results also replicate the findings in Chapter 4 with positive effects observed in the short-term following exposure, particularly in problem solving and visuospatial ability. Overall, the results indicate that particular areas of cognition may be more vulnerable, and others more resilient, to CO exposure.

5.4.1.2 Effects of the Total CO Exposure over both Time Periods on Cognitive Function

The effects of the overall total exposure on cognitive functioning at seven months were predicted to be negative. Support for this was provided, with negative effects of the total exposure observed across a range of functions including cognitive flexibility, resistance to pro-active interference, memory recognition, selective attention, resistance to distractor interference, intra-individual variability and auditory WM. This suggests that an accumulation of two one-month exposure periods results in detrimental impacts on cognitive function. Additionally, the areas where overall negative exposure effects were observed include the majority of those predicted to be associated with longer-term negative impacts from the exposure at T1 and negative or no effects from the exposure at T2. These included memory recognition, auditory WM, resistance to pro-active interference and cognitive flexibility. The results further support the notion that particular areas of cognition may be more vulnerable to CO exposure and that specific areas, such as resistance to pro-active interference and cognitive

flexibility, may not follow an exposure trajectory of *positive-negative* effects, and instead, are negatively impacted only.

However, the overall exposure on performance at seven months was also found to be associated with positive impacts on visual WM. These results are inconsistent with the predicted negative impacts of the total overall exposure and suggest that particular areas, specifically visual WM, are more resilient to CO exposure. Therefore, whilst some cognitive areas may generally be more resilient to CO, with positive impacts observed in the short-term following the exposure at T2, impaired visual WM is possibly a late clinical symptom of less severe exposure that presents following longer exposure durations and/or higher CO levels, above those reported here.

5.4.1.3 Effect of the Total CO Exposure and Age on Cognitive Function

Due to the structural and functional changes to the vasculature and cerebrum associated with ageing and disease, it was predicted that the negative relationship between advancing age and cognition would increase with greater CO exposure. Additionally, based on findings from Study 3, the moderating effect of CO exposure on the relationship between age and memory recognition, visuospatial ability and problem solving was predicted to be more dependent upon an individual's reserve capacity and resilience. Therefore, greater exposure was predicted to be related to positive performance effects in younger older adults and negative effects in old older adults. Support for this was found, with interaction effects present between the total CO exposure and age on cognitive function. The effect of age on cognition was moderated by CO exposure, wherein the negative relationship between age and cognition was only present when the total CO exposure was greater. This was the case for areas of visuospatial ability, problem solving, immediate and delayed memory recall and recognition. Furthermore, greater CO exposure was related to increased performance in younger older adults (59-74yrs) and decreased performance in old older adults (75-97yrs) in delayed memory recall and recognition. However, the positive performance effects on delayed memory recall in younger older adults were weaker than those observed in memory recognition. In relation to immediate memory recall, increased exposure was negatively related to performance in old

older adults only, with no effects observed in younger older adults. Conversely, increasing CO exposure was related to positive performance effects on visuospatial ability and problem solving in younger older adults only, with no effects observed in old older adults.

Overall, greater CO exposure negatively affected aspects of both short and long-term memory (immediate and delayed memory recall and recognition) performance in old older adults, and positively affected long-term memory performance (delayed memory recall and recognition) in younger older adults. Additionally, increased exposure positively affected visuospatial ability and problem solving performance in younger but not old older adults. Furthermore, the positive CO-related effects on memory recognition in the younger older adult group dissipated with increasing CO. This suggests that whilst CO exposure may be associated with both beneficial and detrimental cognitive effects in older adults, these effects, in particular functions, are dependent upon other indicators of health, such as physiological and cognitive reserve capacity, intrinsic capacity and resilience, rather than age alone (see Chapter 4).

5.4.2 Overall Findings from the Cross-Sectional and Current Study

The overall results from Chapter 4 and the current study are presented in Table 5.24.

Table 5.24. Overall impacts of chronic low-level CO exposure on cognition at T1, T2, the total exposure, and interaction effects between age and the initial exposure and age and the total exposure.

Cognitive domain	Time 1 exposure (short-term)					Time 1 exposure (long-term)				Time 2 exposure (short-term)				Age*T1[1] Age*TCO[2]				
	0 ppm	0.5-3 ppm	3.5-6 ppm	6.5-9 ppm	9.5-30 ppm	0 ppm	0.5-3 ppm	3.5-6 ppm	6.5-30 ppm	0 ppm	0.5-3 ppm	3.5-6 ppm	6.5-30 ppm	0 ppm	0.5-3 ppm	3.5-6 ppm	6.5-9 ppm	6.5-30 ppm
Auditory WM (WAIS-DSB)	Y(+)	Y(+)	Y(+)*									T(-)						
Short-term memory (WMS-IR)															Y^2			
Long-term memory (WMS-DR)														Y^2	Y^2			
Long-term memory (WMS-R)	Y(+)	Y(+)	Y(+)										T(-)	$Y^{1,2}$	$Y^{1,2*}$	$Y^{1,2}$	Y^1	Y^1
Short-term memory (WAIS-DSF)										Y(+)	Y(+)	Y(+)						
Divided attention (UFOV-DA)																		
Processing speed (UFOV-PS)								Y(-)				Y(+)						
Visual WM (CORSI-BS)				Y(+)	Y(+)*					T(+)	T(+)							
Planning, problem solving (TOL)			Y(+)	Y(+)														
Visuospatial/problem solving (WAIS-BD)				Y(+)	Y(+)							Y(+)	Y(+)*	Y^1	Y^1	$Y^{1,2}$		
Visuomotor/psychomotor speed (TMTA)													Y(-)					
Cognitive flexibility, RPI (TMT-AB)												T(-)						
Sustained attention, RT, PRI (SART)																		
Sustained attention, IIV (SART)								Y(-)		T(-)	T(-)	T(-)	T(-)*					
Sustained attention, PRI (SART-errors)																		
Selective attention, RDI (UFOV-SA)					Y(+)				Y(-)	T(-)	T(-)							

Y= effect present; *=nearly significant; T= total exposure over both time periods; -/+; direction of effect

RDI: resistance to distractor interference; RPI: resistance to pro-active interference; PRI: pre-potent response inhibition; IIV: intra-individual variability; RT: reaction time

5.4.2.1 Continuum of Effects: Theoretical Perspective

The results indicate that chronic low-level exogenous CO is associated with positive cognitive effects in the short-term following exposure. This is perhaps unsurprising due to the known physiologic and cytoprotective properties of endogenous CO that also potentially arise from low-level exogenous exposure, resulting in beneficial effects on cognitive function such as those reported here. These are likely underpinned by therapeutic mechanisms such as vasodilation that temporarily increase CBF, and are likely to be of particular benefit to individuals where CBF is reduced or restricted, such as in ageing and disease-related pathology. Whether similar beneficial effects would present in healthy individuals with maximal physiological reserve is unknown. The observed beneficial cognitive effects however, appear to be transient, with evidence supporting the perspective that COHb accumulation over time, and the stress this places on the body's physiological resources, reaches a point where the body can no longer compensate and protect for the continuous uptake of CO. Subsequently, a shift from positive to negative effects appears to follow.

The effects of chronic low-level CO exposure can be viewed on a continuum; wherein one end of the spectrum represents the beneficial short-lasting effects, followed by a transition period of no effects that precede the negative, and potentially longer-term, impacts that present at the opposite end with increasing exposure duration and concentration. This transition from *positive to negative*/*positive-no-negative* effects was observed across a range of cognitive domains including auditory WM, memory recognition, selective attention, resistance to distractor interference and processing speed. Specifically, memory recognition, auditory WM, selective attention and resistance to distractor interference were positively affected in the short-term following the first exposure which were followed by an overall negative effect of the total exposure over both exposure points. Longer-term negative impacts at seven months from the exposure at T1 were also present in selective attention and resistance to distractor interference. The effects of CO on processing speed also followed a general trajectory of positive through negative impacts, although no effects were observed in the short-term following the first exposure, positive effects in the short-term following a second exposure period were present alongside negative

longer-term impacts of the initial exposure at seven months. Therefore, exposure to chronic low-level CO for at least one-month from 0.5-6ppm may lead to temporary performance increases in auditory WM and memory recognition in the short-term. However, these positive short-lasting effects were not present following an additional one-month exposure period, and led to negative impacts following accumulation of at least two months exposure between 3.5 and 6ppm. Additionally, chronic exposure to low-level CO from 9.5-30ppm for one-month may be associated with performance increases in selective attention and resistance to distractor interference. Similarly, these positive effects were short-lasting with negative longer-term impacts present at seven months between 6.5-30ppm. Furthermore, accumulation of at least two months exposure appears to negatively impact selective attention and resistance to distractor interference at even extremely low-levels (0.5-3ppm).

The results also indicate that particular areas of cognition including psychomotor speed, intra-individual variability, cognitive flexibility and resistance to pro-active interference may not follow a trajectory of *positive-zero-negative or positive-negative effects* observed in other areas of functioning. Instead, these areas of functioning appear to be related to negative effects only, that present given either sufficient exposure time, time post-exposure or exposure accumulation. CO-related effects in these areas were not observed following the initial exposure in the short-term, neither were any positive effects observed in the long-term or short-term following the exposure at T2. Specifically, the exposure at T2 was associated with detrimental effects on psychomotor speed in the short-term, and overall negative impacts of the total exposure were present in cognitive flexibility, resistance to pro-active interference and intra-individual variability. Negative long-term impacts of the initial exposure were also observed at 7 months on intra-individual variability. These results are supported by evidence from acute exposure studies indicating that impaired cognitive flexibility and psychomotor speed follow low-level exposure to higher concentrations, and suggest that deficits in these areas may also present at lower levels given sufficient exposure time, post-exposure time or following an accumulation of two exposure periods (see Chapter 2 and 4).

Finally, particular aspects of cognition were associated with positive exposure effects only, including short-term memory, visual WM, planning, problem solving and visuospatial ability. Specifically, no CO-related effects were present in the short or long-term following the initial exposure in short-term memory, but positive impacts followed the second exposure period in the short-term. Planning ability was positively affected in the short-term following the initial exposure period. Visuospatial and problem solving ability were positively affected in the short-term following the initial and second exposure periods. However, no longer-term impacts were associated with the first exposure or the total exposure over both periods in these functions. In relation to visual WM, positive effects in the short-term following the initial exposure period were observed as were positive effects of the total exposure over both periods. Whether these are followed by a transient period of no effects, prior to a shift to negative impacts at a certain unknown level is currently unknown. However, with an extensive amount of literature documenting the negative impacts of CO on neuropsychological function, it is likely that negative impacts do follow at a certain unknown level and duration above those reported here.

The results therefore support the view that particular areas of cognition may be more vulnerable, and others more resilient to, chronic low-level CO exposure. Processing speed, intra-individual variability, selective attention and resistance to distractor interference appear to be more sensitive to CO exposure, with longer-term negative impacts associated with the exposure from T1. The total overall exposure across all ranges for intra-individual variability and the two lowest ranges for selective attention and resistance to distractor interference were also associated with negative impacts. Memory recognition, auditory WM, cognitive flexibility, resistance to proactive interference and psychomotor speed also appear to be more vulnerable to CO exposure. These areas were not associated with longer-term negative impacts from the initial exposure but instead were dependent on a second months exposure (negative effects in the short-term following the exposure at T2) or an accumulation of two one-month exposure periods (total overall CO). However, other areas of cognition, including visual WM, planning, problem solving and visuospatial ability, appear to be more resilient to CO exposure with positive effects observed only. These areas show

greater resistance to CO, with negative impacts potentially occurring at higher concentrations or longer exposure durations, or time post-exposure.

The inference that the brain regions that benefit most from CO-related temporary increases in CBF, are also areas most susceptible to damage when levels or exposure durations exceed particular thresholds was also supported by associated cognitive functions. The brain regions identified as vulnerable to ischaemia insult include the hippocampus, basal ganglia and the CWH (Ruitenberg et al., 2005; Moody, Bell, & Challa, 1990; Pullicino, Caplan, & Hommel, 1993; Donnan et al., 1995). These cerebral areas are associated with cognitive functions similar to the pattern of performance improvements and declines observed, with *domain-specific* shifts from positive to negative CO-related effects observed in areas of auditory WM, memory recognition, selective attention, resistance to distractor interference and processing speed. For example, WMH have been associated with deficits in executive functioning (EF) and processing speed (Gunning-Dixon & Raz, 2000). Slowed processing speed is thought to be largely due to diffuse disintegration of CWM integrity (Madden, Bennett, & Song, 2009) and EF relies heavily on complex CWM networks for connectivity between distributed neural systems (Morris, Craik & Gick, 1990; Andres, 2003). Progressive demyelination can disconnect the cortex and subsequently lead to functional disruptions in neurocognitive networks and subsequent EF deficits (Geschwind, 1965; Nickel & Gu, 2018; Gunning-Dixon & Raz, 2000; see Chapter 4 for further details on cognitive functions and their associated brain regions). Prolonged hypoperfusion can then gradually spread to other more ischaemic-resistant brain regions leading to neuronal death in these areas resulting in further cognitive impairment and eventually Alzheimer's Disease (AD) (de la Torre, 2012).

The underlying processes however, are likely to be multifaceted, underpinned by several mechanisms triggered in response to various physiological states, rather than ischaemia alone, such as immunologic and inflammatory responses. These hypoxic-independent mechanisms have been implicated in CO toxicity. For example, CO can cause structural alterations to myelin basic protein triggering immunologic responses which subsequently cause progressive demyelination of

the CWM and inflammation (Weaver, 2009). This demyelination process can result in cognitive impairments in areas that are heavily dependent upon connectivity between brain regions, such as EF (Andres, 2003; Morris, Craik & Gick, 1990; Geschwind, 1965; Nickel & Gu, 2018; Gunning-Dixon & Raz, 2000). Demyelination resulting from immunologic and inflammatory responses may also present following less severe chronic CO exposures. These processes, combined with the ischaemia risk prolonged CO exposures present, may escalate damage resulting in greater cognitive deterioration.

5.4.2.2 Theoretical Perspective: Knowledge Contributions

These findings advance understanding in an area where there is a significant knowledge gap. The proposed model of a CO exposure effect trajectory, whereby various concentrations and durations and their associated effects can be viewed on a continuum from positive through to negative impacts (with a transition period of no effects sometimes present) increases theoretical understanding of less severe exposures, an area where knowledge is extremely limited. Furthermore, it provides a possible explanation for the inconsistent findings within the CO-behavioural literature, in that, the proposed continuum can account for the reported negative effects, absence of effects, and trends towards positive impacts, by small variations in exposure concentration and duration. For example, the results presented here are associated with CO concentrations that are relatively low and without a substantial range in the data (0-29ppm), yet there was great variation not only in the direction of effects but also the areas of cognition affected. This provides invaluable insight into how small variations in the exposure concentration can greatly influence the observed results, without accounting for other substantial differences between studies such as the sample studied (i.e. health status and age). The research findings therefore not only bridge the knowledge gap between the potential beneficial effects and toxicity by providing a possible explanation for the conflicting findings within the literature but also offer a viewpoint that encompasses these inconsistencies into a united perspective, in turn, alleviating some of the confusion that surrounds low-level CO exposure. The proposed perspective is therefore compatible with review papers highlighting the protective and therapeutic effects of CO and the subsequent administration of low-level inhaled CO for neuroprotection in recent

clinical trials, but also the abundance of evidence documenting the toxic effects of CO.

5.4.2.3 Thresholds of Harm: Clinical Perspective

The theoretical viewpoint detailed above explains the pattern of results, from beneficial through to negative effects. However, from a clinical perspective, it is important that focus is directed to the CO level and duration at which particular effects became apparent, the direction of such effects, and the cognitive functions affected. One of the most important findings of the study, in regards to clinical practice and diagnosis, is the ability to highlight particular areas of cognition that are most affected by CO and the thresholds at which harm is initiated. The following section therefore focuses on the level and duration at which negative effects resulted, in order to highlight the areas most and least affected by low-level CO. However, in the same way, it is also possible to identify the cognitive areas that potentially benefit most from low-level inhaled CO for use in clinical trials and importantly the levels at which protective effects occur, and crucially, dissipate. However, this is not the focus here, with the emphasis on thresholds of harm. Additionally, the pattern by which the negative effects became apparent (i.e. whether positive effects or no effects preceded the negative), are not considered in this section, with the focus solely on the level and duration that negative impacts became apparent, irrespective of the trajectory of effects preceding these.

Early clinical signs of exposure: most vulnerable cognition functions

Intra-individual variability appears to be an early clinical sign of chronic low-level exposure, with longer-term negative CO-related effects observed at seven months from 3.5-6ppm following the initial exposure period of at least one month. Following this, impaired selective attention and resistance to distractor interference appear to follow with negative longer-term impacts from the initial one-month exposure period observed at slightly higher exposure concentrations of 6.5-30ppm. The negative impact of CO on these functions was also supported by the detrimental effect of the total exposure over both exposure periods. These were observed at extremely low levels, with all of the CO ranges associated with negative impacts in intra-individual variability and the lowest two ranges for

selective attention and resistance to distractor interference. Therefore, extremely low-level CO (from 3.5-30ppm) for a least one month may lead to longer-term negative impacts intra-individual variability, selective attention and resistance to distractor interference. Furthermore, accumulation of two one-month exposure periods may lead to negative impacts in intra-individual variability, selective attention and resistance to distractor interference, even at extremely low concentrations (0.5-3ppm). Slowed processing speed may also be one of the early signs of chronic exposure to low-level CO, with longer-term negative effects observed at seven months from 3.5-6ppm following the initial exposure period of at least one month. However, positive effects in the short-term following the second exposure period were observed between 3.5 and 6ppm. It is likely that these positive impacts are short lasting and followed by longer-term negative impacts. However, the presence of positive effects following the second exposure period and lack of overall negative effects of the total exposure on processing speed suggests that the exposure level and duration at which positive effects completely dissipate and negative impacts strengthen has not yet been reached.

5.4.2.4 Middle-stage clinical signs of exposure

Following the early signs of chronic low-level exposure, CO-related effects appear to present across a range of cognitive functions including memory recognition, auditory WM, cognitive flexibility, resistance to pro-active interference and psychomotor speed. These areas were not associated with longer-term negative impacts from the initial exposure but instead were dependent on a second months exposure (negative effects in the short-term following the exposure at T2) or an accumulation of two one-month exposure periods (total overall CO), suggesting greater resilience to CO exposure. Specifically, auditory WM, cognitive flexibility and resistance to proactive interference were negatively impacted by the total overall exposure from 3.5-6ppm and memory recognition from 6.5-30ppm. Negative effects in the short-term following the exposure at T2 were observed in psychomotor speed between 6.5 and 30ppm. Therefore, an accumulation of two one-month exposure periods (total CO) between 3.5 and 30ppm may be associated with detrimental impacts on memory recognition, auditory WM, cognitive flexibility and resistance to pro-active interference and exposure for a second one-month period from 6.5-30ppm

with negative effects on psychomotor speed. The overall deleterious effect of the total exposure on these areas of functioning, with the exception of psychomotor speed, potentially indicate longer-term impacts, similar to those associated with the initial exposure at seven months that were observed in other areas of cognition. However, without additional longitudinal follow up this is currently unknown.

Late clinical signs of exposure: more resilient cognitive functions

Finally, particular aspects of cognition appear to be more resistant to CO exposure including short-term memory, visual WM, planning, visuospatial ability and problem solving. Only positive CO-related effects were present in these areas of functioning. Specifically, positive effects in the short-term followed the initial exposure in planning from 3.5-9ppm. However, positive effects were not present following a second one-month exposure period, in the long-term following the initial exposure or an accumulation of both exposure periods (total CO). This potentially suggests that planning ability may be the first of these more resilient functions to be negatively affected by CO exposure, with detrimental impacts potentially observed at higher concentrations or longer exposure durations. However, this inference is based on the absence of observable positive effects longer-term or following an additional exposure, and therefore without further longitudinal study is currently unknown. Short-term memory was positively affected in the short-term following the second exposure period from 0.5-6ppm and visuospatial ability and problem solving in the short-term between 6.5 and 30ppm following the initial exposure and between 3.5-30ppm following the second exposure period. However, positive effects were not present in the long-term following the initial exposure at seven months or associated with the total exposure in either function. The absence of longer-term and overall exposure effects perhaps suggest that the positive effects observed in planning, short-term memory, visuospatial ability and problem solving are short lasting.

Visual WM however, appears to be most resilient to CO, with positive effects present in the short-term following the initial exposure (6.5-30ppm) and positive impacts associated with the total overall exposure over both periods, albeit at lower concentrations (0.5-3ppm). It is likely that detrimental effects in visual WM

follow the observed positive effects at higher concentrations or longer exposure durations. In support of this, the positive effects on visual WM in the short-term following the initial exposure period were observed in the highest ranges (6.5-30ppm), whereas the positive effects of the total exposure were only present in the lowest ranges. This may suggest that a transition period precedes the shift to negative effects, with no effects observed from 3.5-30ppm following at least two one-month exposure periods, and negative impacts likely following at a certain point that exceeds these thresholds. In summary, these areas of cognition, particularly visual WM, appear to be more resistant to CO with no negative impacts observed following at least two months exposure up to levels of 30ppm. However, detrimental effects in these areas likely follow the observed positive effects at higher concentrations or longer exposure durations. Impairments in these areas of functioning, may therefore be late clinical cognitive symptoms of less severe exposure, particularly deficits in visual WM.

5.4.2.4 Clinical Perspective: Implications

The identification of areas most and least affected by CO has important clinical implications for use in diagnosis and treatment and may assist in the determination of exposure severity. For example, the presence of deficits in areas more vulnerable to CO, such as intra-individual variability, may indicate extremely low-level exposure, whereas impairments in areas more resilient, such as visual WM, potentially signify more severe low-level exposure (i.e. longer exposure durations or higher concentrations). However, it is important to note that this arbitrary grading of cognitive functions into a proposed theory of vulnerability to CO, with most through to least, is not without limitation. Although underpinned by inductive reasoning through observation of patterns within the data presented throughout this thesis, evidence from other sources is extremely sparse. Nevertheless, it makes a very significant contribution to knowledge, proposing a theory that explains the effects of low-level CO exposure on cognition, from areas most vulnerable to those most resilient, providing a foundation for future research and ultimately for use in clinical settings.

5.4.3 Impacts of CO on Advancing Age

Perhaps the most concerning findings of the research are the negative impacts chronic low-level CO exposure appears to have on the relationship between advancing age and cognition in areas of visuospatial ability, problem solving, immediate and delayed memory recall and recognition. The results from Study 3 indicated that greater exposure strengthened the negative relationship between advancing age and memory recognition and visuospatial ability and problem solving compared to lower exposure whereby the relationship was weakened. This suggests that greater CO exposure potentially accelerates the decline associated with ageing in these areas. Furthermore, greater exposure was associated with positive effects, and therefore better performance, in younger older adults, and negative effects in old older adults, with performance scores in these cognitive areas decreasing with increasing CO.

Results from the current study revealed a similar pattern, however main effects of age were not present. Instead, the effects of age on performance were completely dependent on CO level, wherein the negative relationship between age and cognition was only present when the total CO exposure was greater. Similar to the findings from Study 3, greater CO exposure was related to increased performance in younger older adults (59-74yrs) and decreased performance in old older adults (75-97yrs) in delayed memory recall and recognition. In relation to immediate memory recall, increased exposure was negatively related to performance in old older adults only, and positive performance effects on visuospatial ability and problem solving were observed in younger older adults only. The results from both studies indicate that greater CO exposure negatively affects aspects of both short and long-term memory (immediate and delayed memory recall and recognition) performance in old older adults, and positively affects long-term memory performance (delayed memory recall and recognition) in younger older adults. Increased CO exposure also has positive impacts on visuospatial ability and problem solving performance in younger older adults, and negative or no effect on performance in old older adults.

The CO-related effects reported may be present in older adult samples only, with physiological mechanisms such as vasodilation temporarily increasing CBF where this is reduced or restricted. However, COHb accumulation over time appears to result in negative impacts in older adults across a range of cognitive domains. Furthermore, particular areas of functioning appear to be more dependent upon physiological and cognitive reserve capacity, intrinsic capacity and resilience, than other areas, with positive effects observed in younger older adults. However, in old older adults, who are more likely to be frail, COHb accumulation and the additional burden this places on biological systems that are potentially close to, or already failing, appears to be detrimental. Chronic exposure to low-level CO may therefore place an already susceptible group at an even greater risk of early cognitive decline and dementia development beyond that associated with ageing and disease. These findings suggest that measures of frailty, rather than age alone, may be better indicators of CO vulnerability and potentially would provide a more accurate account of the impacts of CO in older adults.

The vascular alterations observed in ageing and cardiovascular disease and their effects on CBF along with age-related cerebral changes, such as atrophy of the hippocampus and WMH, have all been associated with greater risk of early cognitive decline and dementia development (David & Taylor, 2004; Belohlavek et al., 2009; Jerskey et al., 2009; Jefferson et al., 2007; Forti et al., 2006; den Heijer et al., 2006; Smith et al., 2008; Bigler et al., 2002). Furthermore, ischaemic sensitive brain areas such as the hippocampus, basal ganglia and the CWM are also areas commonly damaged following CO exposure (O'Donnell et al., 2000; Porter et al., 2002; Varrassi et al., 2017; Gale et al., 1999; Gale & Hopkins, 2004; Hou et al, 2013). The direct binding of CO to haem in these areas may explain their increased vulnerability to CO, with high iron content in brain regions such as the globus pallidus (Auer, Dunn, & Sutherland, 2007). The double burden of the direct binding of CO to haem and ischaemia sensitivity of these areas therefore poses an even greater risk of damage. Moreover, the risk of direct binding of CO to haem may be increased in older adults, with iron accumulation in specific regions associated with the ageing brain (Zecca et al., 2001; Zecca et al., 2004). This accumulation of iron is associated with brain injury and is

observed in neurodegenerative diseases, in higher concentrations than those related to healthy ageing, and may therefore be a significant risk factor (Ward, Zucca, Duyn, Crichton, & Zecca, 2014). It is alarming that the results presented in Study 3 and 4 indicate the possibility that chronic exposure at even low-levels appears to add to this burden, placing an already susceptible group at an even greater risk of early cognitive decline and potentially dementia development beyond that associated with ageing and disease.

5.4.4 Directions for Future Research

The results presented in the current study suggest that chronic exposure to low-level CO can result in longer-term cognitive impairments. Future research should be directed to the longitudinal study of the cognitive impacts of chronic low-level CO exposure in older adults, in order to build on the findings presented, and to extend findings by examining the potential relationship between chronic low-level CO exposure and MCI and dementia development. Evidence of a link between CO exposure and dementia development risk has gained attention over the last decade. Two retrospective studies found that the overall incidence rate of dementia was 1.56 fold (Lai et al., 2016) and 3.63 fold (Wong et al., 2016) higher in CO poisoned patients than in the non-CO poisoned patients, indicating that CO poisoned patients are at a higher risk of developing dementia. Of great concern are the results from epidemiological studies, that indicate chronic exposure to extremely low-level CO may increase risk of dementia (Chang et al., 2014), with air pollution recently identified as a dementia development risk factor in later life (>65) (Livingston et al., 2020). Furthermore, case reports of chronic home exposure also indicate associations between less severe exposures and neuropsychological impairments (Nakamura et al., 2016).

However, whether the impairments reported in the current study are persistent in nature and can result in demyelination or more severe damage such as necrosis is unknown. They are unlikely to cause a hypoxic state severe enough to cause immediate damage but may result in varying degrees of damage given sufficient exposure time. This is supported by imaging findings of the two patients described by Nakamura et al., (2016) with atrophy of the hippocampus, lesions of the basal ganglia and WMH observed. It is possible that both the cognitive

decline and atrophy of the medial temporal lobe, including the hippocampus, were due to the development of AD. However, the observed normalisation of COHb levels in both patients, alleviation of symptoms, and improved cognitive functioning post-exposure suggests that both patients had been exposed to chronic low-level CO. The authors surmised that the clinical manifestations of both patients may, in part, be associated with chronic low-level CO exposure (Nakamura et al., 2016). These findings indicate that prolonged lower exposures may be associated with damage in areas similar to those observed in severely poisoned patients and that COHb accumulation over time may be an important risk factor in dementia development. However, future longitudinal studies are needed that examine the risk for early cognitive decline and dementia development in older adults chronically exposed to low-level CO, in order to answer these important questions.

The findings reported above present significant public health concern, particularly to the older adult population, not only due to increased susceptibility but also the increased risk of home exposure due to retirement and possible restricted mobility. Recently, research has focused on risk reduction strategies in order to delay or prevent dementia by targeting associated risk factors such as diabetes, physical inactivity and social isolation and recently, air pollution. These later life risk factors are viewed as potentially modifiable with a combined estimated percentage decrease of 18% in dementia prevalence if eradicated (Livingston et al., 2020). Potential risk factors for cognitive decline and dementia development, including CO exposure, necessitate identification which in turn may result in preventative measures and reduced risk and cost (Lai et al., 2016; Ranft, Schikowski, Sugiri, Krutmann, & Kramer, 2009).

The results presented here increase understanding of the cognitive effects associated with chronic low-level CO exposure in older adults and the direction of effects at various concentrations, advancing knowledge of the levels at which these exposures present risk to cognitive function. The results also indicate possible patterns of impairment, with specific cognitive functions affected positively and others negatively at different exposure concentration and durations. However, future studies are needed, that examine greater range of CO

data than those reported here, in order to support and build on the findings presented. These studies, in addition to the findings reported, would further assist in the identification of levels at which chronic exposures become harmful to cognitive functioning in older adults and in highlighting patterns of impairment. This information would be invaluable in informing policy, guidelines and safety technology in order to keep those most vulnerable safe and would be invaluable in clinical settings to aid in the diagnosis of low-level CO exposure. The observed differences in the cognitive domains affected, and in the direction of effect, following low-level CO exposures are likely to be due to variations in the concentration, duration, population of study and potential differences in the underlying pathological mechanisms. Studies should be directed to further ascertain the level and duration at which the body's protective, and potentially beneficial, physiological responses become ineffective and harm is initiated, with a particular focus on the specific cognitive areas affected. Additionally, studies examining the effects of CO on the health and functioning of older adults, should include measures of frailty, with the results presented suggesting that this may be a better indicator of CO vulnerability than age alone.

5.4.5 Limitations

The current study has similar limitations to those addressed in the cross-sectional chapter (see Chapter 4). Additional limitations include that the inferences drawn are based on two separate CO recordings of one month periods that were seven months apart. Consequently, the exposure levels in the seven months between monitoring points are unknown, which makes forming conclusions in relation to the underlying exposure that may be responsible difficult. For example, the negative impacts on auditory working memory that became apparent in the short-term at follow-up may have resulted from an accumulation of exposure over both monitoring periods, the exposure in the seven months between monitoring, the second exposure period only or a combination of these. Including longer monitoring periods would be extremely beneficial in future studies.

A further limitation relates to the analysis of the CO exposure data. The CO levels were measured and analysed over two separate times points, with the initial exposure at T1 interpreted to reflect the longer-term impact of exposure on

cognitive performance at T2 and the exposure at T2 reflecting the impact on performance in the short-term following the second exposure period. Thus, the CO measurements were treated as two separate exposures and their effects on cognitive performance analysed as separate effects. However, the two exposure measurements could have been used to estimate a more accurate measure of an individual's longer-term average or usual exposure level, thus accounting for random measurement error. Measurement error occurs when the observed values of an exposure variable fluctuate from their true or usual values resulting in a proportion of recorded values that are higher, and others lower, than the usual values (Hutcheon, Chiolero & Hanley, 2010). It can occur from inaccurate or unreliable measurement instruments (systematic measurement error) and from intra-individual variation (random measurement error) (Lui, 1988; Hutcheon et al., 2010). For example, systematic measurement error in blood pressure measurement may arise from improper cuff size or calibration of equipment, whereas random measurement error can result from variations such as the time of day, recent diet and whether the patient was resting prior to measurement (Knuiman et al., 1998; Hutcheon et al., 2010). Random measurement error in an exposure variable can result in attenuation of the slope of the regression line explaining the relationship between the exposure (X) and outcome (Y), a phenomenon known as the regression dilution bias (RDB). As random measurement error increases in X, the spread of the observed values along the X axis increases, whilst the range of the observations on the Y axis remain constant. The increased horizontal spread of the observed values causes the regression line to flatten, resulting in the underestimation of an association (Hutcheon et al., 2010). It can occur when the observed values are based on a limited number of measurements, which results in an imperfect approximation of the usual values (Hutcheon et al., 2010). For example, many prospective observational studies have reported associations between diastolic blood pressure (DBP), based on a single measurement, and the incidence of stroke and coronary heart disease. The observed values, often taken at the start of a study (baseline), are subject to random fluctuations from an individual's usual DBP, and this use of a single measurement can lead to substantial underestimation of the true association between disease incidence and usual DBP (MacMahon et al., 1990).

Random measurement error can be minimised, and the regression dilution bias corrected for, by taking repeated measurements of X and calculating a measure of the spread of the differences between them in order to more accurately estimate the longer-term average or usual levels. Obtaining repeated measurements therefore corrects for the biasing effects of random fluctuations in baseline measurements of X, allowing for a more accurate examination of the true strength of the relationship between usual values of X (i.e. exposure) on Y (MacMahon et al., 1990; Hutcheon et al., 2010). Therefore, the two separate CO exposure measurements could have been combined in the analysis to provide a more reliable estimate of an individual's longer-term usual or average exposure, thus adjusting for the RDB, as opposed to examining the short and longer-term exposure effects from the separate CO measurements. However, it is important to note that random measurement error was minimised in the current studies due to the substantial number of repeated measurements taken (8064 CO recordings over four weeks as opposed to a single measurement) at both time points. Previous studies have highlighted that increases in ambient CO levels can be transient, making the practice of taking a single measurement inaccurate (Croxford et al., 2005a; Croxford et al., 2005b). Thus, elevated CO levels may not be identified using a single reading and such practices therefore fail to accurately reflect exposure concentrations over time. Random fluctuations in CO levels within the home may arise, for example, from day to day or time of day variations in ventilation or smoking and cooking behaviour. Recording CO measurements over a one-month period, the approach used in the current studies, therefore accounts for these fluctuations resulting in a more accurate estimate of usual CO levels over time. Therefore, the issue relates more to the interpretation of the measurements and the subsequent analysis method i.e. combining the measurements in the analysis to estimate the effect of an individual's longer-term usual exposure on performance as opposed to viewing the measurements as two separate exposures to estimate the short and longer-term effects on functioning.

In relation to the neuropsychological assessments, the majority do not have alternative forms for use in repeated testing raising the possibility of practice effects and potentially compromising test validity. However, the use of alternative

tests can result in reduced test-retest reliability. The decision to use the same assessments at both testing points was viewed to be the superior option due to the relatively long period between testing (7 months) and older adult sample studied, potentially minimising practice effects. Additionally, if practice effects were present, this effect would likely have been observed across all participants and therefore the influence this may have on the reliability of the results is small. Furthermore, the majority of participants indicated that they could not consciously remember the tasks from the prior testing point.

Chapter 6: General Discussion

The current thesis examined the cognitive effects of chronic low-level CO exposure in a sample of older adults, a group identified as particularly vulnerable. The main aims were to:

(i) systematically review the current literature on the cognitive effects of acute low-level exposure in order to identify any existing patterns of impairment

(ii) develop a data analysis method that would enable the examination of CO data alongside neuropsychological data in order to permit the identification of thresholds of harm

(iii) examine the short and longer-term cognitive effects associated with chronic low-level exposure in older adults

(iv) examine the relationship between advancing age and CO on cognitive function.

6.1 Study 1

Study 1 was a systematic review of the experimental literature on the cognitive effects of acute low-level carbon monoxide (CO) exposure (carboxyhaemoglobin (COHb) levels below 15%), with aims to ascertain whether cognitive impairments do follow such exposures, and if so, whether there exists an identifiable pattern of observable deficits. There exists a significant, albeit rather dated, body of literature on the impact of low-level acute exposures. However, findings are inconsistent and no clear synthesis existed that evaluated assessments by both primary and secondary cognitive domains. The review therefore examined the impact of acute low-level CO exposure on cognitive function by evaluating both primary and secondary functions, rather than primary function alone. The results indicated associations between acute low-level CO exposure and impaired pre-potent response inhibition at COHb levels of 5-8%, with performance on tasks requiring inhibition and selective attention unaffected by CO, but deficits present during tasks that relied heavily on inhibitory control and, in addition, task switching. Some evidence of performance declines on other tasks assessing cognitive flexibility were also found at COHb levels between 7 and 10%. No CO-

related effects were present in other executive function (EF) components, such as working memory (WM), including updating and task switching, when performance primarily relied on these constructs. It is possible that a direct association exists between acute low-level CO exposure and impaired inhibition, however given the pattern of results, it is perhaps more likely that such impairments arise only during complex tasks that rely on inhibition and other EFs such as task switching, simultaneously. This increase in cognitive demand may result in reduced cognitive control, and subsequent CO-related impairments across multiple EFs, or deficits may arise from impaired inhibitory control, in turn, affecting other EF abilities. The interrelated nature of EF constructs provides a possible explanation for the findings, with impaired inhibition resulting from increased cognitive load when tasks demand both inhibitory processes and additional EF abilities, such as task switching. Subsequently, deficits in other EF components may become evident as these rely to a certain degree on efficient inhibitory control.

An alternative explanation arises from the viewpoint that inhibition is multifaceted, comprising various constructs of inhibitory processes, including pre-potent response inhibition, resistance to distractor interference and resistance to proactive interference, that rely on distinct brain regions (Hung et at., 2018; Friedman and Miyake, 2004; Nigg, 2000). These tasks are commonly used interchangeably to assess inhibition but have been found not to correlate, indicating the presence of distinct aspects of inhibitory control as opposed to a single underpinning mechanism (Noreen & Macleod, 2015). Therefore, the tasks employed by the reviewed studies may, to a degree, be measuring different aspects of inhibitory processing thus explaining the discrepancies in findings. The results also revealed associations between impaired psychomotor speed at COHb levels of 3-4%, and possible deficits in long-term memory at COHb levels of 4-10%. It is also noteworthy that examination of the effect sizes in two included studies indicated possible associations between low-level exposure and *increased* performance in areas of sustained and divided attention, task switching and psychomotor function. However, the sample size in one of these studies was extremely small (n=4) and neither of the studies were well controlled. In summary, a pattern of deficits emerged that suggests acute low-level exposure

may be related to impaired cognitive flexibility, long-term memory, psychomotor speed and inhibition, particularly when task switching ability is required. However, these inferences were based on the review of a small number of studies, the majority of which had poor design and control measures, were unethical and carried out over 40 years ago. Nevertheless, description and categorisation of cognitive tasks matters, with synthesis by distinct cognitive domains providing an alternative explanation for some of the inconsistencies within the CO behavioural literature.

6.2 Study 2

Study 2 detailed the development of a method to analyse CO exposure data in relation to health and cognitive outcomes. Previous approaches to the study of low-level CO exposure have included acute exposure studies, case reports, home monitoring studies and epidemiological studies. However, these approaches are not without limitation, and the data analysis methods employed are not suitable for examining detailed health data in relation to exposure severity. Briefly, case reports of chronic low-level exposure are based on an individual's experience and often lack information relating to the duration and level of exposure. Determining the degree of exposure and the levels at which observed impairments became apparent is therefore difficult and the ascription of particular symptoms to various CO levels is not possible. Home monitoring studies typically report on exposure levels, the proportion of homes with low-level CO and the percentage of homes exceeding the WHO guideline limits. However, they typically lack neuropsychological testing and detailed health status information of occupants, and therefore any associated exposure effects are not examined. Furthermore, CO data is typically converted to time-weighted averages for comparison with the WHO guidelines. Whilst this method is useful in determining whether individuals are exposed to levels of CO above those recommended, it does not facilitate the analysis of short-lasting peaks with these averaged out over time intervals, nor are lower-levels of exposure, below the WHO guidelines, examined. Epidemiological studies provide invaluable insight into the associations between outdoor CO exposure and health conditions at the population level. However, they do not provide detailed health status information at the individual level, thus any subsequent inferences and conclusions drawn

are limited. Furthermore, the data analysis methods employed in epidemiological studies, such as survival analysis, are not appropriate for use in exploratory research where effect directions are not predetermined. Finally, the majority of experimental studies on acute low-level exposure are over four decades old, include extremely small samples of healthy young adults, and were not well controlled or ethical.

In order to move towards identifying thresholds of harm, the development of analysis methods was required, that enabled the examination of various CO levels and exposure patterns over time, including low-level transient increases along with more continuous rises. Study 2 outlines the development of a CO outcome measure, separated into various ranges, that facilitates the analysis of different exposure patterns and severities, in turn permitting investigation of these factors and how they relate to changes in functioning and health. Several measures were developed and tested in multiple analyses, with the percentage of CO readings between specified ranges selected, as this method provided the most reliable analyses. The results show promise, providing an alternative way to analyse exposure data in relation to health status. The measure provides a technique that permits the examination of exposure pattern and severity, and importantly, enables any associated effects to be examined at different exposure levels. This analysis approach may be fundamental in answering some of the most pertinent research questions within the CO literature, such as whether beneficial effects can result from extremely low-level exposures, and if so, identifying the level and duration at which these effects become apparent and the areas of cognition affected. Importantly, the method facilitates the examination of the levels at which harm is initiated, and the impact of exposure pattern and severity on health and neuropsychological function. Examination of these factors may provide crucial information on whether certain exposure types are more harmful, highlight areas of health and cognitive function most affected and identify the levels at which specific effects become apparent.

6.3 Study 3

Study 3 examined the cognitive effects of chronic low-level CO exposure in older adults, a group identified as particularly vulnerable to CO, with aims to advance

knowledge of the potential beneficial effects of exogenous CO and the levels at which these exposures present risk to health and neuropsychological function. The literature on low-level CO exposure, although limited and inconsistent, indicates that adverse physical health and neuropsychological sequelae can follow both acute and chronic exposure. These findings present significant concern, especially when considered alongside accumulating evidence of raised CO concentrations in a number of UK homes. However, there is also evidence of potential positive cognitive impacts, following both acute low-level exposure (see Study 2) and chronic home exposure (Volans et al., 2007). The known cytoprotective and physiological properties of endogenous CO, may be present following low-level exogenous CO exposure. These protective properties alongside tolerance and adaptation may minimise risk to the central nervous system (CNS) up to a certain dose and duration, playing a protective and potentially beneficial role. However, whether protective properties can result from exogenous CO is currently unclear, as is the threshold at which these mechanisms become ineffective and the exposure becomes toxic. These thresholds are likely to be different depending on the exposure duration and individual differences in the population of study, such as age and health status. Older adults are identified as particularly vulnerable to CO, due to the biological and physiological changes associated with ageing and disease, and are likely to develop toxicity from lower concentrations. Similarly, any beneficial effects may be dependent upon these same factors, with the potential physiological and protective properties of exogenous CO, if present, observed only in vulnerable groups such as older adults who may benefit most from any resulting therapeutic effects. Study 3 explored whether extremely low-level exogenous CO can result in beneficial effects, and if negative effects do follow, areas of impairment and thresholds of harm in older adults. A thorough neuropsychological battery was administered assessing multiple areas of cognition and continuous ambient CO concentrations were monitored in a sample of older adult homes over one month. It was anticipated that the newly developed analysis methods detailed in Study 2 would permit the examination of neuropsychological effects at various exposure concentrations, including extremely low-level CO, and this combined with neuropsychological assessment data would contribute towards determining whether beneficial effects do present, and critically, thresholds of harm.

The results indicated that greater CO exposure was associated with significantly better performance in areas of auditory WM, memory recognition, visual WM, visuospatial ability, planning, problem solving, selective attention and resistance to distractor interference. The findings indicate that chronic low-level CO exposure is related to positive, and therefore beneficial, effects in these areas of cognition. The exposure levels at which these effects became apparent in the short-term are detailed in Figure 6.1.

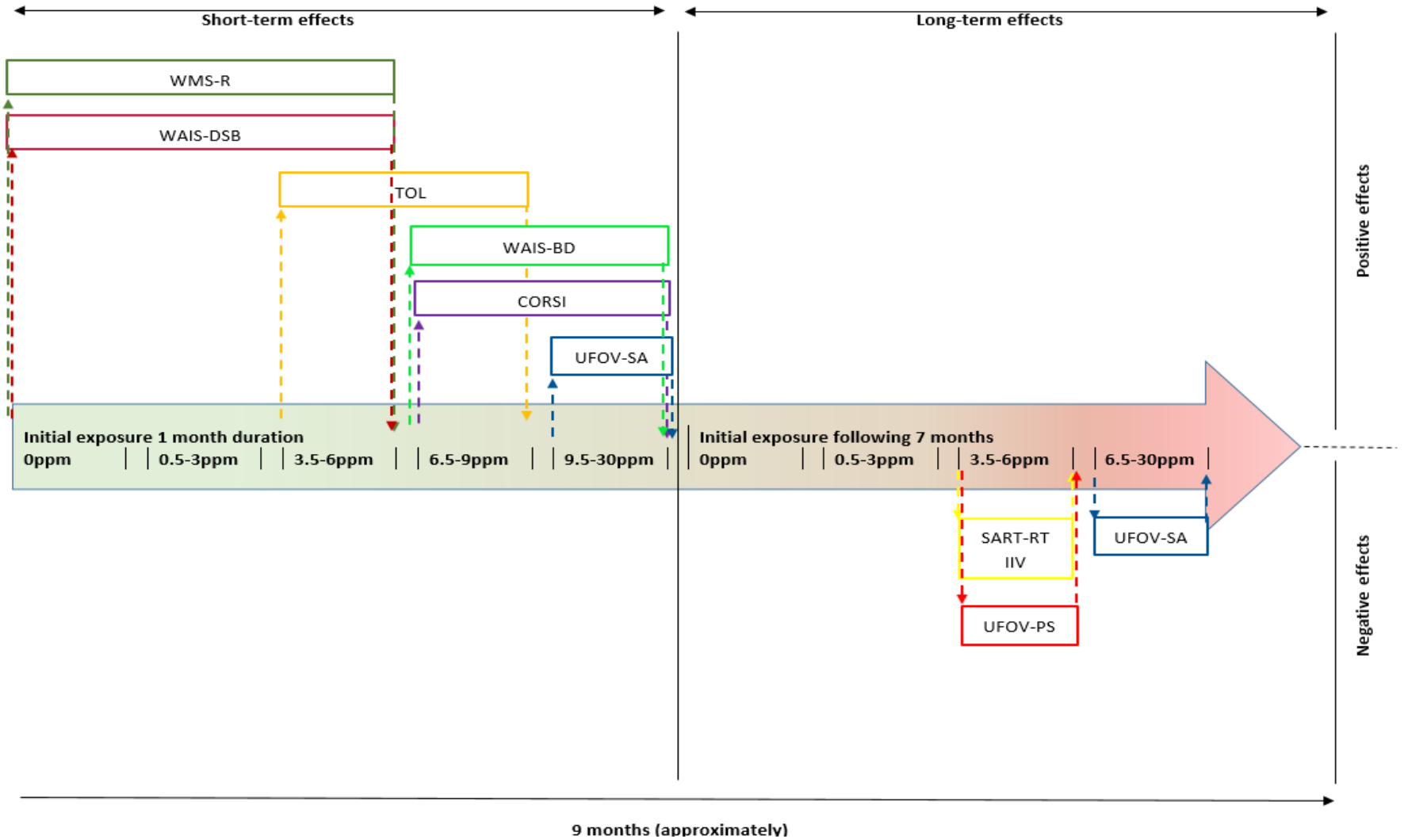


Figure 6.1. Exposure levels at which CO-related positive and negative effects became apparent in the short-term following the T1 exposure and the longer-term CO-related effects present at approximately 7 months.

The observed positive CO-related effects are perhaps not surprising, due to the extremely low-levels of CO recorded, with the highest peak in the data 29ppm, also reflected in the low COHb range observed in the non-smoking participants (0.20-1.40%). At these low levels, endogenous CO has known beneficial effects with therapeutic actions including vasodilation, proliferation, anti-apoptotic factors and anti-inflammatory properties (Prockop & Chichkova, 2007; for reviews see Mahan, 2012; Queiroga, Vercelli & Vieira, 2015). Due to its vasoactive properties, low-level exposure to CO may play a protective role to cognitive functioning by temporarily increasing and maintaining cerebral blood flow (CBF) in individuals where this is compromised, such as older adults. The vascular alterations observed in ageing and cardiovascular disease can lead to suboptimal CBF and chronic hypo-perfusion. The joint effect of these structural and functional changes on blood flow can result in a neuronal energy crisis, followed by neuronal dysfunction and death, contributing to, and increasing the risk of, cognitive decline and dementia (de la Torre, 2012; Mosconi et al., 2009). If chronic low-level exposure is associated with temporary increases in CBF, this may be particularly beneficial to older adults, playing a protective role especially to ischemic-sensitive brain regions, resulting in slightly improved functioning in the cognitive areas they are associated with. In support of this, ischemic-sensitive regions are associated with cognitive functions similar to the pattern of performance improvements observed (see Chapter 4). Exogenous CO therefore appears to result in similar beneficial effects to those associated with endogenous CO, providing an explanation for the results presented and the similar trends towards beneficial effects reported by Volans et al., (2007), with the exposures across studies representing extremely low exposure (overall means: .09ppm and 1.89ppm, respectively).

The protective properties of low-level exogenous CO, if present, are likely to be transient, with physiological resources reaching a point where the body can no longer compensate for the continuous uptake of CO. Subsequently, insufficient CBF and ischemia may follow, resulting in a shift from positive to negative cognitive impacts, with ischemia-sensitive zones most susceptible to damage when levels exceed certain thresholds. COHb accumulation over time may therefore accelerate the neuronal energy crisis-dysfunction-death cascade in

these vulnerable brain regions potentially resulting in deficits in similar cognitive areas to the beneficial effects observed. In support of this, the results revealed a pattern of effects relating to exposure level, with memory recognition and auditory WM positively affected by lower concentrations (≤6ppm), and visual WM, visuospatial ability, planning, problem solving, selective attention and resistance to distractor interference positively affected by higher concentrations (≥3.5ppm). This indicates that auditory WM and memory recognition, may be more sensitive to CO exposure, with a shift from beneficial to negative effects potentially occurring at lower concentrations compared to other areas of cognition. The effects of chronic low-level CO exposure may therefore be viewed on a continuum; with one end representing low-level exposure and potential beneficial effects, followed by negative impacts that present at the opposite end of the spectrum with increasing exposure duration and concentration. Visual WM, planning, problem solving and selective attention appear to be more resilient to CO, with positive effects present at higher exposure concentrations (3.5-30ppm). In these areas of functioning, a shift to negative impacts potentially occurs at higher concentrations or durations, above those observed. Additionally, particular areas of cognition such as psychomotor speed and pre-potent response inhibition may not follow an effect trajectory of *positive-negative* effects, and instead may be associated with negative effects only that present at a certain unknown level, above 29ppm (see Chapter 4).

A key finding of the study was that the relationship between age and memory recognition, visuospatial ability and problem solving was moderated by CO exposure. Results indicated that the negative effect of age on these areas of functioning increases with greater exposure and decreases with lower exposure. Further examination of the interaction effects by age group revealed that lower exposure had little effect on performance between the age groups, whereas increasing exposure was associated with negative performance effects in old older adults (≥75 years), and positive impacts, indicating better performance, in younger older adults (58-74 years). This suggests that whilst CO exposure may be associated with beneficial effects in older adults, these effects in particular areas of functioning are, to a certain degree, dependent upon factors such as physiological and cognitive reserve capacity and resilience (see Chapter 4). In

younger older adults, where CBF is reduced or restricted due to age and disease-related pathology, physiological mechanisms such as vasodilation may be beneficial to cognition up to a certain dose and duration. However, in old older adults, particularly those who are frail with extremely limited physiological reserve and resilience, negative impacts appear to follow CO exposure. In these individuals, exposure to CO, and the additional burden this potentially places on biological systems that are potentially close to, or already, failing appears to be detrimental to specific functions.

The results provide preliminary evidence that chronic exposure, for at least one month, may be positively associated with auditory WM and memory recognition up to levels of 6ppm, and visual WM, visuospatial ability, planning, problem solving, selective attention and resistance to distractor interference from 3.5-30ppm. Furthermore, the negative effect of advancing age on memory recognition, visuospatial ability and problem solving, were, to a degree, dependent upon greater CO exposure, with positive effects observed in younger older adults and negative impacts in old older adults. From a theoretical perspective, the results indicate a trajectory of exposure effects from *positive-negative* with increasing concentration and duration. This process may be initiated at different exposure severities for varying areas of cognition, with the transition to negative effects potentially occurring earlier along the continuum for more vulnerable areas of functioning, and later for other, more resilient areas. Particular areas of cognition however, including psychomotor speed, pre-potent response inhibition, resistance to pro-active interference and cognitive flexibility, may not follow an effect trajectory of *positive-negative* effects, and instead may be associated with negative effects only, that present at a certain unknown level, above 29ppm (see Chapter 2 & 4).

6.4 Study 4

Study 4 examined the longer-term impact of chronic low-level CO exposure on neuropsychological function in older adults, building on the results from the cross-sectional study (Chapter 4), with longitudinal follow up of the same participants including repeated neuropsychological testing and CO monitoring. Increased understanding of the long-term neuropsychological effects associated with

chronic CO exposure, the direction of such effects at various concentrations, differences across various ages within older adult groups and patterns of impairment is needed, if we are to advance knowledge of the levels at which these exposures present risk to health and neuropsychological function. The aims were to examine any potential lasting effects associated with the exposure at Time 1 (T1; cross-sectional study; Chapter 4) and to determine the impact of a second 1-month exposure period (Time 2; T2) on neuropsychological functioning at seven month follow-up. The exposure from T1, assessed at T2, therefore represented the longer-term impact that CO exposure may pose on neuropsychological function, and the exposure at T2 reflected effects in the short-term following exposure. The beneficial effects reported in Chapter 3 are likely to be short lasting, potentially observed in susceptible groups such as older adults only, and ultimately result in impairments given sufficient exposure time. Increased susceptibility in older adults is likely, due to the already sub-optimal CBF and hypo-perfusion associated with the vasculature changes present in ageing and disease. The brain regions that potentially benefit most from CO-related temporary increases in CBF may also be areas most susceptible to damage when levels exceed certain thresholds, due to ischemia sensitivity. This may result in deficits in similar cognitive areas to those where beneficial effects were observed (see Chapter 4).

The theory of a CO effect trajectory from beneficial through to negative effects with increasing exposure duration and concentration was also examined. The results from Study 3 indicate that this transition to negative impacts may vary depending on the area of functioning, with the shift potentially initiated at different exposure severities. For example, memory recognition and auditory WM were positively affected by lower concentrations (≤6ppm). These observed positive effects disappeared with increasing CO and were present up to levels of 6ppm only, suggesting that a transient period of no effects may follow the positive, prior to the shift to negative impacts at a certain unknown level and duration. This indicates that auditory WM and memory recognition, may be more sensitive to CO exposure, with a shift from beneficial to negative effects potentially occurring at lower concentrations compared to other areas of cognition. Visual WM, visuospatial ability, planning, problem solving, selective attention and resistance

to distractor interference however, were positively affected by higher concentrations (≥3.5ppm) suggesting these areas are more resilient. Whether a shift to negative impacts follows in these areas of functioning at higher exposure concentrations and longer durations is unknown. Furthermore, particular areas of functioning, such as psychomotor speed, pre-potent response inhibition, resistance to pro-active interference and cognitive flexibility may not follow an effect trajectory of *positive-negative* effects, and instead may be associated with negative effects only, following longer exposure durations or higher concentrations (see Chapter 2 and 4). Results from Study 3 also indicated that the negative effect of age on memory recognition and visuospatial ability and problem solving increases with greater exposure and decreases with lower exposure. Furthermore, greater exposure was associated with negative performance effects in old older adults (≥75 years), and positive impacts, indicating better performance, in younger older adults (58-74 years). CO exposure may therefore be associated with beneficial effects in older adults, however these effects in particular areas of cognition may be dependent upon factors such as physiological and cognitive reserve capacity and resilience (see Chapter 4).

Study 4 examined these important questions, specifically whether the observed beneficial cognitive effects are short lasting and subsequently result in impairments given sufficient time post-exposure (if the exposure had ceased), but also the level and durations at which these exposures become harmful to specific cognitive functions under conditions of continuous exposure. Specifically, the concentrations at which particular cognitive functions are affected and the direction of such effects, and whether a shift from beneficial to negative effects is a consistent finding across multiple cognitive domains, albeit at different exposure levels, was examined. Results indicated that the exposure at T2 was associated with positive CO-related effects across a range of functions including processing speed, short-term memory, visuospatial ability and problem solving. Negative longer-term impacts from the exposure at Time 1 were also found across a range of cognitive domains including RT intra-individual variability, processing speed, selective attention and resistance to distractor interference at seven months. There was a consistent pattern of results, with

positive effects in the short-term following the exposure at T2 and longer-term negative impacts associated with the exposure from T1. The results replicate the findings in Chapter 4, with positive effects observed in the short-term following exposure, particularly in visuospatial ability and problem solving. As predicted, some of the observed results were inconsistent with this pattern. Negative effects were associated with the exposure at T2 in the short-term in psychomotor speed and short-term positive effects were not present in areas of memory recognition, auditory WM, pre-potent response inhibition, resistance to pro-active interference and cognitive flexibility (see Chapter 5 for details on domain-specific hypotheses and rationale). The results support the notion that particular areas of cognition may be more vulnerable to CO exposure and that specific areas may not follow an exposure trajectory of *positive-negative* effects, and instead, are negatively impacted only.

In relation to the total CO exposure, negative effects were observed in areas of cognitive flexibility, resistance to pro-active interference, memory recognition, selective attention, resistance to distractor interference, intra-individual variability in responding and auditory WM. The total exposure was therefore associated with overall negative effects across a range of cognitive functions as predicted. However, the total exposure was also found to be associated with positive CO-related effects on visual WM. The findings indicate that whilst some cognitive areas may generally be more resilient to CO, impaired visual WM is possibly a late clinical symptom of less severe exposure that presents following longer exposure durations and/or higher CO levels, above those reported here. The exposure levels at which the longer-term effects from the exposure at T1 became apparent for each cognitive function examined, are presented in Figure 6.1 above, and the levels at which the effects presented following the exposure at T2 in the short-term and the total overall exposure are presented in Figure 6.2.

The results also revealed moderation effects between CO and age in similar areas of cognition to those observed in Study 3. Negative relationships between age and cognition however, were only present when the total CO exposure was greater. Increased CO exposure negatively affected aspects of both short and long-term memory (immediate and delayed memory recall and recognition)

performance in old older adults, and positively affected long-term memory performance (delayed memory recall and recognition) in younger older adults. Additionally, increased exposure positively affected visuospatial ability and problem solving performance in younger but not old older adults. This suggests that whilst CO exposure may be associated with both beneficial and detrimental cognitive effects in older adults, these effects in particular functions appear to be more dependent upon other indicators of health, such as physiological and cognitive reserve capacity and resilience, rather than age alone (see Chapter 4). The exposure levels at which significant interaction effects were observed are presented in Figure 6.3 for both the initial exposure at T1 (Study 3) and the total overall exposure over both monitoring periods (Study 4).

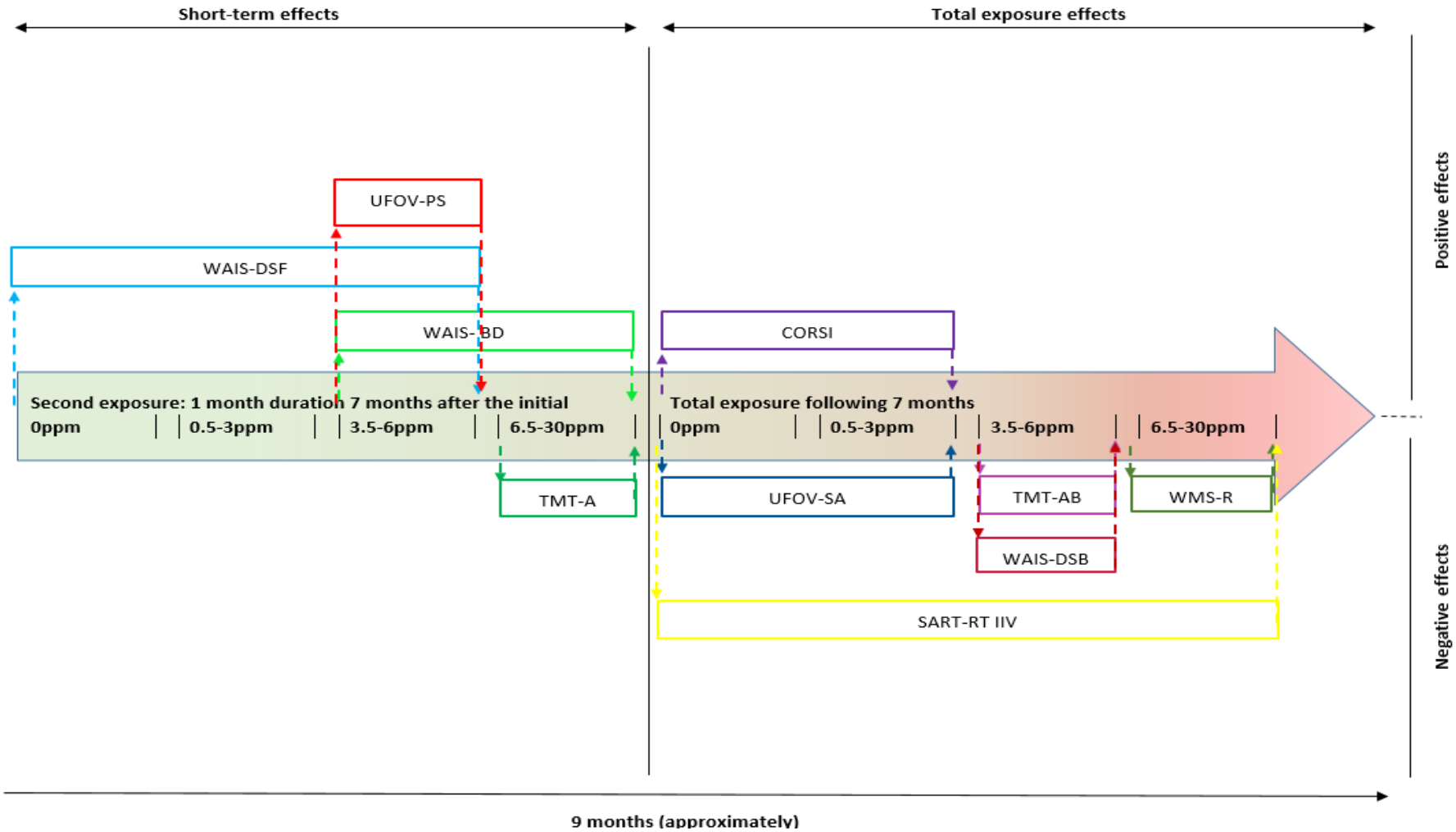


Figure 6.2. Exposure levels at which CO-related positive and negative effects became apparent in the short-term following the T2 exposure and the effects related to the total CO exposure summated over T1 and T2 at approximately 7 months.

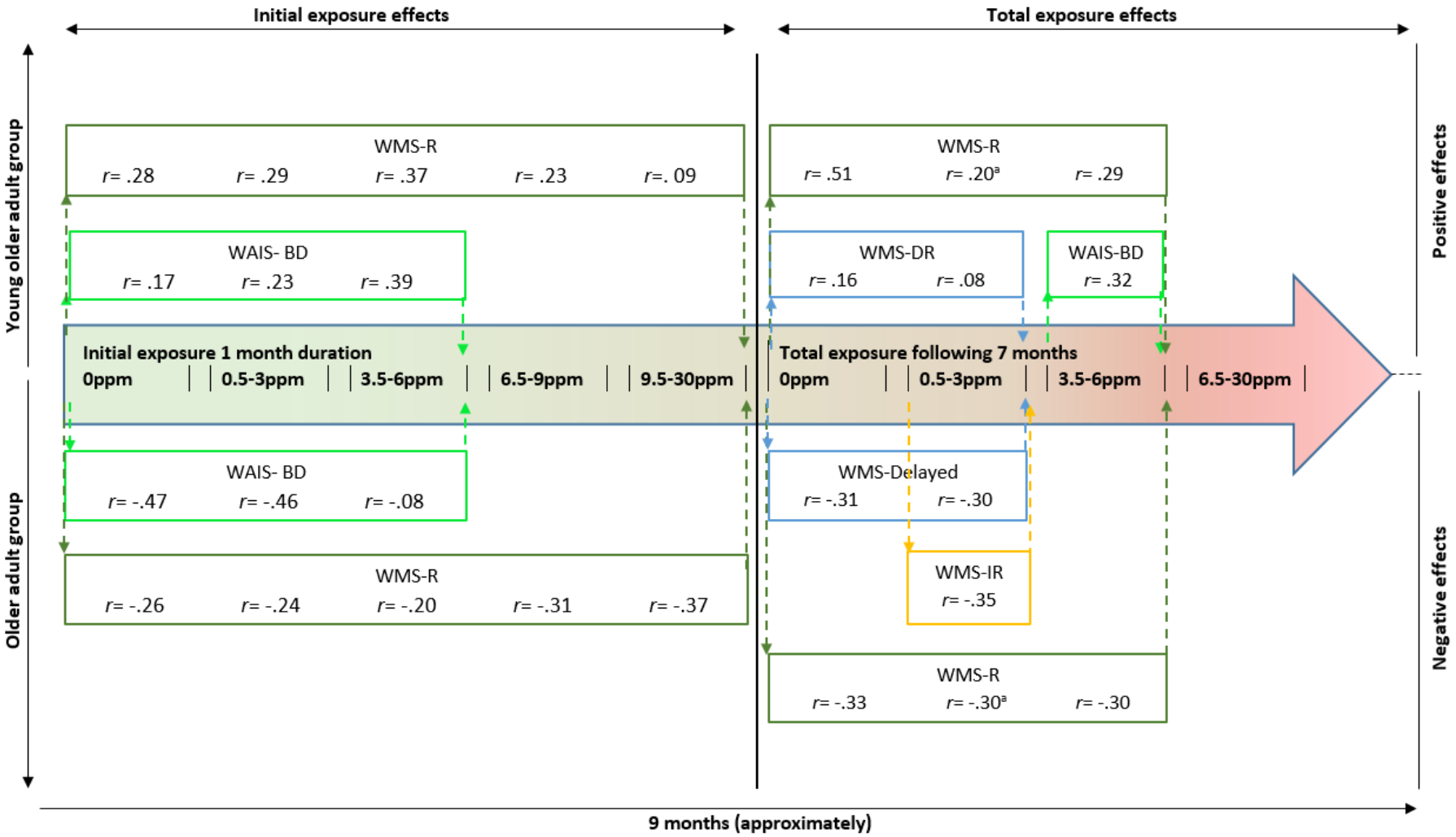


Figure 6.3. Interaction effects between age and CO at T1 on WAIS-BD and WMS-R scores, and interaction effects between age and the total CO exposure summated over T1 and T2 on WAIS-BD scores, WMS-IR, WMS-DR and WMS-R scores. Interaction effects are separated into positive and negative and younger older adults and old older adults.

6.5 Overall Implications of the Research

6.5.1 Theoretical Perspective

The results from the cross-sectional and longitudinal studies support the view that the impacts of chronic low-level CO exposure follow an effect trajectory that can be represented on a continuum: from extremely low-level exposure and positive effects through higher concentrations and negative impacts. This transition from *positive to negative* or *positive-no-negative* effects was present across a range of cognitive domains including auditory WM, memory recognition, selective attention, resistance to distractor interference and processing speed. The results also indicate that particular areas of cognition including psychomotor speed, intra-individual variability, cognitive flexibility and resistance to pro-active interference may not follow a trajectory of *positive-negative effects* observed in other areas of functioning. Instead, these areas of functioning appear to be related to negative effects only that result given either sufficient exposure time, post-exposure time or exposure accumulation. Finally, particular aspects of cognition were associated with positive exposure effects only, including short-term memory, visual WM, planning, problem solving and visuospatial ability. Whether these are followed by a transition period of no effects, prior to a shift to negative impacts at higher exposure concentrations and durations is currently unknown. However, with an extensive amount of literature documenting the negative impacts of CO on neuropsychological function, it is likely that negative impacts do follow at levels above those reported here.

The results also support the viewpoint that the brain regions that benefit most from CO-related temporary increases in CBF, are also areas most susceptible to damage when levels or exposure durations exceed particular thresholds. The brain regions identified as vulnerable to ischemia insult (such as the hippocampus, basal ganglia and CWM) are areas associated with cognitive functions similar to the pattern of performance improvements and declines observed, with *domain-specific* shifts from positive to negative CO-related effects. The underlying processes however, are likely to be multifaceted, underpinned by several mechanisms triggered in response to various physiological states, rather than ischemia alone, such as immunologic and inflammatory responses. These hypoxic-independent mechanisms have been

implicated in CO toxicity. These processes, combined with the ischemia risk prolonged CO exposures present, may escalate damage resulting in greater cognitive deterioration. Overall, the results indicate that particular areas of cognition may be more vulnerable, and others more resilient to, chronic low-level CO exposure. Processing speed, intra-individual variability, selective attention and resistance to distractor interference appear to be most sensitive to CO exposure, with longer-term negative impacts associated with the exposure from T1. This was also supported by the negative impact of the total overall exposure on intra-individual variability, selective attention and resistance to distractor interference. Memory recognition, auditory WM, cognitive flexibility, resistance to proactive interference and psychomotor speed also appear to be more vulnerable to CO exposure with negative impacts present following an accumulation of two one month exposure periods (total overall CO), or in the short-term following the exposure at T2. However, other areas of cognition, including visual WM, planning, problem solving and visuospatial ability, appear to be more resilient to CO exposure with positive effects observed only. These areas show greater resistance to CO, with negative impacts potentially occurring at higher concentrations or longer exposure durations, or time post-exposure.

The proposed model of a CO exposure effect trajectory, whereby various concentrations and durations and their associated effects can be viewed on a continuum from positive through to negative impacts (with a transition period of no effects sometimes present), increases theoretical understanding of less severe exposures, an area where knowledge is extremely limited. Furthermore, it provides a possible explanation for the inconsistent findings within the CO-behavioural literature in that, the proposed continuum can account for the reported negative effects, absence of effects, and trends towards positive impacts, by small variations in exposure concentration and duration. The research findings therefore not only bridge the knowledge gap between the potential beneficial effects and toxicity by providing a possible explanation for the conflicting findings within the literature, but also offer a viewpoint that encompasses these inconsistencies into a united perspective, in turn, alleviating some of the confusion that surrounds low-level CO exposure. The proposed perspective is therefore compatible with evidence highlighting the protective and

therapeutic effects of CO and the subsequent administration of low-level inhaled CO for neuroprotection in recent clinical trials, but also the abundance of evidence documenting the toxic effects of CO.

6.5.2 Clinical Perspective

From a clinical perspective, it is important to focus on the CO level at which particular effects became apparent, the direction of such effects and the cognitive functions affected. One of the most important findings of the study, in regards to clinical practice and diagnoses, is the ability to highlight particular areas of cognition that are most affected by CO and the thresholds at which harm is initiated, irrespective of the trajectory of effects preceding the negative impacts. The results indicate that cognitive functions can be grouped into early, middle and late-stage clinical signs of exposure based on the level and duration at which negative effects were observed.

Greater intra-individual variability, slowed processing speed and impaired selective attention and resistance to distractor interference appear to be early clinical signs of chronic low-level exposure. Following these early cognitive signs, middle-stage clinical symptoms appear to present across a range of cognitive functions including impaired memory recognition, auditory WM, cognitive flexibility, resistance to pro-active interference and psychomotor speed. Finally, particular aspects of cognition appear to be more resistant to CO exposure and may be late clinical signs of exposure including short-term memory, visual WM, planning, visuospatial ability and problem solving, with only positive CO-related effects present in these areas of functioning at the exposure levels and durations recorded in these studies (see Study 4, Chapter 5 and Figures 6.1 and 6.2 for details on the concentrations and durations that these effects become apparent).

The identification of areas most and least affected by CO has important clinical implications for use in diagnosis and treatment and may assist in the determination of exposure severity. For example, the presence of deficits in areas more vulnerable to CO, such as intra-individual variability, may indicate extremely low-level exposure, whereas impairments in both areas more vulnerable and most resilient, such as visual WM, potentially signify more severe low-level

exposure (i.e. longer exposure durations or higher concentrations). The research presented throughout this thesis makes a significant contribution to knowledge, proposing a theory that explains the effects of low-level CO exposure on cognition, from areas most vulnerable to those most resilient, and provides a grading framework indicating exposure severity for future research and ultimately for use in clinical settings.

6.5.3 Older Adult Vulnerability

Perhaps the most concerning findings of the research is the negative impact chronic low-level CO exposure appears to have on the relationship between advancing age and cognition. The results from Study 3 indicate that greater CO exposure accelerates the decline associated with ageing in areas of memory recognition, visuospatial ability and problem solving. Furthermore, greater exposure was associated with positive performance effects in younger older adults, and negative effects in old older adults. Results from Study 4 revealed a similar pattern, with the effects of age on performance dependent on CO level, whereby the negative relationship between age and cognition was present only when the total CO exposure was greater. Similar to the findings from Study 3, greater CO exposure was related to increased performance in younger older adults (59-74yrs) in visuospatial ability, problem solving and long-term memory, and decreased performance in old older adults (75-97yrs) in aspects of short and long-term memory performance. These findings suggest that measures of frailty, rather than age alone, may be better indicators of CO vulnerability and potentially would provide a more accurate account of the impacts of CO in older adults.

In conclusion, the positive CO-related effects reported in Study 3 and 4 may be present in older adult samples only, with physiological mechanisms such as vasodilation temporarily increasing CBF when this is reduced or restricted. However, COHb accumulation over time appears to result in negative impacts in older adults across a range of cognitive domains. Furthermore, particular areas of functioning appear to be more vulnerable and others more resistant to CO exposure, and some more dependent upon health indicators such as physiological and cognitive reserve capacity and resilience. In old older adults, particularly those who are more likely to be frail, COHb accumulation and the

additional burden this places on biological systems that may be failing, appears to be detrimental, especially to memory function. Chronic exposure to low-level CO therefore may place an already susceptible group at an even greater risk of early cognitive decline and dementia development beyond that associated with ageing and disease.

6.5.4 Exposure Guidelines, Policy, Legislation and Safety Technology

The analysis methods outlined in Study 2 provide a promising technique that may facilitate the determination of more accurate thresholds at which low-level exposures become harmful to neuropsychological function and health. Importantly, the method permits the separation of varying exposure patterns, accounts for exposure severity and provides an analysis technique that enables the examination of potential effects at various exposure levels. Therefore, the influence of these exposure factors on health can be thoroughly investigated which, in turn, may provide new evidence to underpin exposure guidelines and inform policy, legislation and safety technology in order to keep those most vulnerable safe. The current WHO recommendations (1999; 2010) are informed and underpinned by extremely dated research, the majority of which was carried out over 4 decades ago. It is clear that research is needed in order to assess whether these guideline limits require revision. Furthermore, CO alarms do not protect against chronic low-level CO exposure with the majority designed only to detect relatively high levels of ambient CO. Some alarms have visual displays indicating the CO level, but they do not alert occupants to low-level or chronic exposure (Shrubsole, Symonds, & Taylor, 2017). Furthermore, British alarm standards are not in accordance with the WHO (2010) recommendations with higher levels of 50ppm for between 60 and 90 minutes required prior to alarm activation, compared to the WHO recommendation of 31ppm for 1 hour. These levels appear to be extremely high when considered alongside the results presented throughout this thesis, for example, the observed detrimental impacts on intra-individual variability at levels of >3.5ppm following a one-month exposure period. The guidelines for chronic exposure outlined by WHO (2010) are closer to these limits with chronic exposure for 24 hours set at 6ppm. This guideline has recently been lowered to 3.5ppm (4 mg/m^3) (WHO, 2021), which is a huge

movement towards public safety. However, these are guidelines only, intended to keep the public safe with limited influence as they are not underpinned by legislation and therefore enforcement in domestic environments is problematic (Shrubsole, Symonds, & Taylor, 2017; APPCOG, 2017). If we are to move towards keeping the public safe, the study of vulnerable groups within the population, such as older adults and those with pre-existing disease, is needed in order to determine 'safe' exposure limits. The method detailed provides a potential approach to continue this process, providing a technique that can identify the levels and duration at which both acute and chronic low-level exposures shift from potential beneficial effects to toxicity, the associated health and neuropsychological effects at various concentrations and the impact of different exposure patterns. Furthermore, guidelines vary depending on the publication body, causing some degree of confusion. Therefore, the development of new evidence based exposure limits that are consistent across publication bodies would alleviate this confusion, resulting in a unified approach to protecting the public across all relevant partners.

6.6 General Discussion

Why some cognitive functions are more vulnerable to low-level CO exposure, and others potentially benefit, is currently unknown. The sensitivity of specific brain regions to ischemia provides a possible explanation for the majority of the reported results, with CO-related effects observed in aspects of cognition that are commonly associated with those areas identified as particularly vulnerable. However, the conflicting overall positive effects on specific executive functions such as visual working memory are not easily explained by potential increases in CBF followed by decreases in oxygen availability to these vulnerable areas. For example, damage to the prefrontal cortex (PFC) is associated with declines in EF (Park, 2000; Park et al., 2001; West, 1996; Cabeza, 2002; Logan et al., 2002; Rosen et al., 2002; Grady & Craik, 2000). Therefore, executive components may have been expected to show similar impairments, due to their shared dependence upon the functionality of the PFC. However, aspects of EF including visual WM were associated with overall positive effects, whereas auditory WM, selective attention, cognitive flexibility, and components of inhibition including resistance to distractor and pro-active interference, were

related to negative impacts. This suggests that whilst EF may broadly rely on the functionality of the PFC, with shared overlap in their underlying neuronal networks, they may to a certain degree, be dependent upon distinct regions. This functional differentiation between executive constructs may therefore explain the inconsistent CO-related effects found across different aspects of EF, with shared reliance on the PFC but subtle differences in activation that are dissociable and component-specific.

Perhaps the most striking example of this is the opposing direction of effects on visual and auditory WM. The differentiation between auditory and visual WM has been detailed in models of working memory for decades, with features such as the phonological loop holding auditory information and the visual-spatial sketchpad storing visual information (Baddeley, 1986; Baddeley & Logie, 1999; Baddeley, & Hitch, 1974; Baddeley, 2003; Zimmer, 2008). Functional imaging studies have revealed that the fronto-parietal network, implicated in WM, is activated irrespective of stimulus type (Nystrom et al., 2000; Wager & Smith, 2003; Owen et al., 2005). These findings suggest that a dissociation between auditory and visual information processing may not be present within the WM network, with shared reliance on a core network irrespective of sensory modality (Schneiders et al., 2012). From this, it could be anticipated that both visual and auditory WM would show a similar pattern of CO-related effects due to their shared reliance on the structural integrity and functional connectivity between frontal and parietal regions (Petrides & Pandya, 2002; Mecklinger & Opitz, 2003). However, a shift from positive to negative effects was observed in auditory WM, whereas the positive effects on visual WM remained at follow up. These results support a more modality-specific model of activity, rather than complete shared reliance on a core neural network, with the fronto-parietal network largely activated during tasks reliant upon WM but slight differences in activation patterns dependent upon input. For example, other functional imaging studies comparing WM for visual and auditory information have reported subtle differences in prefrontal and fronto-parietal activity that varied by sensory input (Rämä & Courtney, 2005; Protzner & McIntosh, 2007). This provides evidence for a functional differentiation within pre-frontal and parietal regions that are modality-specific (Schneiders et al., 2012). The results therefore provide support

for the presence of subtle differences in neural networks and activation areas between executive components, with different CO-related effects observed between functions with considerable overlap in their neural underpinnings.

A key finding from the research is that none of the observed longer-term positive or overall exposure effects relied heavily on inhibition. Instead, tasks requiring inhibitory control were found to be negatively affected by CO. The presence of CO-related effects on inhibition appears to be a relatively consistent finding throughout Study 3 and 4, with longer-term negative impacts observed in resistance to distractor interference and overall negative effects found in resistance to pro-active interference. Furthermore, impaired pre-potent response inhibition was the main study finding when the literature on acute low-level CO exposure was systematically reviewed (see Study 1). Although focused upon the acute low-level experimental literature, the CO-related effects typically became apparent in the final fourth hour of exposure, at higher CO concentrations. This suggests that negative CO-related effects on pre-potent response inhibition become apparent following potentially longer exposure durations and higher concentrations than those observed here. There were also noticeable differences between the levels and durations at which the components of resistance to distractor and pro-active interference were affected. The results therefore in turn support the viewpoint that inhibition is multifaceted comprising various constructs of inhibitory processes that rely on distinct brain regions as opposed to a single underpinning mechanism (Hung et al., 2018; Noreen & Macleod, 2015).

It is important to note that the observed positive exposure effects on particular areas of functioning may, in fact, represent cognitive areas less susceptible, and functions where positive CO-related effects were not present indicate areas more vulnerable, to the negative effects of CO. Therefore, the observed positive impacts may not reflect beneficial CO-related effects *per-se*, but instead represent areas more resilient to the negative impacts of exposure. However, of the areas of functioning where positive effects were observed at T1 (see Study 3, Chapter 4), negative impacts were associated with half of these areas when the total exposure of both monitoring periods was examined. Furthermore, of the areas where positive effects were not observed at T1, negative effects were not

present in the majority of these areas when the total exposure was examined. This indicates that the observed positive effects do not reflect areas more resilient to CO, when compared to functions where positive impacts were not present. In turn, this provides support for an association between low-level exogenous CO and positive impacts. However, whether positive effects can result from chronic exposure to low-level environmental CO is currently unclear. Nevertheless, the results presented throughout this thesis indicate that particular areas of cognitive functioning are more vulnerable, and others more resilient to CO exposure, irrespective of whether the observed positive effects represent beneficial effects. Future studies are needed that examine the effects of chronic exposure to extremely low exogenous CO as are those that investigate the potential physiologic mechanisms, such as vasodilation, that may underpin such effects.

6.7 Limitations

Limitations for each of the studies are presented at the end of each chapter. The first main limitations relate to the data loggers and the data analysis methods. The data loggers were positioned in the room where the participant indicated they spent most of their time in order to reflect individual exposure. However, in terms of reflecting ambient CO levels within the home more generally, CO measurement in future studies may be more accurate if taken in rooms containing the main sources of CO, such as the kitchen where boilers and gas cookers are typically located. Ideally, the monitoring of CO in several locations would be invaluable, particularly when the research aim is to ascertain not only ambient home CO levels but also the associated exposure effects. The monitoring of CO in various rooms would also provide crucial information relating to the contribution of different appliances to raised CO levels and highlight those that are potentially more dangerous. A further limitation relates to the analysis method used to examine the CO data. The separation and examination of CO data in specified ranges, although extremely useful in examining exposure effects at various exposure concentrations, increased the risk of Type 1 errors due to the increased number of significance tests required. This risk could have be reduced by selecting fewer ranges, for example 0.5-6 and 6.5-30ppm, and is a consideration for future research. Alternative approaches to analysing CO data include, for example, the identification of exposure patterns within the data with differences

between them on levels of functioning examined. In addition, the inclusion of a large number of cognitive measures further increased the number of statistical tests required and therefore the risk of Type 1 errors. Alternative approaches to reduce this risk include reducing the measures into a smaller number of variables, using for example factor analysis, prior to running the main analyses, examining fewer cognitive domains and lowering the alpha value to 0.01.

The observational design of the study also resulted in a small range of CO within the monitored homes. Subsequently, analyses of the higher CO ranges were based only on a small number of observations, increasing the risk of type II errors and reduced power. Furthermore, the resulting sample size was smaller, at 106 participants, than the estimated 130 calculated using G power. Although larger than many previous studies in the CO behavioural literature, the study still may have been underpowered for definitive hypothesis testing due to the anticipated low effect size (.25) and the relatively small sample studied. Future research examining the effects of low-level CO exposure, where small effect sizes are anticipated, should aim to increase the sample size, in turn, increasing the power of future studies. In relation to the CO data, monitoring a greater number of homes may potentially lead to a wider range of CO measurements, however this would not necessarily result from simply increasing the sample size. Other factors that may increase the likelihood of observing greater variance in CO concentrations include monitoring homes in several geographical locations, including both urban and rural areas, potentially capturing differences in, for example, the fuels used to heat the home. The finding that CO levels within the monitored homes were relatively low is reassuring; however, if we are to identify the levels at which exposures become harmful, the analysis of a greater CO range is required.

A final limitation relates to the monitoring of two separate one-month periods that were seven months apart. Consequently, the exposure levels in the seven months between monitoring points are unknown, which makes forming conclusions on the underlying exposure responsible for resulting effects difficult. For example, negative impacts that became apparent in the short-term at follow-up may have resulted from an accumulation of exposure over both monitoring

periods, the unknown exposure levels in the seven months between monitoring, the second exposure period only, or a combination of these. Employing advanced technology capable of monitoring CO levels over longer periods would be extremely beneficial in future studies.

6.8 Directions for Future Research

A further longitudinal study including an additional follow-up of the same participants would extend the research allowing for potential causal inferences to be made via incidence rates on the relationship between chronic low-level CO exposure and mild cognitive impairment (MCI) and dementia development. The commonly observed brain abnormalities in CO poisoned patients are comparable to those observed in patients with vascular dementia and Alzheimer's disease (AD) (Bigler et al., 2002). Therefore, CO poisoned patients may be at higher risk of early cognitive decline and AD (Weaver, 2009). Results of studies of severe acute poisoning and case reports of lower chronic exposures indicate an association between CO exposure and dementia development risk (Lai et al., 2016; Nakamura et al., 2016; Wong et al., 2016). Furthermore, associations between air pollution exposure, including CO, and increased dementia risk have also been reported (Chang et al., 2014; Peters et al., 2019). Recently, research has focused on risk reduction strategies in order to delay or prevent dementia by targeting associated risk factors such as diabetes, physical inactivity and social isolation. Air pollution has recently been highlighted as a dementia development risk factor in later life (>65). These later life risk factors are viewed as potentially modifiable with a combined estimated percentage decrease of 18% in dementia prevalence if eradicated (Livingston et al., 2020). Potential risk factors for cognitive decline and dementia development, including CO exposure, necessitate identification, which, in turn, may result in preventative measures and reduced risk (Lai et al., 2016; Ranft et al., 2009). The results presented throughout this thesis suggest that chronic exposure to low-level CO can result in longer-term cognitive impairments. However, whether they increase the risk of MCI and dementia development is currently unknown. The timing of such research has never been more imperative due to evidence indicating that CO poisoned patients may be at higher risk of dementia, including a significant review by the Lancet Dementia Commission (Livingston et al, 2020) confirming the role

of air pollution, including CO, as a risk factor. Additionally, the risk of exposure in the home amongst other age groups has also greatly increased by alterations in behaviour and working resulting from the COVID-19 pandemic. Post lockdown, some businesses continue to encourage working from home where possible, and this, coupled with the negative emotional impact the national lockdown is likely to have caused, adds to the concern. Individuals may be more apprehensive to leave the home or simply have become accustomed to, and more comfortable with, remaining at home. It is now more pertinent than ever to increase knowledge and understanding of the effects associated with chronic CO exposure.

The results make an important contribution to knowledge in the CO-behavioural literature, providing preliminary evidence towards understanding the specific cognitive functions that may be affected by low-level exposure and patterns of impairment. The studies also contribute evidence towards determining thresholds at which chronic low-level exposure to CO becomes harmful to neuropsychological function in older adults. However, there is still a way to go before thresholds of harm are identified and those most vulnerable are kept safe. Further understanding of the neuropsychological effects associated with chronic CO exposure, effect directions at various concentrations, specific cognitive functions affected and thresholds of harm is needed, if we are to advance knowledge of the levels at which these exposures present risk to neuropsychological function and therefore risk of serious declines such as dementias. Furthermore, research highlighting specific patterns of cognitive impairment would be invaluable in clinical settings to aid in the diagnosis of low-level CO exposure. Replication of the findings presented throughout this thesis would have a huge impact on policy, guidelines and safety technology, resulting in real world outcomes. A logical direction for future research would be to extend the recruitment area to include both rural and urban profiles. Collection of a larger data set to incorporate a wider area would capture different geographical and socio-economic profiles including different property types, levels of deprivation, tenures and appliances within the home. This may result in a wider range of CO not only for the examination of thresholds of harm, replication of previous findings and strengthening of conclusions, but also to address some of the limitations

detailed above. Additionally, including various geographic regions in future studies could substantially increase sample sizes and thus power, through larger scale recruitment methods that rely on multiple Fire and Rescue Services from different regions, rather than Coventry alone. Working in partnership with Gas Distribution Networks for larger scale recruitment on to CO research studies also presents an alternative method to increase recruitment of participants and thus sample size. However, larger studies with increased sample sizes both within and between different regions would add additional pressure on local Fire and Rescue Services, with greater number of visits to deploy and retrieve data loggers, change batteries and download and safety check CO levels required, which may not be feasible. Such studies may therefore require the development of advanced technology that is capable of measuring CO levels over longer periods of time, such as mains powered devices. Technology that has the ability to provide real-time feedback on CO levels within properties, that can be accessed via a platform outside of the home, such as the fire station, would also be extremely valuable. This would not only minimise the invested time of the Fire Service, in terms of visiting properties, but would also keep occupants safer and address some of the limitations detailed above that arise when examining CO levels over two separate one-month periods. Larger scale studies that incorporate such technologies could provide detailed information on CO levels within homes over, for example, a one year period, which would be invaluable in ascertaining the prevalence of CO within UK homes and thus the magnitude of the problem.

Finally, the results of the studies presented in this thesis provide preliminary evidence of the areas of functioning that may be more vulnerable, and those more resilient to low-level CO exposure. These initial results provide a foundation for future studies examining the effects on low-level CO exposure on neuropsychological function that could be used to guide the selection of particular cognitive variables of study, thus reducing the number of measures. This would not only lower the risk of error by reducing statistical testing but would also facilitate the collection of data from larger samples due to reduced time required assessing each participant.

6.9 Ethical implications

Prior to the commencement of the research, the planning stages involved numerous ethical considerations and detailed protocols were developed with the Fire Service in order to keep participants safe. Throughout the project, the research was conducted in adherence to, and under strict ethical procedures. Prior to being recruited onto the study, each participant received a 'safe and well visit' from Fire Officers. During these visits, CO measurements within the home were taken and standard Fire Service protocols are in place when CO is detected. Fire Service protocols are as follows:

- Residents are provided with advice when the CO level within the home is 0-19 ppm.
- An incident is raised if the CO reading is ≥20 ppm, in line with the Health and Safety Executive (HSE) workplace exposure limits (EH40, 2005; updated in 2017), with occupational exposure limits for CO: Long-term exposure limit (8-hr TWA reference period): 20ppm; Short-term exposure limit (15 minute reference period): 100ppm. When Fire Officers visit properties, an incident is raised when the CO levels are ≥20ppm, as the duration of exposure is usually unknown.
- Fire Officers isolate the gas supply, ventilate the property, and wait on scene until a gas safe engineer has visited the property.
- In cases where individuals require medical attention, the ambulance service is contacted.

The research protocol dictated that occupants of homes identified as having CO levels ≥20ppm during these visits would not be informed about the research project, and therefore were excluded from the study. However, none of the homes visited during the research recruitment period had CO levels ≥20ppm. Once recruited onto the study, Fire Officers installed CO alarms in all properties in order to keep participants safe from the beginning, throughout and after study completion, minimising the risk of CO exposure at higher concentrations.

After the CO data loggers had been in the property for one month, Fire Officers collected the equipment and downloaded the data. Each data file was thoroughly

checked by one of the lead Fire Officers on the project team to ensure that CO levels did not exceed ≥20ppm for the stated 8-hour duration (HSE; 2017). For additional safety, the data files were also checked in reference to the World Health Organisation (2010) recommendations, which are substantially lower than current European alarm standards and the HSE (2017) guidelines. Only after the data files had been checked were they shared with the researcher. One property revealed concentrations above these levels and was excluded from the research. The Fire Service followed protocols including informing the resident and revisiting the property to discuss concerns and to check CO levels and identify potential hazards. The resident indicated that she had not been experiencing any symptoms or ill health. As the property was privately owned, the occupant was advised to contact Gas Safe. However, after examination of the data and conversations with the equipment company, Fire Officers believed the raised CO levels were due to an equipment malfunction. For additional safety purposes, a further data logger was deployed to the property with continuous CO measurements taken over two weeks. The CO data file did not reveal any further CO levels of concern.

Prior to the second visit, all participants received a follow up visit from the Fire Service to reinstall the data loggers and to provide intervention. The initial research protocol stipulated that only homes with higher levels of CO would be revisited by Fire Officers for intervention. However, as none of the homes had CO levels above the HSE guidelines, or even exceeding the WHO (2010) recommendations (with the exception of the property mentioned above), the Fire Service did not consider any of the properties to be classified as having ‘higher’ CO levels. Due to this and to ensure the continued safety of the participants, protocols were amended so that all properties on the project received an intervention by the Fire Service. During the intervention, participants were informed that none of the homes had CO concentrations above the safety guidelines or that were considered ‘unsafe’. The Fire Service provided health and safety information regarding CO sources, safety and prevention, and the associated health risks to raise awareness and educate. The CO alarm was also checked during the visit. The same protocols detailed above were followed after the second data collection period. None of the properties had CO levels that

exceeded the HSE (2017) guidelines or those recommended by the WHO (2010). Therefore, the CO concentrations analysed throughout this thesis represent extremely low-level background CO concentrations that individuals are likely exposed to daily, in both indoor and outdoor environments.

6.10 Summary

In summary, the results presented in this thesis indicate that chronic CO exposure (≤29ppm) for at least one month may be associated with short-term positive impacts on cognitive function in older adults in areas of auditory WM, memory recognition, visual WM, visuospatial ability, planning, problem solving, selective attention and resistance to distractor interference. However, the majority of these effects were short-lasting and led to negative impacts either given sufficient time post exposure or an accumulation of two one-month exposure periods. This shift of effects was observed across a range of functions including memory recognition, auditory WM, selective attention and resistance to distractor interference. However, particular areas of functioning including psychomotor speed, intra-individual variability, cognitive flexibility and resistance to pro-active interference appear to be related to negative effects only that result given either sufficient time post-exposure or exposure accumulation. Other aspects of cognition appear to be more resilient to CO including short-term memory, visual WM, planning, problem solving and visuospatial ability with only positive exposure effects observed. Finally, CO exposure appears to moderate the relationship between advancing age and cognition in areas of immediate and delayed memory recall and recognition, visuospatial ability and problem solving. Greater CO exposure was related to increased performance in younger older adults (59-74yrs) in visuospatial ability, problem solving and long-term memory, and decreased performance in old older adults (75-97yrs) in aspects of short and long-term memory performance. These findings suggest that measures of frailty, rather than age alone, may be better indicators of CO vulnerability and potentially would provide a more accurate account of the impacts of CO in older adults.

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Appendices

Appendix 1 (A1): List of Tables

A1.1 Study 1, Chapter 2 (Systematic literature review)

Table A1.1.1. Demographic information, study design, exposure type, level and duration of the included studies

Study	Participant (n) health and smoking status	Age M (SD) and/or range	Sex (n)	Study design	Exposure type	Experimental design	Exposure level	Exposure duration
Salvatore, 1974	6 healthy non-smokers	22.3; 20-27	M= 3 F= 3	Experimental Within	Acute	Unblinded	800ppm	20 minutes
Rummo & Sarlanis, 1974	7 healthy; 6 non-smokers	19-27	M= 6 F= 1	Experimental Within	Acute	Single blind	800ppm	20 minutes
Otto, Benignus, & Prah, 1979	13 healthy non-smokers	22.9; 19-30	M= 13	Experimental Within	Acute	Double blind	0, 75, 150ppm	2.23 hours
Harbin et al., 1988	33 healthy non-smokers (young group) 22 healthy non-smokers (older group)	22.8; 18-28 68.7; 60-86	M= 33 M= 22	Experimental Mixed	Acute	Double blind	200ppm initial 50ppm maintained throughout study	1 hour at 200ppm 2 hours testing session
Benignus et al., 1987	24 healthy non-smokers 12 exposure group 12 controls	24.0 (2.83); 19-31	M= 24	Experimental Mixed RCT	Acute	Double blind	0, 100ppm	4 hours
Roche et al., 1981	18 healthy non-smokers	20-30	M= 12 F= 6	Experimental Within	Acute	Double blind	40-60ml initial to reach COHb of 5% 28ppm maintained throughout study	10 minutes to reach COHb of 5% 60 minutes testing session
Putz, 1979	30 healthy non-smokers 10 control group 10 low exposure group (35ppm) 10 high exposure group (70ppm)	18-26	M= 20 F= 10	Experimental Mixed RCT	Acute	Double blind	4.4 (0.5) ppm 35.7 (0.2) ppm 74.1 (1.3) ppm	4 hours
Wright & Shephard, 1978	8 Healthy non-smokers Noise and isolation conditions	19-28	M= 7	Experimental Mixed RCT	Acute	Single blind	0ml, 40, 70, 100ml initial 25ml each hour to maintain desired COHb levels.	4 hours
Amitai et al., 1998	45 healthy students; 6 smokers (experimental group) 47 healthy students; 8 smokers (control group, age and sex matched)	Experimental group: 21.8 Control group: 22.2	M= 12 F= 33 M= 17 F= 30	Experimental Between	Acute	Unblinded	Concentrations ranged between 17-100; M: 61 (24) ppm	1.5- 2.5 hours
O'Donnell et al., 1971a	9 healthy non-smokers	19-22	M= 9	Experimental Within	Acute	Double blind	0, 50, 125 ppm maintained throughout study	3 x 1 hour sessions
Benignus et al., 1977	52 healthy non-smokers 0ppm exposure n= 17 (control group) 100ppm exposure n= 16 200ppm exposure n= 19	22.25; 18-34	M= 52	Experimental Mixed RCT	Acute	Double blind	0, 100, 200ppm	Approx. 3.5 hours.
Stewart et al., 1970	18 healthy 3 smokers 25 experiments: 1-8 same participants 9- 13 different participants Experiments 22-25 were toxicologists	24-42	M= 18	Experimental Between Correlation	Acute	Double blind	0, 25, 50, 100, 200, 500, 1000ppm	0ppm (8 hours), 25ppm (8 hours), 50ppm (1, 3, 8, 24 hours), 100ppm (1, 3, 8 hours), 200ppm (4 hours), 500ppm (1.8, 2.3 hours), 1000ppm (0.5 hours)
Beard & Wertheim, 1967	18 healthy non-smokers	NR	NR	Experimental Within	Acute	Single blind	0, 50, 100, 175, 250ppm	4 hours
Horvath et al., 1971	10 healthy non-smokers	21-32	M= 18	Experimental Within	Acute	Single blind	0, 26, 111ppm maintained throughout study	1 hour prior to test 2 hour testing session
O'Donnell, Chikos & Theodore, 1971b	4 healthy non-smokers	20-42	M= 4	Experimental Within	Acute	Double blind	0, 75, 150ppm	7 hours whilst participants slept 1.5 hour testing session

Schulte, 1963	49 healthy included smokers number NR	37.5; 25-55	M= 49	Experimental Between RCT Correlation	Acute	Single blind	0, 100ppm	Maintained for task duration (NR)
McFarland, 1973	28 healthy included smokers number NR	20-50	NR	Experimental Within	Acute	Single blind	0, 720ppm	Exposed until 1 of the 2 levels reached (11% or 17%). Approx. 80-minute exposure prior and re-exposed between tasks to regain desired COHb levels.
Wright, Randell & Shephard, 1973	50 healthy 25 CO exposure group (13 smokers) 25 control group (8 smokers)	17-65	M= 32 F= 18	Experimental Mixed RCT	Acute	Double blind	80ml	3-40 minutes
Groll-Knapp et al., 1982	10 non-smokers (younger adults) 10 non-smokers (older adults)	20-25 55-72	M= 5 F= 5 M= 7 F= 3	Experimental Mixed	Acute	Double blind	0, 100ppm (younger) 0, 95ppm (older group)	8 hours whilst participants slept.
Gliner, Horvath & Mihenic, 1983	15 healthy	23.9; 20-32	M= 7 F= 8	Experimental Within	Acute	Single blind	0, 100ppm	60 minute prior to task 90 minute testing session
Ramsey, 1972	80 non-smokers 20 healthy 20 with anaemia 20 with emphysema. 20 healthy controls	NR	NR	Experimental Mixed	Acute	Single blind	300ppm	45 minute
Benignus et al., 1990	74 Healthy 5 groups: Control group (n=14) 5% fast COHb formation (n=15) 5% slow formation (n=15) 12% fast formation (n=15) 17% fast formation (n=15)	23.42 (3.99); 18-35	M= 74	Experimental Mixed RCT	Acute	Double blind	Prior / During Control 0 / 0 Low-slow 0 / 70 Low-fast 2,600 / 32 Medium-fast 6,000 / 86 High-fast 9,600 / 149	Fast COHb formation groups: 4-5 minutes prior. 240 minutes testing session. Slow 5% COHb group: 240 minutes testing session.
Ramsey, 1973	60 healthy 20 control group 20 exposed to 650ppm 20 exposed to 950ppm	19-21	M= 60	Experimental Mixed	Acute	Double blind	650ppm 950ppm	45 minutes
Stewart et al., 1973	27 healthy 3 smokers Subjects divided into 3 groups (isolated, group, audiometric booth)	22-43	M= 23 F= 4	Experimental Mixed Correlation	Acute	Double blind	>2, 50, 100, 200 and 500ppm	Up to 5 hours designed for COHb levels not to exceed 20%
Bunnell & Horvath, 1988	15 healthy non-smokers 3 desired COHb levels: 0.7-1.0% control group, 7% , 10%	M: 20.3 F: 22.1 18-29	M= 9 F= 6	Experimental Within	Acute	Single blind	Initial dose of CO NR. 45ppm to maintain COHb of 7% 65ppm to maintain COHb of 10%	4 minutes prior 55 minutes plus time to complete 5 cognitive tasks (NR)
Bunnell & Horvath, 1989	16 Healthy non-smokers 3 desired COHb levels: 0.7-1.0% control group, 7%, 10%	18-28	M= 16	Experimental Within	Acute	Single blind	Initial dose of CO NR. 45ppm to maintain COHb of 7% 65ppm to maintain COHb of 10%	4 minutes prior 55 minutes plus time to complete 5 cognitive tasks (NR)

NR= Not reported; ppm= Parts per million; RCT= Randomised controlled trial; CO= Carbon monoxide; COHb= Carboxyhaemoglobin.

Table A1.1.2. COHb acquisition technique, mean COHb levels for control group and experimental group pre and post exposure, tasks and corresponding cognitive domains, reported CO-related effects and effect sizes.

Study	COHb acquisition technique	Mean COHb % (SD) Exp. group before exposure	Mean COHb (%) control group	Mean COHb % (SD) range Exp. group during or post-exposure	Mean COHb (%) control group after exposure	Task and cognitive domain	Reported effects pertinent to review	Effect Size Cohen's d[1]
Salvatore, 1974	Ecolyzer expired air	NR	PSAC	Before trial: 1: 7.98 (.33) 2: 6.63 (.69) 3: 5.27 (.64) 4: 4.22 (.58) After trial: 1: 7.16 (.38) 2: 6.04 (.72) 3: 4.67 (.65) 4: 3.65 (.47)	N/A	RT to visual stimuli (static and dynamic conditions): attention and RT.	Significant increase in target detection time in the CO exposure conditions compared to the control in the dynamic task condition (p<.025).	**RT**↓ Static / Dynamic Low *0.07* / Low *0.23* High *0.28* / High *1.33* Collapsed *0.18* / Collapsed *0.78*
Rummo & Sarlanis, 1974	CO-Oximeter and expired air.	<1.5 2.6 smoker	PSAC	Before task: 7.6 After task: 6.0	N/A	Vigilance driving task and concurrent light detection task: divided attention, task switching (EF) and psychomotor function. RT driving task: divided attention and RT.	Significant increase in RT to speed changes in the lead car under the CO exposure condition compared to the control condition (p<.01). No significant differences in RTs between CO exposure condition and control condition in the light detection task.	**RT**↓ Exposure time (minutes) 30: *1.06*; 60: *0.46*; 90: *0.61*; 120: *0.63*; Total: *1.77* X
Otto, Benignus & Prah, 1979	Venous blood samples	0.16 (0.24)	PSAC	0ppm: 0.16 (0.24) 75ppm: 3.77 (0.47) 150ppm: 7.81 (0.84)	N/A	Auditory time discrimination task: sustained attention and updating (EF).	No significant differences between CO exposure condition and control condition.	X
Harbin et al., 1988	Blood samples	1.3 1.3	PSAC	Young group increased to 5.6 Older group increased to 5.0	N/A	RT to illuminating lights: attention and RT.	No significant differences between the exposure condition and control condition in mean RT (p>.05).	**RT**↓ Alternatives 1 / 2 / 4 / 8 Young: *0.07* / *-0.29* / *0.09* / *-0.25* Older: *0.37* / *0.78* / *0.51* / *0.73*
Benignus et al., 1987	Blood samples	1.36 (0.18) range 1.07-1.57	Mean 1.42 (0.39) range 0.9-2.32	8.24 (0.49), range 7.57-9.03	1.22 (0.24) range 0.87-1.55	Tracking task (fast and slow) and concurrent monitoring task: psychomotor function, divided attention, task switching and inhibition (EF). RT monitoring task: divided attention and RT.	Significant increase in tracking error scores in the CO group compared to the control group given sufficient exposure time (p<.01). No significant differences in RTs between the exposure group and control group on the monitoring task over time.	**Tracking error scores**↓ Hour: 1 / 2 / 3 / 4 Slow FF: *-0.11* / *-0.04* / *0.28* / *0.64* Fast FF: *0.21* / *0.00* / *0.48* / *0.75* X
Roche et al., 1981	Blood samples	Control Before: 1.07 (0.42) During: 1.07 (0.55) After: 0.97 (0.41)	PSAC	CO condition Before 1.01 (0.53) During: 5.25 (1.01) After: 4.95 (0 .87)	N/A	Monitoring task (high/low signal frequency): sustained attention.	No significant differences in signal detection and false positive responses between CO and control conditions in either task condition high or low frequency (p>.05).	**% signals detected**↑ / **% false positives**↓ Time (mins): Low SR / High SR / Low SR / High SR 0-15: *0.24* / *0.25* / *0.00* / *0.08* 16-30: *0.43* / *-0.28* / *0.14* / *0.33* 31-45: *-1.17* / *-0.42* / *-0.50* / *-0.33* 46-60: *-0.34* / *-0.39* / *-0.78* / *-0.39*
Putz, 1979	Breath Ecolyzer	Low exposure group:	1.0	Low exposure group After: 3.03 (0.71)	1.0	Tracking task (fast and slow) and concurrent monitoring task:	Significant increase in tracking error scores in the high level CO condition (70ppm) compared	X

	and blood samples	1.5 (0.27) High exposure group: 1.3 (0.39)		High exposure group After: 5.1 (0.57)		psychomotor function, divided attention, task switching and inhibition (EF). RT monitoring task: divided attention and RT.	to the control condition during the 4th hour of exposure but only in the high frequency (difficulty) tracking condition (p<.01). Significant increase in RT on the monitoring task in the high CO group between 2-4 hour compared to the control group (p<.01).	X
Wright & Shephard, 1978	Estimated using Dahlstrom formula	0ml noise: 1.02 (0.28) Isolation: 1.04 (0.31) 100ml noise: 0.89 (0.22) Isolation: 0.90 (0.31)	PSAC	0ml noise after exposure: 1.01 (0.27), after task: 0.91 (0.23). 0ml isolation after exposure 1.03 (0.30), after task 0.93 (0.25). 100ml CO noise after exposure 8.28 (1.27), after task 8.06 (1.92). 100ml CO isolation, after exposure: 7.78 (1.61), after task 8.94 (2.03)	N/A	Auditory tone discrimination task: sustained attention and updating (EF).	No significant difference in mean correct responses between the CO exposure or control condition in either noise/ isolation conditions or hour of exposure on (p>.05).	X
Amitai et al., 1998	Venous blood samples	NR	NR	4.0 (range: 1-11)	NR	WMS and WAIS: short-term and long-term memory. Digit-symbol: psychomotor function and speed. Block design: visuospatial ability and problem solving (EF). DSF and DSB: auditory short-term memory and working memory. TMT parts A and B: inhibition, cognitive flexibility (EF) and psychomotor function speed. RAVLT: verbal memory and learning ability.	Significant differences between control and experimental group in: DSF p=.02, short-term semantic memory p=.01, long-term semantic memory p=.01, long-term figural memory p=.02, block design p=0.01, TMT A p=.04, digit-symbol p=.004. No significant differences in: DSB, short-term figural memory, immediate memory, learning, recall and identification (RAVLT), TMT B.	**Task** [↑] DSF *-0.52* DSB *-0.16* STM Semantic *-0.86* LTM Semantic *-0.57* STM Figural *-0.29* LTM Figural *-0.53* RAVLT Immediate *0.23* RAVLT Learning *-0.16* RAVLT Recall *0.20* RAVLT Identification *0.10* Digit Symbol *-0.61* Block Design *-0.56* TMT A[↓] *0.43* TMT B[↓] *0.35*
O'Donnell et al., 1971a	Venous blood samples	NR	PSAC	0ppm: 0.96 50ppm: 2.98 125ppm: 6.64	N/A	Time estimation (intervals of 10s): sustained attention. CITT: psychomotor function.	Significantly longer time estimation in the 50 ppm condition compared to the control during the 135-150 minute period (p<.05). Significant decrease in tracking ability in the 50 and 125 ppm exposure conditions compared to the control in the 105-120 minute time period (p<.05).	X X
Benignus et al., 1977	Venous blood samples	NR	NR	100ppm 4.61 (0.90) 200ppm 12.62 (1.36)	0ppm 0.01 (0.46)	Numeric- monitoring task: sustained attention and updating (EF).	No significant differences in performance levels between the two CO exposure groups and the control group (p=.619).	X

Stewart et al., 1970	Breathalyser and venous blood samples CO-Oximeter	50ppm pre-exposure: 0.7 (0.4-1.5)	N/A	50ppm: 2.1 (1 hour), 3.8 (3 hours), 5.9 (8 hours), 7.9 (24 hours) 500ppm: 6.4-16.6 (1 hour), 21.9-23.0 (2 hours) 1000ppm: 31.8 (0.5 hours)	N/A	Driving simulator task: divided attention, task switching (EF) and psychomotor function. Driving simulator (DS): divided attention and RT. AAA hand steadiness task (HS), the Crawford collar and pin (CCP) test and screw test (CS): fine motor control, psychomotor function and speed. Flanagan hand co-ordination test: visuospatial ability. Light and auditory tone time estimation task: sustained attention and updating (EF).	No significant differences in performance on any task between control and exposure conditions (25, 50, 100, 200, 500ppm). 1000ppm exposure reached after 2 hours and maintained for 30 minutes caused decreased performance on collar and pin task.	Experiments averaged across similar CO levels Exp. N 3/5 7 4/8 11/13 COppm 25.6 49.4 98.8 **DS**↓ *-0.48* *-0.42* *-0.50* **HS** *0.07* *0.56* *-0.01* **CCP**↑ *0.32* *1.55* *0.01* **CS**↑ *0.27* *0.22* *0.31* **Tone/light time estimation task**↑ Exp. N / CO ppm / Duration 7 / 39.6 / 0.1 7 / 49.0 / 7 11/13 / 94.2 / 0.5 8 / 98.2 / 4 8/11/13 / 97.5 / 8.2	r COHb -0.197 -0.028 -0.251 -0.106 *-0.50* *-0.21* *-0.65* *-0.24* *-0.41*
Beard & Wertheim, 1967	NR	NR	PSAC	NR	N/A	Auditory tone discrimination task: sustained attention and updating (EF).	Significant decrease in mean percent correct responses in all CO exposures conditions 50, 100, 175, 250ppm (30-50 minutes) compared to control condition (0-30 minutes) $p<.02$.	X
Horvath et al., 1971	Blood samples	0ppm 0.8 (0.23) 26ppm 0.8 (0.57) 111ppm 0.9 (0.46)	PSAC	0ppm 60 minutes: 0.8 (0.23) 135-140 minutes: 0.8 (0.21) 26ppm 60 minutes: 1.6 (0.60) 135-140 minutes: 2.3 (0.55) 111ppm 60 minutes: 4.2 (1.15) 135-140 minutes: 6.6 (1.27)	N/A	Monitoring task: sustained attention.	Significant difference in mean correct signal detections between CO condition (111ppm) and control condition ($p<.05$).	X
O'Donnell, Chikos & Theodore, 1971b	Venous blood	0ppm (control exposure) 0.6 (0.5-0.8)	PSAC	75ppm exposure: 5.9 (5.1-6.8) 150ppm exposure: 12.7 (11.6-12.9)	N/A	CFFT: speed of processing. Tracking task: psychomotor function. Concurrent monitoring task (moderate workload): divided attention, task switching and psychomotor function. Second concurrent monitoring task (high workload): additional domain of working memory. RT monitoring task: divided attention, and RT. Time estimation (10 and 30s) and auditory tone discrimination task: sustained attention and updating (EF). Mental arithmetic task: working memory.	No significant performance differences on any task, or in performance under the moderate or high workload, between the control and exposure conditions ($p>.05$).	**Task**↓ / 75ppm / 150ppm 10s / *-0.39* / *-0.52* 30s / *0.03* / *-0.15* Tone task / *-0.06* / *0.03* CFF / *-0.05* / *0.02* Mental Arithmetic / *-0.13* / *0.28* Moderate WL-Tracking / *-0.29* / *0.22* Monitoring / *0.50* / *0.06* High WL-Tracking / *-0.74* / *-0.38* Monitoring / *0.35* / *-0.42*
Schulte, 1963	Blood samples	NR	0.0	Ranges between 0-20.4 throughout testing.	NR	RT task responding to colours and letters: attention and RT.	Significant positive correlation between mean number of errors in the choice letter/colour,	Correlations (r) / COHb Level

						Plural noun underlying test and T crossing test: psychomotor function and speed. Mental arithmetic test: Working memory.	mental arithmetic (MA) test, T-crossing (TC) test, and COHb level. Significant positive correlation between mean completion time in the plural noun underlying (PNU) test, mental arithmetic and T-crossing test time of the plural noun-underlying test and COHb level.	Errors in Letter 0.906 Errors in colour 0.847 Completion time PNU 0.812 Completion time MA 0.665 Completion Time TC 0.792 Errors in PNU 0.053 Errors MA 0.590 Errors TC 0.539
McFarland, 1973	Blood samples and oximeter	NR	PSAC	<4 11 17	N/A	Concurrently responding to lights in the central field of vision and periphery task responding to lights presented in the periphery: divided attention, task switching (EF) and psychomotor function. Driving task: short term and working memory. Visual RT light task: divided attention and RT.	No significant differences between control and CO conditions on the central and periphery task. Greater variability in responses in the 17% COHb condition when compared to the control on the peripheral task. Significantly less occlusion time at 50 mph during the driving task in the CO condition compared to control condition.	X X
Wright, Randell & Shephard, 1973	Estimated using Dahlstrom formula	Smokers: 3.9 (2.6) M 5.0 (2.5) F Non-smokers: 1.2 (0.6) M 1.5 (1.0) F	Smokers: 4.7 (2.5) M 7.3 (1.3) F Non-smokers: 1.2 (0.6) M 1.1 (0.8) F	Mean increase of 3.4 (1.8)	Smokers: 4.7 (2.5) M 7.3 (1.3) F Non-smokers: 1.2 (0.6) M 1.1 (0.8) F	Driving task brake reaction time driving simulator: attention and RT. Hand steadiness (HS) task: fine motor control and psychomotor function.	No significant differences in hand steadiness task. No significant differences in RT between exposure and control group in initial parametric testing. Significant differences only when scores were analysed with non-parametric tests.	**RT**↓ *0.14* **HS**↑ *-0.11*
Groll-Knapp et al., 1982	Blood samples for older group	NR	PSAC	Younger group: after 7-8 hours exposure: 10 Older group: 7.97	N/A	Memory test recall of word list (6 minutes and 8 hours): Immediate and delayed recall.	Significant increase in the number of words remembered (recalled) in the morning compared to evening only in the control condition for the younger group (p<.05).	X
Gliner, Horvath & Mihenic, 1983	Venous blood samples	1.0	PSAC	100ppm: 1 hour after exposure prior to task: 3.45 Task completion: 5.78 0ppm: Levels remained at approx. 1	N/A	Tracking task (3 levels of difficulty): psychomotor function. Concurrent monitoring task: divided attention, task switching and inhibition (EF). Monitoring task also performed separately: sustained attention and inhibition (EF).	Significant decrease in percentage of signals detected on the monitoring task in the CO exposure condition when compared to the control during the final 30 minutes only when performed separately (p<.05).	X
Ramsey, 1972	Blood samples	Normal: 0.79 (0.49) Emphysema: 1.21 (0.53) Anaemic: 0.72 (0.47) Exposed groups average: 0.91	0.49 (0.39)	Normal: 5.06 (1.22) Emphysema: 4.69 (2.20) Anaemic: 6.47 (1.75) Exposed groups average: 5.41 Difference: 4.50 (average mean increase across exposed groups)	0.49 (0.38)	RT to visual stimuli: attention and RT.	No significant differences in RT within or between the groups over time (before/after exposure) (p>.05). Collectively the exposed groups showed a significant increase in RT after exposure (p=.02).	**RT**↓ Normal *0.32* Emphysema *1.83* Anaemic *1.09* Exposed average *1.27*

Benignus et al., (1990)	Blood samples	All groups prior to exposure: 1.11 (0.29), range 0.60-1.90.	All groups prior to exposure: 1.11 (0.29), range 0.60-1.90.	Post bag breathing Low slow: 1.0 (0.22) 0.5-1.4 Low fast: 5.0 (0.48) 4.1-5.8 Medium fast: 9.7 (1.13) 8.0-11.9 High fast: 12.82 (1.12) 11.3-15.5 Post experiment Low slow: 6.1 (0.62) 4.6-7.2 Low fast: 5.6 (0.41) 4.9-6.3 Medium fast: 11.4 (0.74) 10.0-12.8 High fast: 16.6 (0.79) 15.6-17.9	Postbag breathing: 0.9 (0.20) 0.5-1.2, post experiment: 0.9 (0.23) 0.4-1.2.	Tracking task (fast and slow): psychomotor function. Concurrent monitoring task: divided attention, task switching and inhibition (EF). Separate monitoring task: sustained attention and updating (EF).	No significant differences in tracking errors or in performance on the monitoring tasks between any groups (p>.05).	**Tracking error hour 4**$^{\downarrow}$ COHb formation group / Raw score / Base-line Adjusted Low-slow: *0.64* / *0.35* Low-fast: *0.87* / *0.46* Medium-fast: *0.55* / *0.49* High fast: *1.26* / *0.70* X
Ramsey (1973)	Venous blood samples	650ppm: 0.92 (0.61) 950ppm: 0.85 (0.32)	0.81 (0.27)	650ppm group mean: 8.53 (1.50) 950ppm group: 12.07 (2.27)	Mean: 0.78 (0.21)	CFFT: speed of processing. RT task responding to visual stimuli (coloured lights): attention and RT.	No significant CO related effects over time or between the groups on the CFFT. Significant increase in RT between pre and post exposure means in both the 650 (p=.005) and 950ppm (p=.006) conditions. Significant increase in RT in the 650 and 950ppm exposure groups collectively compared to the control group (p<.05).	CO ppm / **RT**$^{\downarrow}$ 650: *0.84* 950: *0.73*
Stewart et al., (1973)	Venous blood samples	NR	PSAC	Range: 0.4-20.	N/A	Time estimation 10s and 30s: sustained attention. BW Auditory tone discrimination task: sustained attention and updating (EF). Marquette time estimation test (MTE): sustained attention, updating (EF) and RT.	Significant decrease in mean correct responses on the auditory discrimination task in the CO exposure condition (COHb level 9.74%) when compared to the control, only within the booth setting (p<0.05). Significant difference between baseline scores and performance after exposure on estimating 30s intervals in the isolated setting only (p<.05). No significant CO-related effects on RTs on the Marquette time estimation test.	**BW time estimation (TE)**$^{\uparrow}$ COHb level % / Group (G) / Isolated (I) / Booth (B) 0.00-2.00: *-0.03* 2.01-4.00: *-0.03* 4.01-8.00: *-0.08* / *0.07* / *-0.56* 8.01-12.00: *0.02* / *0.12* / *0.17* 12.01-16.00: *-0.22* / *-0.67* 16.01-20.00: *-0.08* **10s TE**$^{\uparrow}$ 0.00-2.00: *0.18* / *-0.10* / *-0.03* 2.01-4.00: *0.10* 4.01-8.00: *0.04* / *- 0.27* / *-0.45* 8.01-12.00: *0.11* / *-0.25* / *0.12* 12.01-16.00: *-0.04* / *-1.31* 16.01-20.00: *-0.07* **30s TE**$^{\uparrow}$ 0.00-2.00: *-0.14* / *- 0.42* / *-0.14* 2.01-4.00: *0.01*

								4.01-8.00	*-0.03*	*-0.78*	*-0.21*
								8.01-12.00	*-0.16*	*-0.29*	*-0.12*
								12.01-16.00	*0.12*		*-2.04*
								16.01-20.00	*-0.32*		
Bunnell & Horvath (1988)	Blood samples and CO-oximeter	NR	PSAC	Control Rest condition: 0.66 35% exercise condition: 0.82 60% exercise condition 0.7 7.0 target level Rest condition: 6.74 35% exercise condition: 7.16 60% exercise condition: 7.4 10.0 target level: Rest condition: 9.31 35% exercise condition: 9.99 60% exercise condition: 10.2	N/A	Sitting resting or walking at 35% and 60% of maximum aerobic capacity (Vo_2max). Manikin task: visuospatial ability, attention and RT. The Sternberg task: sustained attention, working memory and sensory memory. Stroop word-colour task Part 1: Attention. Part 2 and Part 3 Cognitive flexibility (adaptation to a new response set) and interference (inhibition and selective attention). Visual search task: sustained attention and RT. Tracking Task: psychomotor function. Concurrent tracking and mathematical equations: Psychomotor function, divided attention, task switching (EF).	No significant CO effects on performance in the Manikin task, Sternberg task, or Tracking task when completed singly or concurrently. The average difference (interference) between the number of responses in part 2 and 3 of the Stroop task was significantly greater in both CO conditions (7 and 10%) compared to the control condition (p=.008). Significant decrease in Stroop 3 total scores in both CO conditions compared to the control condition (p=.004). Significant interaction between RT in the visual search task, CO and workload (p<.004). During the rest condition, mean RT at a COHb level of 10% was less than the control condition. In contrast, in the 60% workload condition mean RT at a COHb level of 10% was greater than in the control condition.	X			
Bunnell & Horvath (1989)	Blood samples and CO-oximeter	NR	PSAC	Control Rest condition: 1.0 35% exercise condition: 1.0 60% exercise condition 1.0 7.0 target level Rest condition: 6.9 35% exercise condition: 7.5 60% exercise condition: 7.9 10.0 target level: Rest condition: 9.4 35% exercise condition: 10.2 60% exercise condition: 10.9	N/A	Same tasks as above.	No significant CO effects on performance in the Manikin task, Sternberg task, Visual search task or Tracking task when completed singly or concurrently. Significant interaction between CO exposure and workload in the Stroop 3 total scores reflecting increased response times as COHb increased during the 60% condition (p=0.04). Interference scores significantly increased with increasing COHb level only in the 60% condition (p=.07).	X			

NR= Not reported. PSAC= Participants served as controls. RT= Reaction time (speed of processing and psychomotor speed). EF= Executive functioning. WAIS= Wechsler adult intelligence scale. WMS= Wechsler memory scale. TMTA/B= Trail making task A/B.RAVLT= Rey Auditory Verbal Learning Test. DSF= Digit span forward. DSB= Digit span backward. CITT=. Critical instability tracking task. CFFT= Critical flicker fusion task.

[1]Classification of effect sizes: trivial (Cohen's d ≤ .2); small (Cohen's d > .2); moderate (Cohen's d > .5); large (Cohen's d > .8); very large (Cohen's d > 1.3).

↑ Positive numbers show a positive effect of CO; ↓Positive numbers show a negative effect of CO.

X= Impossible to calculate effect sizes based on reported results.

Table A1.1.3. MMAT Critical appraisal results for the included studies

Study	S1	S2	2.1	2.2	2.3	2.4	2.5	3.1	3.2	3.3	3.4	3.5
1. Salvatore, 1974	Y	Y	-	-	-	-	-	Y	Y	Y	N	CT
2. Rummo & Sarlanis, 1974	Y	Y	-	-	-	-	-	N	Y	CT	Y	Y
3. Otto et al., 1979	Y	Y	-	-	-	-	-	N	Y	N	Y	Y
4. Harbin et al., 1988	Y	Y	-	-	-	-	-	Y	Y	Y	Y	Y
5. Benignus et al., 1987	Y	Y	CT	Y	Y	Y	Y	-	-	-	-	-
6. Roche et al., 1981	Y	Y	-	-	-	-	-	Y	Y	Y	Y	Y
7. Putz, 1979	Y	Y	CT	Y	Y	Y	Y	-	-	-	-	-
8. Wright & Shephard, 1978	Y	Y	-	-	-	-	-	N	Y	Y	N	CT
9. Amitai et al., 1998	Y	Y	-	-	-	-	-	Y	Y	Y	N	CT
10. O'Donnell et al., 1971a	Y	Y	-	-	-	-	-	N	Y	Y	Y	Y
11. Benignus et al., 1977	Y	Y	CT	Y	Y	Y	Y	-	-	-	-	-
12. Stewart et al., 1970	Y	Y	-	-	-	-	-	N	Y	N	Y	Y
13. Beard & Wertheim, 1967	Y	Y	-	-	-	-	-	CT	Y	Y	N	Y
14. Horvath et al., 1971	Y	Y	-	-	-	-	-	Y	Y	Y	Y	Y
15. O'Donnell et al., 1971b	Y	Y	-	-	-	-	-	N	Y	Y	N	Y
16. Schulte, 1963	Y	Y	CT	CT	Y	N	Y	-	-	-	-	-
17. McFarland, 1973	Y	Y	-	-	-	-	-	CT	Y	N	N	Y
18. Wright, Randell & Shephard, 1973	Y	Y	CT	N	Y	Y	Y	-	-	-	-	-
19. Groll-Knapp et al., 1982	Y	Y	-	-	-	-	-	Y	Y	Y	N	Y
20. Gliner et al., 1983	Y	Y	-	-	-	-	-	Y	Y	Y	N	Y
21. Ramsey, 1972	Y	Y	-	-	-	-	-	CT	CT	Y	Y	Y
22. Benignus et al., 1990	Y	Y	CT	Y	Y	Y	Y	-	-	-	-	-
23. Ramsey, 1973	Y	Y	CT	Y	Y	Y	Y	-	-	-	-	-
24. Stewart et al., 1973	Y	Y	CT	CT	Y	Y	Y	-	-	-	-	-
25. Bunnell & Horvath, 1988	Y	Y	-	-	-	-	-	Y	Y	CT	Y	Y
26. Bunnell & Horvath, 1989	Y	Y	-	-	-	-	-	N	Y	CT	Y	Y

Table A1.1.4. Mixed Methods Appraisal Tool (MMAT), version 2018

Category of study designs	**Methodological quality criteria**
Screening questions	S1. Are there clear research questions?
	S2. Do the collected data allow to address the research questions?
2. Quantitative randomized controlled trials	2.1. Is randomization appropriately performed?
	2.2. Are the groups comparable at baseline?
	2.3. Are there complete outcome data?
	2.4. Are outcome assessors blinded to the intervention provided?
	2.5 Did the participants adhere to the assigned intervention?
3. Quantitative nonrandomized	3.1. Are the participants representative of the target population?
	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?
	3.3. Are there complete outcome data?
	3.4. Are the confounders accounted for in the design and analysis?
	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?

Table A1.1.5. Risk of Bias Assessment results for the included studies; risk-of-bias in non-randomized studies of interventions (ROBINS-I) and Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) assessment tools

ROBINS-I	**Bias due to confounding**	**Bias in selection of participants**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall Bias**
Salvatore, 1974	Serious	Low	Serious	Low	Low	Serious	Low	Serious
Rummo & Sarlanis, 1974	Low	Low	Serious	Low	Low	Serious	Moderate	Serious
Otto et al., 1979	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Harbin et al., 1988	Low	Low	Low	Low	Low	Low	Low	Low
Roche et al., 1981	Low	Low	Low	Low	Low	Low	Low	Low
Wright & Shephard 1978	Serious	Low	Serious	Low	Low	Serious	Low	Serious
Amitai et al., 1998	Serious	Low	Serious	Moderate	Low	Serious	Low	Serious
O'Donnell et al., 1971a	Low	Low	Low	Low	Low	Low	Low	Low
Stewart et al., 1970	Low	Low	Low	Low	Moderate	Moderate	Low	Moderate
Beard & Wertheim, 1967	Serious	Low	Serious	Low	Low	Serious	Low	Serious
Horvath et al., 1971	Low	Low	Serious	Low	Low	Serious	Low	Serious
O'Donnell et al., 1971b	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
McFarland, 1973	Serious	Low	Serious	Low	Serious	Serious	Moderate	Serious
Groll-Knapp et al., 1982	Serious	Low	Serious	Low	Low	Low	Moderate	Serious
Gliner et al., 1983	Serious	Low	Serious	Low	Low	Serious	Low	Serious
Ramsey, 1972	Moderate	Low	Serious	Low	Low	Serious	Low	Serious
Bunnell & Horvath, 1988	Low	Low	Serious	Low	Serious	Serious	Moderate	Serious
Bunnell & Horvath, 1989	Low	Low	Serious	Low	Serious	Serious	Serious	Serious

RoB 2	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**			**Overall bias**
Benignus et al., 1987	Low	Low	Low	Low	Low	X	X	Low
Putz, 1979	Low	Low	Low	Low	Low	X	X	Low
Benignus et al., 1977	Low	Low	Low	Low	Some concerns	X	X	Some concerns
Schulte, 1963	High	Low	Low	High	Low	X	X	High
Wright, Randell & Shephard, 1973	Low	Low	Low	High	Some concerns	X	X	High
Benignus et al., 1990	Low	Low	Low	Low	Low	X	X	Low
Ramsey, 1973	Some concerns	Low	Low	Low	Some concerns	X	X	Some concerns
Stewart et al., 1973	Low	Low	Low	Low	Low	X	X	Low

Table A1.1.6. Task descriptions and assignment to cognitive domains.

Study	Task Description	Cognitive Domain
Amitai et al., 1998	Block Design (WAIS)	Visuospatial Ability and Problem Solving
Stewart et al., 1970	Flanagan Test - drawing spirals freehand.	Visuospatial Ability
Bunnell & Horvath, 1988; 1989	Manikin Task- a figure displayed in various orientations holding an orange block in one hand and a blue block in the other. Participants had to indicate which hand held the block that matched the colour of the base upon which the manikin stood.	
O'Donnell et al., 1971a Stewart et al., 1973 O'Donnell et al., 1971b	Time Estimation Task - estimating 10 and 30s intervals.	Sustained Attention
Roche et al., 1981 Horvath et al., 1971	Visual Monitoring Task - participants pressed one of two buttons in response to a series of light pulses that were either bright (signals) or dim (non-signals).	
Otto et al., 1979 Wright & Shephard, 1978 Beard & Wertheim, 1967 O'Donnell et al., 1971b	Auditory Time Discrimination Task- discrimination between a pair of tones the first 1000Hz for a 1s duration followed by a second tone between 0.675 and 1.325s. Participants judged whether the second tone was shorter than, equal to, or longer than the first.	Sustained Attention and Updating (Executive Function)
Stewart et al., 1973 Stewart et al., 1970; 1973 Benignus et al., 1977 Benignus et al., 1990	Marquette Light and Auditory Tone Time Discrimination Task - stimuli presented for 1, 3, or 5s duration, participants had to push a button for an interval of time estimated to be equal in length to the original tone or light stimuli. Numeric Monitoring Task - a sequence of single digit numerals were displayed randomly for 50ms and participants had to press a button when three consecutive even or odd digits were displayed. Auditory Monitoring Task - detecting the middle pitch of three tones.	
Gliner et al., 1983	Visual Monitoring Task - responding only to bright light pulses dispersed in a series containing both dim and bright lights.	Sustained Attention and Inhibition (Executive Function)
Benignus et al., 1987 Putz, 1979	Tracking and Visual Monitoring Task - keeping a beam of light centred on a stationary target using a joystick (two tracking conditions fast and slow) whilst concurrently responding with a button press to light pulses to	Divided Attention, Task switching, Inhibition (Executive Function) and Psychomotor Function

Gliner et al., 1983	either the left or right of the screen that were either bright (signal) or dim (non-signal) with responses made only to signals.	
Benignus et al., 1990	Tracking and Visual Monitoring Task - keeping a moving vertical line centred on a screen using a hand control with three levels of task difficulty (the instability of line was increased until the participant could no longer track it) whilst concurrently responding to light pulses that would either be bright (signal) or dim (non-signal) with responses made only to signals. Tracking and Visual Monitoring Task - keeping a beam of light centred on a stationary target whilst concurrently responding with a button press to bright lights in a series of light flashes.	
Bunnell & Horvath, 1988; 1989	Tracking Task - keeping a moving square within a large target square using a joystick both singly and whilst concurrently answering mathematical equations displayed in the bottom of the screen.	Divided Attention, Task Switching (Executive Function) and Psychomotor Function
Rummo & Sarlanis, 1974	Driving Task - following a lead car at a specified distance and responding to speed changes (speeding up and slowing down) whilst concurrently responding to randomly presented light on the dashboard by depressing a foot pedal.	
Stewart et al., 1970	Driving Stimulator - participants had to respond to one of three stimuli by either turning the steering wheel right or left or by removing their foot from the accelerator pedal and depressing the brake	
McFarland, 1973	Responding to red and green lights presented randomly in the central field of vision (responses made with foot pedals) whilst also responding to six lights where one would illuminate randomly presented in the periphery by pressing a finger button.	
O'Donnell et al., 1971b	Tracking and Visual Monitoring Task - keeping a needle dial centred whilst monitoring three dials located above the tracking dial. At different time points, one of the 3 dials would go off centre requiring adjustment (moderate workload). A high workload condition was also employed which included the same tasks as above with the addition of a further concurrent monitoring task (remembering the amount of times that three separate lights flashed in a randomised order).	High workload additional domain of Working Memory
Stewart et al., 1970	The AAA Hand Steadiness Task - passing a metal wand down through a narrowing V-shaped vertical slot. Contact with the sides created an electrical circuit and a light illuminated (scored in terms of wand position). The Crawford Collar and Pin Task - picking up a pin with forceps, placing it upright in a hole, and then using the forceps to place the collar over the pin. The Crawford Screw Task - driving a screw through a threaded hole using a screwdriver (both scored in terms of number completed in 3 minutes).	Fine Motor Control, Psychomotor Function and Speed
O'Donnell et al., 1971a	Critical Instability Tracking Task - keeping a needle from going off the scale of a display dial by manipulating a control stick.	
Bunnell & Horvath, 1988; 1989	Tracking Task - keeping a moving square within a large target square.	

Schulte, 1963	Plural Noun-underlying Task (completion time reported) and T crossing Task (completion time and errors reported).	
Amitai et al., 1998	Digit-symbol Task (WAIS). Trail Making Part A Task	
Wright, Randell & Shephard,1973	Hand-steadiness task- passing a stylus through two narrowing metal plates without touching the sides.	
Ramsey, 1973 O'Donnell et al., 1971b	The Critical Flicker Fusion task - frequency at which a flickering light is indistinguishable from a continuous light.	Speed of Processing
Salvatore, 1974	RT to Visual Light Stimuli - participants had to detect a light beam presented either right or left of a fixation point under two conditions static (target remained once presented) and dynamic (moving target).	RT (Speed of Processing and Psychomotor Speed), and Attention
Harbin et al., 1988	RT to Visual Light Stimuli - a box containing eight lights one of which would illuminate requiring participants to press a button as quickly as possible.	
Schulte, 1963	RT to Visual Stimuli - responding to colours or letters.	
Wright, Randell & Shephard,1973	RT in a Driving Task - brake RTs measured using accelerator and brake pedals. When the accelerator was depressed a green light was displayed, when this turned red the participant had to press the brake pedal.	
Ramsey, 1972	RT to Visual Stimuli.	
Ramsey, 1973	Visual Choice RT Task - responding to coloured lights.	
Bunnell & Horvath, 1988; 1989	RT measured in the Manikin Task (detailed above). RT measured in The Sternberg Task - a series of 4 digits were presented followed by a probe digit, participants indicate whether the target digit was amongst the 4 digits previously presented. Visual Search Task - matrices containing a target letter randomly presented amongst non-target letters.	
Bunnell & Horvath, 1989	RT measured in the Stroop Word Colour Task (3 parts) - part 1 consisted of the words green, blue and red appearing on a screen in black (response made to the colour of the word). In part 2 the same words appeared in colours that may or may not have corresponded to the word (responses made corresponding to identifying the word read rather than the colour). Part 3 consisted of the same stimuli used in part 2 however; responses were made to the colour of the word.	
Rummo & Sarlanis, 1974	RT in a Driving Task - following a lead car at a specified distance and responding to speed changes (speeding up and slowing down) whilst concurrently responding to randomly presented light on the dashboard by depressing a foot pedal.	RT and Divided Attention
Benignus et al., 1987	RT measured in the Monitoring Task - responding to illuminating lights on either side of a screen (responses were made to bright lights only) whilst concurrently carrying out a tracking task.	
Putz, 1979		

Stewart et al., 1970	RT measured in the Monitoring Task - responding to illuminating lights on either side of a screen (responses were made to bright lights only) whilst concurrently carrying out a tracking task.	
O'Donnell et al., 1971b	RT in a Driving Simulator - participants had to respond to one of three stimuli by either turning the steering wheel right or left or by removing their foot from the accelerator pedal and depressing the brake	
McFarland, 1973	RT measured in the Monitoring Task- monitoring three dials located above the tracking dial. At different time points, one of the 3 dials would go off centre requiring adjustment, whilst concurrently carrying out a tracking task.	
Bunnell and Horvath, 1988; 1989	RT to red and green lights presented randomly in the central field of vision (responses made with foot pedals) whilst also responding to six lights where one would illuminate randomly presented in the periphery by pressing a finger button.	
	RT to answering mathematical problems whilst concurrently completing a tracking task.	
Stewart et al., 1973	RT during the Marquette Light and Auditory Tone Time Discrimination Task (detailed above).	RT and Sustained Attention
McFarland, 1973	Driving Task - driving a car down a road and remaining in lane at two different speeds (30 and 50 mph). Participants wore a face shield that occluded vision was lifted by depressing a foot pedal enabling them view of the road for a set period of time.	Working Memory and Short term/ sensory memory
Bunnell and Horvath, 1988; 1989	The Sternberg Task (detailed above).	
O'Donnell et al., 1971b	High workload condition: additional concurrent monitoring task (remembering the amount of times that three separate lights flashed in a randomised order). Mental Arithmetic Task	
Schulte, 1963	Mental Arithmetic Task	
Amitai et al., 1998	Digit Span Forward, Digit Span Backward (WAIS). Memory (WMS-R). RAVLT	
Amitai et al., 1998	WMS-R. RAVLT	Learning Ability and Long-term Memory
Groll-Knapp et al., 1982	Memory Test - 3-minute learning period of a list of words followed by a recall at 6 minutes and a further recall after 8 hours of sleep.	
Bunnell & Horvath, 1988; 1989	Stroop Word-colour Task (detailed above).	Cognitive Flexibility (adaptation to a new response set) and Interference (inhibition and selective attention)
Amitai et al., 1998	Trail Making Task Part B	

WAIS=Wechsler Adult Intelligence Scale; WMS-R= Wechsler Memory Scale revised; RAVLT=The Rey Auditory Verbal Learning Test; RT= reaction time.

A1.2: Study 3, Chapter 4 (Cross-sectional study)

Table A1.2.1. Regression model details with the percentage of CO readings between 6.5-9ppm and 9.5-30ppm at predicting variance in WAIS BD scores and the interaction effect between age and CO at each level.

WAIS BD	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	5.252***		5.276***		5.203***					
Age	-.024	-.198*	-.021	-.178*	-.027	-.223**	-.238	-.272	-.208	.043
NART	-.056	-.589***	-.057	-.603***	-.058	-.608***	-.603	-.631	-.599	.359
Smoking	-.442	-.120	-.464	-.126	-.526	-.143	-.027	-.184	-.138	.019
0ppm			-.013	-.111	.010	.080	-.077	.078	.058	.003
Age*CO					.003	.278**	.147	.265	.202	.041
R^2	.406		.417		.458			**Variance explained (%)**		
F	22.509		17.542		16.408			Independent		46.5
ΔR^2			.012		.041			Shared		.00
ΔF			1.974		7.336					

N= 103, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	5.255***		5.291***		5.210***					
Age	-.025	-.203*	-.023	-.193*	-.036	-.299***	-.267	-.351	-.269	.072
NART	-.055	-.571***	-.056	-.579***	-.053	-.550***	-.595	-.599	-.538	.289
Smoking	-.448	-.122	-.485	-.132	-.597	-.163*	-.030	-.213	-.156	.024
0.5-3ppm			.017	.101	-.014	-.082	.073	-.094	-.068	.005
Age*CO					-.006	-.344***	-.229	-.362	-.279	.078
R^2	.397		.407		.485			**Variance explained (%)**		
F	21.531		16.662		18.071			Independent		46.8
ΔR^2			.010		.078			Shared		1.7
ΔF			1.635		14.460					

N= 102, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	5.258***		5.335***		5.295***					
Age	-.018	-.156	-.018	-.153	-.041	-.352**	-.201	-.272	-.213	.045
NART	-.053	-.577***	-.051	-.555***	-.050	-.542***	-.586	-.573	-.528	.279
Smoking	-.666	-.181*	-.609	-.165*	-.587	-.160*	-.112	-.202	-.156	.024
3.5-6ppm			.295	.136	.168	.077	.241	.094	.071	.005
Age*CO					-.069	-.257*	-.024	-.199	-.154	.024
R^2	.390		.407		.431			**Variance explained (%)**		
F	20.428		16.330		14.241			Independent		37.7
ΔR^2			.018		.024			Shared		5.4
ΔF			2.852		3.895					

N= 100, *p<.05, **p<.01 ** p<.001 ***

	Model 1	**Model 2**	**Model 3**	**Correlations**

Variable	B	β	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	5.255***		5.308***		5.296***					
Age	-.017	-.147	-.014	-.126	-.017	-.148	-.150	-.112	-.084	.007
NART	-.054	-.594***	-.052	-.568***	-.052	-.569***	-.593	-.598	-.560	.314
Smoking	-.742	-.211*	-.731	-.208**	-.742	-.211*	-.143	-.260	-.202	.041
6.5-9ppm			.922	.183*	.784	.155	.278	.103	.078	.006
Age*CO					-.028	-.037	-.092	-.021	-.016	.000
R^2	.404		.436		.437			**Variance explained (%)**		
F	22.159		18.778		14.883			Independent		36.8
ΔR^2			.032		.000			Shared		6.9
ΔF			5.549		.043					

N= 102, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	5.220***		5.228***		5.217***					
Age	-.010	-.085	-.004	-.033	-.005	-.045	-.195	-.048	-.035	.001
NART	-.052	-.553***	-.047	-.498***	-.047	-.497***	-.596	-.532	-.468	.219
HSH	-.054	-.140	-.077	-.198*	-.078	-.201*	-.314	-.225	-.172	.030
9.5-30ppm			.865	.247**	.713	.203	.325	.114	.086	.007
Age*CO					-.030	-.049	-.239	-.027	-.020	.000
R^2	.390		.445		.446			**Variance explained (%)**		
F	21.297		19.855		15.750			Independent		25.7
ΔR^2			.055		.000			Shared		18.9
ΔF			9.865		.073					

N= 104, *p<.05, **p<.01 ** p<.001 ***

Table A1.2.2. Regression model details with the percentage of CO readings at 0ppm and between 0.5-3ppm, 3.5-6ppm, 6.5-9ppm and 9.5-30ppm predicting variance in WMS-R scores and the interaction effect between age and CO at each level.

WMS-R	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	18.942***		18.988***		18.661***					
Age	-.094	-.263**	-.072	-.203*	-.093	-.261**	-.342	-.267	-.225	.051
NART	-.088	-.311**	-.091	-.324***	-.093	-.330***	-.370	-.363	-.318	.101
HSH	-.128	-.109	-.171	-.146	-.145	-.124	-.296	-.132	-.108	.017
0ppm			-.050	-.198*	.054	.216	-.206	.135	.111	.012
Age*CO					.011	.475**	.280	.296	.252	.064
R^2	.238		.273		.337			**Variance explained (%)**		
F	10.387		9.301		9.952			Independent		24.5
ΔR^2			.036		.064			Shared		9.2
ΔF			4.845		9.399					

N= 104, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	Part^2

Constant	18.946***		19.000***		18.683***					
Age	-.108	-.304**	-.092	-.257**	-.110	-.308**	-.342	-.332	-.290	.084
NART	-.094	-.335***	-.103	-.364***	-.101	-.359***	-.370	-.393	-.353	.125
0.5-3ppm			.057	.200*	-.058	-.202	.213	-.120	-.099	.010
Age*CO					-.012	-.456**	-.270	-.269	-.230	.053
R^2	.228		.265		.318			**Variance explained (%)**		
F	14.924		12.040		11.563			Independent		27.2
ΔR^2			.037		.053			Shared		4.6
ΔF			5.070		7.709					

N= 104, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	18.977***		19.161***		18.634***					
Age	-.091	-.260**	-.081	-.231*	-.140	-.400***	-.291	-.391	-.346	.120
NART	-.099	-.357***	-.099	-.357***	-.114	-.413***	-.380	-.445	-.405	.164
3.5-6ppm			.848	.175*	-.754	-.156	.219	-.128	-.105	.011
Age*CO					-.231	-.467***	-.207	-.353	-.307	.094
R^2	.211		.241		.336			**Variance explained (%)**		
F	13.276		10.396		12.262			Independent		38.9
ΔR^2			.030		.094			Shared		.000
ΔF			3.868		13.790					

N= 102, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	18.977***		19.036***		18.193***					
Age	-.091	-.260**	-.089	-.253**	-.248	-.706***	-.291	-.458	-.422	.178
NART	-.099	-.357***	-.096	-.348***	-.102	-.369***	-.380	-.406	-.363	.132
6.5-9ppm			1.006	.066	-7.709	-.506**	.148	-.300	-.257	.066
Age*CO					-1.776	-.764***	-.080	-.384	-.340	.116
R^2	.211		.216		.331			**Variance explained (%)**		
F	13.276		8.984		12.003			Independent		49.2
ΔR^2			.004		.115			Shared		.000
ΔF			.527		16.733					

N= 102, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	18.987***		18.984***		18.484***					
Age	-.101	-.287**	-.103	-.290**	-.178	-.503***	-.320	-.448	-.414	.171
NART	-.095	-.336***	-.096	-.341***	-.095	-.336***	-.365	-.369	-.329	.108
9.5-30ppm			-.323	-.031	-7.453	-.709**	.071	-.340	-.299	.089
Age*CO					-1.374	-.754***	-.110	-.358	-.317	.100
R^2	.214		.215		.316			**Variance explained (%)**		
F	13.766		9.135		11.422			Independent		46.8
ΔR^2			.001		.101			Shared		.000
ΔF			.114		14.565					

N= 104, *p<.05, **p<.01 ** p<.001 ***

Table A1.2.3. Regression model details with the percentage of CO between 6.5-9ppm predicting variance in CORSI scores.

CORSI	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	5.603***		5.601***		5.583***					
Age	-.010	-.081	-.006	-.047	-.006	-.054	-.121	-.058	-.053	.003
NART	-.034	-.355***	-.031	-.324**	-.031	-.324**	-.365	-.333	-.318	.101
6.5-9ppm			.481	.215*	.275	.123	.276	.088	.080	.006
Age*CO					-.030	-.121	-.257	-.088	-.080	.006
R^2	.139		.183		.190			**Variance explained (%)**		
F	8.015		7.328		5.673			Independent		11.6
ΔR^2			.044		.006			Shared		7.4
ΔF			5.265		.760					

N= 102, *p<.05, **p<.01 ** p<.001 ***

Table A1.1.4. Regression model details with the percentage of CO between 3.5-6ppm and 6.5-9ppm predicting variance in TOL scores.

TOL	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	2.598***		2.578***		2.576***					
Age	-.009	-.121	-.004	-.063	-.004	-.062	-.121	-.063	-.060	.004
3.5-6ppm			.170	.264**	.175	.271	.278	.185	.180	.032
Age*CO					.000	.010	-.194	.007	.007	.000
R^2	.015		.081		.081			**Variance explained (%)**		
F	1.512		4.401		2.906			Independent		3.6
ΔR^2			.066		.000			Shared		4.5
ΔF			7.196		.005					

N= 103, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	2.593***		2.593***		2.603***					
Age	-.009	-.127	-.006	-.090	-.007	-.096	-.127	-.097	-.094	.009
6.5-9ppm			.297	.218*	.191	.141	.234	.094	.092	.008
Age*CO					-.015	-.102	-.214	-.069	-.067	.005
R^2	.016		.062		.067			**Variance explained (%)**		
F	1.677		3.365		2.393			Independent		2.2
ΔR^2			.046		.005			Shared		4.5
ΔF			4.986		.484					

N= 104, *p<.05, **p<.01 ** p<.001 ***

Table A1.2.5. Regression model details with the percentage of CO at 0ppm and between 0.5-3ppm and 3.5-6ppm predicting variance in DSB scores.

DSB	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	2.038***		2.050***		2.045***					

Age	-.005	-.160	-.004	-.116	-.004	-.126	-.216	-.146	-.120	.014
NART	-.013	-.496***	-.014	-.521***	-.014	-.522***	-.514	-.534	-.515	.265
0ppm			-.007	-.216*	-.006	-.172	-.189	-.150	-.123	.015
Age*CO					.000	.063	.122	.056	.046	.002
R^2	.290		.334		.336			**Variance explained (%)**		
F	20.601		16.713		12.528			Independent		29.6
ΔR^2			.044		.002			Shared		4.0
ΔF			6.638		.317					

N= 104, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	2.038***		2.053***		2.048***					
Age	-.005	-.160	-.004	-.115	-.004	-.124	-.216	-.143	-.118	.014
NART	-.013	-.496***	-.015	-.537***	-.015	-.537***	-.514	-.542	-.525	.276
0.5-3ppm			.009	.221*	.008	.183	.156	.162	.134	.018
Age*CO					.000	-.056	-.092	-.051	-.041	.002
R^2	.290		.335		.337			**Variance explained (%)**		
F	20.601		16.808		12.577			Independent		31.0
ΔR^2			.045		.002			Shared		2.7
ΔF			6.840		.257					

N= 104, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	2.033***		2.063***		2.065***					
Age	-.003	-.099	-.003	-.098	-.002	-.049	-.167	-.035	-.030	.001
NART	-.014	-.499***	-.013	-.474***	-.013	-.477***	-.512	-.486	-.465	.216
3.5-6ppm			.106	.163[a]	.115	.177[a]	.239	.192	.164	.027
Age*CO					.005	.063	.073	.044	.037	.001
R^2	.272		.298		.299			**Variance explained (%)**		
F	18.290		13.711		10.245			Independent		24.5
ΔR^2			.026		.001			Shared		5.4
ΔF			3.586		.190					

N= 101, *p<.05, **p<.01 ** p<.001 ***

Table A1.2.6. Regression model details with the percentage of CO between 9.5-30ppm predicting variance in UFOV SA scores.

UFOVSA	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	17.094***		17.075***		17.137***					
Age	.282	.574***	.273	.555***	.282	.574***	.596	.555	.475	.226
NART	.134	.338***	.124	.312***	.123	.311***	.375	.394	.305	.093
9.5-30ppm			-2.171	-.150*	-1.291	-.089	-.284	-.053	-.038	.001
Age*CO					.170	.067	.106	.040	.028	.001
R^2	.469		.490		.491			**Variance explained (%)**		
F	43.737		31.438		23.413			Independent		32.1

ΔR^2	.021	.001	Shared	17.0
ΔF	4.100	.154		

N= 102, **p*<.05, ***p*<.01 ** *p*<.001 ***

A1.3: Study 4, Chapter 5 (Longitudinal study)

Table A1.3.1. Regression model with the percentage of CO at 0ppm and between 0.5-3ppm and 3.5-6ppm T1 and T2 predicting variance in DSF scores.

WAIS DSF	**Model 1**		**Model 2**		**Correlations**			
Variable	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	3.520***		3.686***					
HSH	.111	.203*	.085	.155	.113	.220	.157	.025
NART	-.037	-.339**	-.030	-.273**	-.486	-.341	-.252	.064
DSF T1	.385	.396***	.391	.402***	.502	.465	.366	.134
0ppm T1			.029	.143	.184	.230	.165	.027
0ppm T2			-.111	-.338***	-.374	-.234	-.168	.028
R^2	.386		.505			**Variance explained (%)**		
F	14.466		13.657			Independent		28.8
ΔR^2			.119			Shared		22.6
ΔF			8.026					

N= 73; [a]= nearly significant, **p*<.05, ***p*<.01 ** *p*<.001 ***

	Model 1		**Model 2**		**Correlations**			
Variable	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	3.520***		3.684***					
HSH	.111	.203*	.088	.160	.113	.222	.160	.026
NART	-.037	-.339**	-.031	-.280**	-.486	-.340	-.254	.065
DSF T1	.385	.396***	.388	.399***	.502	.453	.357	.127
0.5-3ppm T1			-.031	-.144	-.217	-.187	-.134	.018
0.5-3ppm T2			.118	.329***	.359	.239	.173	.030
R^2	.386		.504			**Variance explained (%)**		
F	14.466		13.594			Independent		26.9
ΔR^2			.117			Shared		23.8
ΔF			7.929					

N= 73, **p*<.05, ***p*<.01 ** *p*<.001 ***

	Model 1		**Model 2**		**Correlations**			
Variable	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	3.569***		3.589***					
HSH	.120	.221*	.102	.189*	.163	.284	.210	.044
NART	-.039	-.365**	-.032	-.294**	-.521	-.343	-.259	.067
DSF T1	.374	.379***	.394	.399***	.501	.463	.370	.137
3.5-6ppm T1			-.379	-.172	-.011	-.160	-.115	.013
3.5-6ppm T2			.987	.296**	.306	.348	.263	.069
R^2	.416		.477			**Variance explained (%)**		
F	16.634		12.391			Independent		35.0
ΔR^2			.061			Shared		14.7
ΔF			3.935					

N= 74, **p*<.05, ***p*<.01 ** *p*<.001 ***

Table A1.3.2.Regression model with the percentage of CO between 3.5-6ppm T1 and T2 predicting variance in UFOV PS scores.

UFOV PS	**Model 1**	**Model 2**	**Correlations**

Variable	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	.625***		.608***					
NART	-.002	-.077	-.004	-.156	.069	-.190	-.149	.022
UFOV PS T1	.554	.560***	.551	.557***	.539	.551	.508	.258
3.5-6ppm T1			.123	.280*	.264	.255	.204	.042
3.5-6ppm T2			-.204	-.250*	-.057	-.196	-.154	.024
R^2	.296		.378			**Variance explained (%)**		
F	14.951		10.461			Independent		37.6
ΔR^2			.081			Shared		3.1
ΔF			4.498					

N= 74, *p<.05, **p<.01 ** p<.001 ***

Table A1.3.3. Regression model with the percentage of CO between 3.5-6ppm and 6.5-30ppm T1 and T2 predicting variance in WAIS BD scores.

WAIS BD	**Model 1**		**Model 2**		**Correlations**			
Variable	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	.530		.754*					
Age	-.011	-.089	-.016	-.127[a]	-.229	-.233	-.120	.014
WAIS BD T1	.899	.837***	.871	.812***	.852	.842	.778	.605
3.5-6ppm T1			-.245	-.129	.022	-.197	-.100	.010
3.5-6ppm T2			.583	.161*	.207	.249	.128	.016
R^2	.734		.751			**Variance explained (%)**		
F	96.473		51.319			Independent		64.5
ΔR^2			.017			Shared		10.7
ΔF			2.375					

N= 73; [a]= nearly significant; *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Correlations**			
Variable	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	.553		.768					
Age	-.011	-.093	-.014	-.122	-.221	-.237	-.127	.016
WAIS BD T1	.894	.821***	.888	.815***	.835	.839	.805	.648
6.5-30ppm T1			-.730	-.065	.023	-.139	-.073	.005
6.5-30ppm T2			2.200	.171[a]	.104	.233	.125	.016
R^2	.706		.724			**Variance explained (%)**		
F	81.672		43.228			Independent		68.9
ΔR^2			.018			Shared		3.9
ΔF			2.112					

N= 71; [a]= nearly significant; *p<.05, **p<.01 ** p<.001 ***

Table A1.3.4. Regression model with the percentage of CO between 6.5-30ppm T1 and T2 predicting variance in TMTA scores.

TMTA	**Model 1**		**Model 2**		**Correlations**			
Variable	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	1.133***		1.153***					
NART	.002	.178*	.003	.230*	.322	.314	.218	.048
TMTA T1	.079	.655***	.081	.673***	.694	.692	.633	.401

6.5-30ppm T1			-.242	-.141	-.020	-.209	-.141	.020
6.5-30ppm T2			.540	.274*	.028	.298	.206	.042
R^2	.512		.551			**Variance explained (%)**		
F	35.704		20.279			Independent		52.2
ΔR^2			.039			Shared		4.1
ΔF			2.880					

N= 71, *p<.05, **p<.01 ** p<.001 ***

Table A1.3.5. Regression model with the percentage of CO at 0ppm, between 0.5-3ppm and 3.5-6ppm T1 and T2 predicting variance in SART IIV scores.

SART-IIV	**Model 1**		**Model 2**		**Correlations**			
Variable	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	.398***		.394***					
NART	.001	.204*	.001	.156	.233	.201	.157	.025
SART IIV T1	.466	.512***	.481	.528***	.523	.593	.562	.316
3.5-6ppm T1			.030	.242*	.193	.337	.273	.075
3.5-6ppm T2			-.025	-.109	-.035	-.217	-.170	.029
R^2	.315		.363			**Variance explained (%)**		
F	16.804		10.120			Independent		49.8
ΔR^2			.048			Shared		
ΔF			2.669					

N= 76, *p<.05, **p<.01 ** p<.001 ***

Table A1.3.6. Regression model with the percentage of CO between 6.5-30ppm T1 and T2 predicting variance in UFOV SA scores.

UFOV-SA	**Model 1**		**Model 2**		**Correlations**			
Variable	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	1.972		1.604					
Hours in home	.408	.183**	.482	.216**	.305	.398	.197	.039
Depression	-.145	-.113[a]	-.182	-.142*	.077	-.265	-.125	.016
UFOV-SA T1	.864	.846***	.881	.863***	.863	.877	.828	.686
6.5-30ppm T1			1.111	.131*	-.090	.250	.117	.014
6.5-30ppm T2			-1.518	-.084	-.062	-.090	-.041	.002
R^2	.778		.793			**Variance explained (%)**		
F	81.705		52.116			Independent		75.8
ΔR^2			.015			Shared		3.6
ΔF			2.496					

N= 74, *p<.05, **p<.01 ** p<.001 ***

Table A1.3.7. Regression model with the percentage of total CO readings and age*total exposure at 0ppm and between 0.5-3ppm, 3.5-6ppm and 6.5-30ppm predicting variance in WMS recognition scores.

WMS-R	**Model 1**	**Model 2**	**Model 3**	**Correlations**

Variable	B	β	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	11.794***		12.144***		13.427***					
Age	-.032	-.103	-.029	-.095	-.050	-.163	-.297	-.196	-.140	.020
NART	-.068	-.300**	-.074	-.324**	-.083	-.366***	-.477	-.409	-.314	.099
WMS-R T1	.387	.479***	.372	.460***	.291	.360**	.627	.359	.270	.073
T 0ppm			-.033	-.071	.050	.107	-.104	.102	.072	.005
Age*CO					.011	.275*	.258	.240	.174	.030
R^2	.474		.478		.508			**Variance explained (%)**		
F	21.313		16.030		14.264			Independent		22.7
ΔR^2			.004		.030			Shared		28.1
ΔF			.570		4.234					

N= 75, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	11.883***		11.999***		13.364***					
Age	-.033	-.107	-.028	-.093	-.046	-.152	-.298	-.183	-.131	.017
NART	-.070	-.309**	-.072	-.319**	-.085	-.376***	-.477	-.426	-.331	.110
WMS-R T1	.383	.474***	.378	.469***	.296	.367**	.621	.369	.279	.078
T 0.5-3ppm			.031	.079	-.038	-.098	.106	-.092	-.065	.004
Age*CO					-.011	-.259[a]	-.245	-.224	-.162	.026
R^2	.474		.480		.506			**Variance explained (%)**		
F	21.625		16.376		14.338			Independent		23.5
ΔR^2			.006		.026			Shared		27.1
ΔF			.804		3.698					

N= 76, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	12.808***		12.867***		10.955***					
Age	-.013	-.043	-.013	-.044	.093	.315	-.175	.217	.159	.025
NART	-.075	-.339**	-.080	-.364**	-.076	-.343**	-.530	-.384	-.298	.089
WMS-R T1	.333	.418***	.319	.401***	.421	.529***	.582	.490	.403	.162
T 3.5-6ppm				-.105	-.584	-.090	-.063	-.121	-.087	.008
Age*CO					.311	.408*	.112	.285	.213	.045
R^2	.430		.441		.486			**Variance explained (%)**		
F	17.383		13.409		12.685			Independent		32.9
ΔR^2			.010		.045			Shared		15.7
ΔF			1.277		5.913					

N= 73, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	Part^2
Constant	12.229***		12.551***		12.503***					
Age	-.024	-.081	-.023	-.077	-.020	-.069	-.227	-.076	-.055	.003
NART	-.070	-.321**	-.077	-.350***	-.077	-.352***	-.489	-.411	-.321	.103
WMS-R T1	.363	.451***	.336	.418***	.338	.421***	.594	.451	.360	.130
T 6.5-30ppm			-1.866	-.226*	-1.881	-.227*	-.247	-.298	-.222	.049
Age*CO					.019	.149	-.061	.018	.013	.000
R^2	.443		.493		.493			**Variance explained (%)**		
F	18.817		16.984		13.402			Independent		28.5

ΔR^2	.050	.000	Shared	20.8
ΔF	6.841	.022		

N= 75, *p<.05, **p<.01 ** p<.001 ***

Table A1.3.8. Regression model with the percentage of total CO readings and age*total exposure between 3.5-6ppm predicting variance in DSB scores.

DSB	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	1.798*		1.111		1.066					
Age	-.031	-.229*	-.030	-.219*	-.053	-.387*	-.269	-.284	-.225	.051
NART	-.034	-.336**	-.035	-.339**	-.033	-.318**	-.487	-.346	-.280	.078
DSB T1	1.157	.305**	1.412	.372**	1.438	.379**	.474	.390	.322	.104
T 3.5-6ppm			-.621	-.206*	-.623	-.207*	-.035	-.249	-.195	.038
Age*CO					-.073	-.208	.116	-.157	-.121	.015
R^2	.370		.407		.422			**Variance explained (%)**		
F	13.483		11.689		9.786			Independent		28.6
ΔR^2			.038		.015			Shared		13.6
ΔF			4.346		1.697					

N= 73, *p<.05, **p<.01 ** p<.001 ***

Table A1.3.9. Regression model with the percentage of total CO readings and age*total exposure between 3.5-6ppm predicting variance in WAIS-BD scores.

WAIS-BD	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	.842*		.858*		.553					
Age	-.014	-.115	-.014	-.116	.018	.143	-.304	.158	.081	.007
WAIS-BD T1	.840	.812***	.838	.810***	.893	.863***	.839	.841	.780	.608
T 3.5-6ppm			.019	.007	-.008	-.003	.213	-.005	-.003	.000
Age*CO					.099	.309**	.220	.335	.179	.032
R^2	.716		.716		.748			**Variance explained (%)**		
F	88.185		57.964		50.433			Independent		64.7
ΔR^2			.000		.032			Shared		10.1
ΔF			.011		8.625					

N= 73, *p<.05, **p<.01 ** p<.001 ***

Table A1.3.10. Regression model with the percentage of total CO readings and age*total exposure at 0ppm and between 0.5-3ppm predicting variance in CORSI BS scores.

CORSI	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	8.768		8.363		8.552					
Age	-.233	-.166	-.157	-.111	-.108	-.076	-.346	-.084	-.065	.004
Hours in home	-1.113	-.210*	-1.058	-.200*	-1.094	-.206*	-.277	-.245	-.196	.038
CORSI T1	4.084	.459***	4.306	.484***	4.401	.495***	.510	.519	.472	.223
T 0ppm			-.414	-.200*	-.659	-.318*	-.228	-.253	-.204	.042

Age*CO				-.026	-.152	.077	-.130	-.102	.010
R^2	.350		.386		.397		**Variance explained (%)**		
F	12.549		10.861		8.942		Independent		31.7
ΔR^2			.037		.010		Shared		8.0
ΔF			4.121		1.162				

N= 74, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	7.808		6.994		7.138					
Age	-.208	-.153	-.132	-.097	-.072	-.053	-.345	-.059	-.045	.002
Hours in home	-1.058	-.206*	-1.015	-.198*	-1.073	-.209*	-.273	-.256	-.199	.040
CORSI T1	4.318	.501***	4.599	.534***	4.726	.549***	.550	.567	.518	.268
T 0.5-3ppm			.434	.195*	.768	.345*	.195	.275	.215	.046
Age*CO					.036	.190	-.052	.163	.124	.015
R^2	.385		.419		.435		**Variance explained (%)**			
F	14.395		12.284		10.310		Independent		37.1	
ΔR^2			.035		.015		Shared		6.4	
ΔF			4.045		1.822					

N= 73, *p<.05, **p<.01 ** p<.001 ***

Table A1.3.11. Regression model with the percentage of total CO readings and age*total exposure between 3.5-6ppm predicting variance in TMTAB scores.

TMTAB	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	.963***		.967***		.962***					
Age	.007	.169*	.006	.157[a]	.007	.169	.425	.215	.135	.018
Hours in home	.034	.224**	.037	.240**	.037	.238**	.419	.334	.218	.048
NART	.006	.200*	.006	.193*	.006	.193*	.432	.262	.167	.028
TMTAB T1	.490	.492***	.504	.505***	.506	.508***	.709	.546	.401	.161
T 3.5-6ppm			.116	.148*	.115	.146[a]	.089	.229	.144	.021
Age*CO					.002	.024	-.205	.034	.021	.000
R^2	.601		.622		.623		**Variance explained (%)**			
F	26.743		23.077		18.991		Independent		27.6	
ΔR^2			.021		.000		Shared		34.7	
ΔF			3.958		.079					

N= 76; [a]= nearly significant;*p<.05, **p<.01 ** p<.001 ***

Table A1.3.12. Regression model with the percentage of total CO readings and age*total exposure at 0ppm and between 0.5-3ppm, 3.5-6ppm and 6.5-30ppm predicting variance in SART-IIV scores.

SART IIV	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	.381***		.384***		.384***					
Age	.002	.197*	.003	.268**	.003	.265**	.224	.312	.247	.061
SART IIV T1	.532	.552***	.549	.569***	.548	.569***	.561	.601	.567	.322

0ppm T			-.004	-.289**	-.004	-.279*	-.183	-.234	-.181	.033
Age*CO					1.560	.013	.194	.011	.009	.000
R^2	.354		.432		.432			**Variance explained (%)**		
F	19.705		17.999		13.313			Independent		41.6
ΔR^2			.078		.000			Shared		1.6
ΔF			9.781		.009					

N= 75, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	.407***		.417***		.411***					
Age	.001	.112	.002	.177	.002	.165	.181	.195	.158	.025
SART IIV T1	.446	.482***	.430	.465***	.439	.475***	.498	.505	.466	.217
0.5-3ppm T			.004	.320**	.003	.237	.295	.203	.165	.027
Age*CO					.000	-.117	-.248	-.103	-.083	.007
R^2	.260		.358		.365			**Variance explained (%)**		
F	12.996		13.575		10.344			Independent		27.6
ΔR^2			.098		.007			Shared		8.9
ΔF			11.163		.776					

N= 77, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	.373***		.387***		.387***					
Age	.002	.221*	.002	.233*	.002	.213	.251	.101	.075	.006
NART	.001	.155	.002	.207*	.002	.207*	.196	.261	.200	.040
SART IIV T1	.549	.559***	.558	.567***	.558	.568***	.573	.607	.565	.319
3.5-6ppm T			.055	.218*	.054	.213[a]	.122	.226	.172	.030
Age*CO					-.001	-.021	-.246	-.010	-.007	.000
R^2	.406		.451		.451			**Variance explained (%)**		
F	15.518		13.751		10.839			Independent		39.5
ΔR^2			.044		.000			Shared		5.6
ΔF			5.423		.006					

N= 72, *p<.05, **p<.01 ** p<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	.401***		.398***		.401***					
Age	.001	.128	.001	.115	.000	.013	.175	.014	.011	.000
NART	.001	.202*	.002	.214*	.002	.253*	.233	.301	.246	.061
SART IIV T1	.456	.501***	.480	.527***	.476	.522***	.523	.551	.514	.264
6.5-30ppm T			.050	.185[a]	.058	.213*	.102	.257	.207	.043
Age*CO					-.008	-.204	-.187	-.215	-.171	.029
R^2	.332		.365		.394			**Variance explained (%)**		
F	11.908		10.202		9.116			Independent		39.7
ΔR^2			.033		.029			Shared		0.0
ΔF			3.730		3.395					

N= 76, *p<.05, **p<.01 ** p<.001 ***

Table A1.3.13. Regression model with the percentage of total CO readings and age*total exposure at 0ppm and between 0.5-3ppm predicting variance in UFOV-SA scores.

UFOV-SA	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	1.557		2.268[a]		2.299[a]					
Age	-.002	-.003	.024	.045	.025	.047	.570	.079	.034	.001
Hours in home	.376	.168**	.404	.180**	.399	.178**	.276	.353	.161	.026
Depression	-.172	-.136*	-.192	-.152**	-.191	-.150*	.053	-.312	-.140	.020
UFOV-SA T1	.887	.873***	.855	.841***	.855	.841***	.878	.830	.636	.404
T 0ppm			-.099	-.125*	-.110	-.137	-.094	-.212	-.093	.009
Age*CO					-.001	-.018	.093	-.029	-.012	.000
R^2	.803		.817		.817			**Variance explained (%)**		
F	68.423		58.976		48.452			Independent		46.0
ΔR^2			.014		.000			Shared		35.7
ΔF			4.970		.055					

N= 72; [a]= nearly significant; **p*<.05, ***p*<.01 ** *p*<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	1.557		2.399[a]		2.413[a]					
Age	-.002	-.003	.027	.051	.028	.052	.570	.085	.037	.001
Hours in home	.376	.168**	.401	.179**	.398	.177**	.276	.351	.160	.026
Depression	-.172	-.136*	-.188	-.149*	-.188	-.148*	.053	-.308	-.138	.019
UFOV-SA T1	.887	.873***	.847	.833***	.847	.833***	.878	.825	.623	.388
T 0.5-3ppm			.112	.127*	.117	.133	.128	.201	.088	.008
Age*CO					.001	.008	-.115	.012	.005	.000
R^2	.803		.817		.818			**Variance explained (%)**		
F	68.423		59.119		48.529			Independent		44.2
ΔR^2			.014		.000			Shared		37.6
ΔF			5.111		.010					

N= 72, **p*<.05, ***p*<.01 ** *p*<.001 ***

Table A1.3.14.Regression model with the percentage of total CO readings and age*total exposure between 0.5-3ppm predicting variance in WMS-IR scores.

WMS-IR	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	1.059**		1.088**		1.170**					
Age	-.009	-.068	-.011	-.078	-.013	-.097	-.318	-.154	-.086	.007
NART	-.019	-.186*	-.019	-.184*	-.021	-.204*	-.554	-.291	-.168	.028
WMS-IRT1	.652	.684***	.646	.678***	.641	.673	.807	.686	.519	.269
T 0.5-3ppm			-.007	-.040	-.031	-.174[a]	-.091	-.216	-.122	.015
Age*CO					-.004	-.191*	.034	-.238	-.135	.018
R^2	.676		.678		.696			**Variance explained (%)**		
F	50.879		37.896		32.552			Independent		33.7
ΔR^2			.002		.018			Shared		35.9
ΔF			.336		4.277					

N= 77; [a]= nearly significant; **p*<.05, ***p*<.01 ** *p*<.001 ***

Table A1.3.15. Regression model with the percentage of total CO readings and age*total exposure at 0ppm and between 0.5-3ppm predicting variance in WMS-DR scores.

WMS-DR	**Model 1**		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	5.045***		5.043***		4.931***					
Age	.005	.034	.005	.034	-.015	-.109	-.306	-.125	-.072	.005
NART	-.022	-.230**	-.022	-.230**	-.022	-.229**	-.559	-.328	-.198	.039
WMS-DR T1	.097	.686***	.097	.686***	.092	.653***	.782	.657	.497	.247
T 0ppm			-.001	-.003	-.007	-.021	.107	-.037	-.021	.000
Age*CO					.007	.193*	.023	.241	.142	.020
R^2	.654		.654		.674			**Variance explained (%)**		
F	42.836		31.656		27.308			Independent		31.1
ΔR^2			.000		.020			Shared		36.3
ΔF			.002		4.085					

N= 72, **p*<.05, ***p*<.01 ** *p*<.001 ***

	Model 1		**Model 2**		**Model 3**		**Correlations**			
Variable	B	β	B	β	B	β	Zero-order	Partial	Part	$Part^2$
Constant	5.114***		5.110***		5.060					
Age	.003	.025	.004	.031	-.001	-.008	-.325	-.012	-.007	.000
NART	-.017	-.183*	-.017	-.186*	-.021	-.224	-.497	-.318	-.191	.036
WMS-DR T1	.102	.724***	.102	.725***	.095	.677	.792	.666	.507	.257
T 0.5-3ppm			.004	.027	-.019	-.116	.035	-.140	-.080	.006
Age*CO					-.004	-.204*	-.154	-.239	-.140	.020
R^2	.657		.658		.677			**Variance explained (%)**		
F	45.943		34.080		29.361			Independent		31.9
ΔR^2			.001		.020			Shared		35.8
ΔF			.139		4.248					

N= 76, **p*<.05, ***p*<.01 ** *p*<.001 ***

Appendix 2 (A2): Study Materials

A2.1 Participant Recruitment Leaflet

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Gas Safety Trust

Research Study

Neuropsychological impact of chronic low-level carbon monoxide exposure in older adults

Carbon monoxide (CO) is a:

- Tasteless
- Odourless
- Colourless
- Non irritable gas

Carbon monoxide is produced when fuels such as wood, coal, and gas do not burn fully. Common sources of carbon monoxide:

- Motor vehicle exhausts
- Cigarette smoke
- Malfunctioning, inadequately ventilated, and poorly maintained cooking and heating appliances

You are invited to take part in a research study investigating the possible health effects of low-level carbon monoxide within the home (all below levels at which a CO alarm would trigger). The study requires information from people who reside in the West Midlands area and are 60 years of age or older.

It's completely up to you to decide whether or not you take part.

If you decide you would like to take part, you will be re-visited by the Fire Service who will leave a carbon monoxide data logger and alarm in your home for 1-month. This will continuously record the level of carbon monoxide within your home.

You will also be visited by the researcher at home who will carry out a series of different tasks with you including: memory, attention, and speed tasks, and other thinking type tasks such as planning and problem solving. There will also be a series of medical and health questionnaires.

The tests and questionnaires will take around 2 hours 30 minutes to complete.

Repeated carbon monoxide monitoring and assessments will be carried out at 6 months and 12 months after the initial visit.

If you have any questions about the study, or are interested in taking part please contact Beth Cheshire:

Email: b.cheshire@lancaster.ac.uk

Tel: 07895494277

A2.2 Expression of Interest Form

Health & Medicine | Lancaster University

Expression of Interest Form

Study Title: Neuropsychological impact of chronic low-level carbon monoxide exposure in older adults

You have been invited to take part in a research project examining the possible health effects of low-level carbon monoxide (CO) within the home. You are being asked if you would like to take part in the study as you are one of the people who have agreed to the Fire Service placing a CO data logger in your home. Please mark each box below with your initials if you agree to the Fire Service sharing your personal details with, and to be contacted by, the researcher (Beth Cheshire) regarding taking part in the study.

	Please initial each statement you agree with
1. I consent to the Fire Service sharing my personal details (name, contact number, address, and the information documented on the Safe and Well visit form) with Beth Cheshire (the researcher) at Lancaster University.	☐
2. I consent to being contacted by Beth Cheshire by telephone to discuss taking part in the study and to arrange my participation.	☐

Name_____**Signature**_____ **Date** _____

A2.3 Participant Information Sheet

Health & Medicine | Lancaster University

Participant Information Sheet

Neuropsychological impact of chronic low-level carbon monoxide exposure in older adults

For further information about how Lancaster University processes personal data for research purposes and your data rights please visit our webpage: www.lancaster.ac.uk/research/data-protection

My name is Beth Cheshire and I am conducting this research as a part of a PhD programme within the Faculty of Health and Medicine at Lancaster University, Lancaster, United Kingdom.

What is the study about?

Carbon monoxide is a colourless, odourless, tasteless, and non-irritable gas that is undetectable to the human senses. Carbon monoxide is produced when fuels such as wood, coal, and gas do not burn fully. Common sources of carbon monoxide include motor vehicle exhausts, industrial processes and natural sources such as wildfires. Levels of carbon monoxide are also present indoors and can accumulate from cigarette smoke and from malfunctioning, inadequately ventilated, and poorly maintained heating and cooking appliances.

The purpose of this study is to investigate the possible health effects of low-level carbon monoxide within the home. This will be examined by continuously monitoring and recording the levels of carbon monoxide within the home over a 1-month duration over three separate time points (initially, 6 months, and 12 months later). This information will be combined with scores on a variety of tests such as memory and attention tasks and with information gathered from you in health and mental health questionnaires.

The following information sheet provides details about why the research is being conducted and what it involves. Please take time to read the following information carefully as before taking part it is important that you understand the nature of the study and what your participation will involve. Please feel free to ask any questions you may have regarding the study or your participation before you proceed.

Why have I been approached?

You have been approached because the study requires information from people who reside in the West Midlands area and are 60 years of age or older. You have not been approached because of any concerns about the level of carbon monoxide in your home or any other health concerns.

Do I have to take part?
No. It's completely up to you to decide whether or not you take part.

If you do decide to take part, you will be asked to sign an Expression of Interest form when the Fire Service visit you at home. This is your agreement to them sharing your personal details with the researcher (name, address, contact details, and information from the safe and well visit form), and agreeing to be contacted regarding taking part in the study. You will then be asked to sign a consent form which will be completed with you when you are visited at home by the researcher. By signing the consent form, you are agreeing to take part in the study. However, even after signing this form you will still have the right to withdraw from the study during the assessments and up until publication, without giving a reason.

If after completion of either the initial testing point or follow-ups, you decide you would like to withdraw your data, then please contact a member of the research team via the contact details provided below. If you do not wish to take part or you want to withdraw at a future time point, this will not affect any care or support you receive. You will be required to sign a consent form at each of the testing points (initially, 6 months, and 1 year). However, if you decide that you would no longer like to take part at either of the follow up testing points (6 months and 1 year), it may not be possible to withdraw your previous data as it may have already been included in a publication.

What will I be asked to do if I take part?
If you decide you would like to take part, you will be visited by the Fire Service who will leave a carbon monoxide data logger in your home for 1-month. This will continuously monitor and record the levels of carbon monoxide within your home and will be collected at the end of the 1-month period.

During this time you will be visited by the researcher at home who will carry out a series of different tasks with you. Firstly, you will be asked to answer questions about your education level, smoking status, home appliances, property type, tenure, any benefits you receive and about the amount of hours you spend each day within the home. There will also be a set of medical and health questionnaires relating to any physical or psychiatric illnesses, current symptoms, quality of life, how you see your own health, previous falls, and use of health and social care services. You will then be asked to complete a short questionnaire relating to feelings of anxiety and depression. This will be followed by a series of both computer and paper-based short assessments of your memory, language and other thinking and attention type tasks (such as planning and problem solving abilities). There will be full instructions and a set of practice trials and opportunities to ask questions to ensure you understand the tasks before you begin.

The final part of the study will involve measuring your blood pressure and the level of carbon monoxide in your exhaled breath using a breath carbon monoxide monitor. You will be required to hold your breath for a few seconds and then breathe out slowly into a tube which is attached to the monitor. Repeated carbon monoxide monitoring and assessments will be carried out at 6 months and 12 months after the initial visit using the same process and tasks detailed above.

The tests and questionnaires will take around 2 hours 30 minutes to complete, but you are welcome to have a break at any time.

How will the information I provide be kept safe?

The information you provide is confidential. The data collected for this study will be stored securely and only the researchers conducting the study will have access to any information that identifies you and only anonymised data will be used for research purposes.

- We will give you a participant number so we do not need to put your name on any of the data. The code linking your name and participant number will be on the consent form only, and will be kept in a locked cabinet separate from paper copies of questionnaires.
- All your identifying personal data will be confidential and will be kept separately from your assessment scores and will be destroyed once the research project has finished.
- The files on the computer will be encrypted (that is no-one other than the researcher will be able to access them) and the computer itself is password protected.
- Paper copies of questionnaires will be kept securely in a locked cabinet for 5 years. At the end of this period, they will be destroyed.
- Anonymised data on the computer will be deposited and archived in Lancaster University's institutional data repository for a minimum of 10 years and may be re-used after completion of the study. However, access to the data will only be shared on request by genuine researchers who provide information regarding proposed use. Access will be granted on a case-by-case basis by the Faculty of Health and Medicine.

There are some limits to confidentiality: during the home assessments if something makes me think that you, or someone else, is at significant risk of harm, I will have to break confidentiality and speak to a member of the Fire Service and the University research supervisor about this. If possible, I will tell you if I have to do this.

What will happen to my information?

All the data collected will be anonymised and then combined with the results from the other participants ready for analysis. The results will be summarised and reported in a thesis and may be submitted for publication in an academic or professional journal. If you are interested in the study's' findings a letter outlining the results and summarising the overall findings can be sent to you once the study is completed.

Are there any risks?

There are no risks anticipated with participating in this study. Pulse carbon monoxide-oximeters and breath carbon monoxide monitors are safe and non-invasive devices. The devices will be disinfected between participants and disposable mouthpieces will be used for the breath carbon monoxide monitors.

You should be aware that both the paper based assessments and computer based tasks are designed to be quite challenging, which might make you feel a bit under pressure. Nevertheless, there will be opportunities to rest and ask questions in between tasks to

alleviate some of this pressure. If at any point you decide that you do not wish to continue then you will be able to withdraw from the study.

We can assure you that taking part in the study does not mean that you are being assessed for care home admission or for specific diagnoses such as dementia, or that the fire service found the CO in your home to be too high during their initial safe and well check. If you have any concerns about your performance on any of the tasks, we advise you to seek medical advice from your GP. If you have any questions about the study, please do not hesitate to contact a member of the research team via the email addresses provided below. If you experience any distress following participation you are encouraged to contact the sources of support provided below.

Are there any benefits to taking part?

Although there are no direct benefits to you of the planned outcome of the research, we hope the research findings will have useful impacts for gas safety policy. However, there are some benefits to taking part. If low-levels of carbon monoxide are detected in your home (all below levels which would trigger a carbon monoxide alarm), the Fire Service will visit you and provide information and advice on the sources of carbon monoxide, safety and prevention. Therefore, you will directly benefit from the early detection of low-levels of carbon monoxide within your home and from education on carbon monoxide, which may subsequently lead to reduced levels of carbon monoxide within the home and lower the risk of carbon monoxide poisoning.

You will also be provided with a free carbon monoxide alarm from the Fire Service at the beginning of the study, which will ensure you are protected from higher levels of carbon monoxide and the risk of carbon monoxide poisoning. You will be able to keep the carbon monoxide alarm after the study.

Who has reviewed the project?

This study has been reviewed and approved by the Faculty of Health and Medicine Research Ethics Committee at Lancaster University.

Where can I obtain further information about the study if I need it?

If you have any questions about the study, please do not hesitate to contact research team via the contact details provided below:

Ms Beth Cheshire b.cheshire@lancaster.ac.uk Tel: 07895494277

Prof Carol Holland c.a.holland@lancaster.ac.uk Tel: 01524 510436

Dr Trevor Crawford t.crawford@lancaster.ac.uk Tel: 01524 593761

Complaints

If you wish to make a complaint or raise concerns about any aspect of this study and do not want to speak to the researcher, you can contact:

Dr Thomas Keegan Tel: (01524) 594539

Director of PG Research; Email: t.keegan@lancaster.ac.uk
Faculty of Health and Medicine
Division of Health Research
Lancaster University
Lancaster
LA1 4YG

If you wish to speak to someone outside of the Division of Health Research, you may also contact:

Professor Roger Pickup Tel: 01524 593746
Associate Dean for Research Email: r.pickup@lancaster.ac.uk
Faculty of Health and Medicine
Division of Biomedical and Life Sciences
Lancaster University
Lancaster
LA1 4YG

Thank you for taking the time to read this information sheet.

Resources in the event of distress
Should you feel distressed either as a result of taking part, or in the future, the following resources may be of assistance:

If you have any concerns about gas or fire safety please contact:

West Midlands Fire Service
Headquarters
99 Vauxhall Road
Birmingham B7 4HW
Email: contact@wmfs.net
Safe and Well Tel: 0800 389 5525
Fire Control Tel: 0121 3806860

If you would like a gas engineer to check your home appliances please contact:

Gas Safe Register
Email: https://www.gassaferegister.co.uk/
Tel: 0800 408 5500

If you have any queries or concerns relating to benefit entitlement/ help with making a claim, home security and safety, home maintenance and repairs, hand rails and other aids, Coventry City Council services, carer support, falls safety, help with heating or help with housing issues please contact:

Age UK Coventry Contact and Connect

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Tel: 024 7625 8176
Email: contactandconnect@ageukcoventry.org.uk

If you have any concerns about your performance on any of the tasks, we advise you to seek medical advice from your GP.

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Research Study

Neuropsychological impact of chronic low-level carbon monoxide exposure in older adults

Researcher:
Ms Beth Cheshire
Email: b.cheshire@lancaster.ac.uk
Phone: 07895494277

Invitation

You are invited to take part in a **research study** about low-levels of Carbon monoxide in the home and the possible effects this may have on health.

Please read this information carefully.

And **ask** any questions.

You are invited to take part because the study requires information from people who live in the **West Midlands area** and are **60 years of age** or older.

You have not been approached because of any concerns about the level of carbon monoxide in your home or any other health concerns.

The research study will involve the Fire Service **measuring the levels of carbon monoxide within your home** and you will be visited by the researcher who will **measure your health.**

We will be collecting this information 3 times (initially, and then 6 and 12 months later). This is to see what has changed.

The Fire Service will place a carbon monoxide data logger in your home for 1 month. This will record the levels of carbon monoxide within your home. The Fire Service will have already taken a carbon monoxide reading from your house and will have made sure the levels are very low.

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You will be given a free carbon monoxide alarm to keep in your home just in case the carbon monoxide level does rise during the study. **This will keep you protected from higher levels of carbon monoxide.**

The researcher will collect the following information from you:

- Memory and language tests and other thinking and attention type tasks
- Well-being (whether you've been feeling happy or a bit low recently)
- Whether you think your health is good or not, and some questions about your quality of life
- General questions relating to your health and social care use, how many hours you spend within the home a day and the appliances you have in your home.

We will also measure your blood pressure and the level of CO in your breath.

A breath CO monitor will be used to measure the amount of CO in your breath. You will be required to hold your breath for a few seconds and then breathe out slowly into a tube which is attached to the monitor.

The tests and questionnaires will take around <u>2 hours 30 minutes</u> to complete.

You are welcome to ask for a break at any point.

A researcher will visit you at your home, at a time convenient for you.

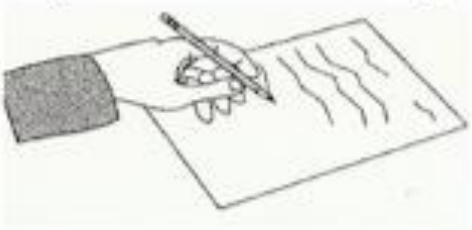
Taking Part – it's up to you…

You **do not have to take part.** It's **your choice**.

If you do, you will need to sign two **forms**.

Firstly, you will be asked to sign an Expression of Interest form from the Fire Service. By signing this form you will be **agreeing to** the Fire Service **sharing your details** with the researcher and that you would like to be **contacted by them** about taking part in the study.

You will then be asked to sign a **Consent form.** This will be completed with you when you are visited at home by the researcher. This is your agreement to take part in the study.



You can **stop** at any time during the assessments.

It's **your** choice.

It's **OK** to stop.

You don't have to tell us why. Your care and rights will not be affected in any way.

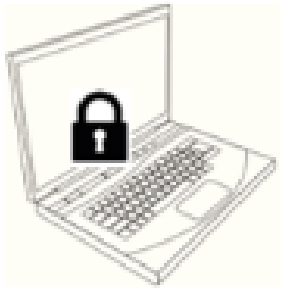
If after taking part you decide you would no longer like to be involved in the study you can withdraw your data at any time up until publication by contacting the researcher.

However, if you do stop taking part at a later date, you may not be able to withdraw your data from a previous visit as it may already have been included in a publication.

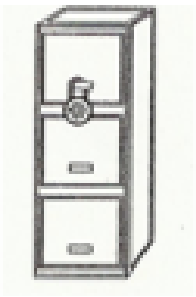
Health & Medicine | Lancaster University

Privacy and Confidentiality

Everything you say is **confidential** unless you tell us something that indicates that you or someone else is at risk of harm. We would discuss this with you before telling anyone else.



All your assessment details will be kept on a **computer** that is protected with a **password**. This information will **NOT** be kept with your name, address, or contact details.



Written details will be **locked** in a **cabinet**.

The researchers will analyse all the information carefully. We will keep your identifying/personal information for the duration of the research. After this it will be destroyed.

Your anonymised paper based assessment scores will be kept for 5 years (these will **NOT** have your name on) and will then be destroyed.

Your assessment scores will be transferred onto a computer and will be kept for a minimum of 10 years and will be stored on a secure system.

We hope to work out what effects, if any, low levels of CO has on health.

After the study we may **publish** the results in **journals** and **present** them at **conferences.**

We will be careful to ensure people cannot identify anyone who has taken part from the results.

You can have a **copy** of the **overall** results of the study.

We work at Lancaster University.

If there is a **problem** or you are **worried**, speak to the **researcher.** They will try to fix it.

If you need to **complain**, please contact Professor Roger Pickup, Associate Dean for Research; Email: r.pickup@lancaster.ac.uk or telephone: 01524 593746

If you have any **questions please contact Beth Cheshire**

Email: b.cheshire@lancaster.ac.uk

Tel: 07895494277

Resources in the event of distress

Should you feel distressed either as a result of taking part, or in the future, the following resources may be of assistance:

If you have any concerns about **gas or fire safety** please contact:

West Midlands Fire Service

Health & Medicine | Lancaster University

Headquarters
99 Vauxhall Road
Birmingham B7 4HW
Email: contact@wmfs.net
Safe and Well Tel: 0800 389 5525
Fire Control Tel: 0121 3806860

If you would like a **gas engineer** to check your home appliances please contact:
Gas Safe Register

Email: https://www.gassaferegister.co.uk/
Tel: 0800 408 5500

If you have any queries or concerns relating to benefit entitlement/ help with making a claim, home security and safety, home maintenance and repairs, hand rails and other aids, Coventry City Council services, carer support, falls safety, help with heating or help with housing issues please contact:
Age UK Coventry Contact and Connect

Tel: 024 7625 8176
Email: contactandconnect@ageukcoventry.org.uk

If you have any concerns about your performance on any of the tasks, we advise you to seek medical advice from your GP.

A2.4 Consent Form

Health & Medicine | Lancaster University

Consent Form

Study Title: Neuropsychological impacts of chronic low-level carbon monoxide exposure in older adults

We are asking if you would like to take part in a research project examining the possible health effects of low-level carbon monoxide (CO) within the home. Before you consent to participating in the study we ask that you read the participant information sheet and mark each box below with your initials if you agree. If you have any questions or queries before signing the consent form, please speak to the principal investigator, Beth Cheshire.

	Please initial each statement you agree with
1. I confirm that I have read the information sheet and fully understand what is expected of me within this study.	☐
2. I confirm that I have had the opportunity to ask any questions and to have them answered.	☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time during the assessments and withdraw my data up until publication without giving any reason.	☐
4. I understand that the information from my assessments and questionnaires will be pooled with other participants' responses, anonymised and analyses from them may be published.	☐
5. I consent to information from my questionnaires and assessments being used in reports, publications, and conferences, but that no identifying information will be made public.	☐
6. I understand that the researcher will discuss data with their supervisors as needed.	☐
7. I understand that any information I give will remain confidential and anonymous unless it is thought that there is a risk of harm to myself or others, in which case the principal investigator will need to share this information with the Fire Service and their research supervisor.	☐
8. I consent to Lancaster University keeping identifying information for the duration of the research and the anonymised paper-based questionnaires and assessments for 5 years unless I withdraw. If I do decide to withdraw, I understand that my data will be destroyed.	☐
9. I consent to my anonymised electronic data being deposited in and archived in Lancaster University's institutional data repository for a minimum of 10 years and understand that it may be re-used after completion of the study.	☐
10. I consent to take part in the above study.	☐

Name of Participant_____ **Signature**_____ **Date** _____

Name of Researcher _____**Signature** _____**Date** _____

A2.5 Debrief Form

Health & Medicine | Lancaster University

Debrief Form

Study Title: Neuropsychological impacts of chronic low-level carbon monoxide exposure in older adults

Thank you for your participation.

The research you have participated in today is examining whether or not low-levels of carbon monoxide (all below levels that would trigger a carbon monoxide alarm) are present within a selection of homes in the Coventry area. If we find that low levels are present within some of the homes, we aim to try and work out whether or not this affects people's health over a period of time. At present, the number of people who have low levels of carbon monoxide within their home, and the effects this may have on health are unknown. Studies are needed to help us understand whether people have low levels of carbon monoxide in their homes and to see whether this has any effects on health.

All the data collected will be anonymised (your name will not be against any of your test scores) and then combined with the results from the other participants ready for analysis. The results will be summarised and reported in a thesis (the student's report of the research submitted to the University at the end of the degree programme). The results may also be submitted for publication in an academic or professional journal. If you are interested in the study's findings a letter outlining the results and summarising the overall findings can be sent to you once the study is completed. Please tell the researcher or contact her on the email below if you would like this.

You can request to withdraw your data up until publication, without giving a reason. If you would like to withdraw your data then please contact a member of the research team via the email addresses provided below. If you do not wish to take part or you want to withdraw at a future time point, this will not affect any care or support you receive. However, if you decide that you would no longer like to take part at either of the follow up testing points (6 months and 1 year), you may not be able to withdraw your earlier data as it may have already been included in a publication.

The information you provide is confidential. The data collected for this study will be stored securely and only the research team will have access to this data. All your identifying personal data will be confidential and will be kept separately from your assessment scores and will be destroyed once the research project has finished. Anonymised paper based questionnaires will be kept securely in a locked cabinet for 5 years. At the end of this period, they will be destroyed, unless you decide to withdraw from the study at which point both your paper based and computer data will be destroyed at the time. Anonymised data on the computer will be deposited and archived in Lancaster University's institutional data repository for a minimum of 10 years and may be re-used after completion of the study. However, access to the data will only be shared on request by genuine researchers who provide information regarding proposed use. Access will be granted on a case-by-case basis by the Faculty of Health and Medicine.

Sources of support
We can assure you that taking part in the study does not mean that you have been assessed for care home admission or for specific diagnoses such as dementia, or that the fire service found the carbon monoxide level in your home to be too high during their initial safe and well visit. If you have any concerns about your performance on any of the tasks, we advise you to seek medical advice from your GP. If you have any questions about the study, please do not hesitate to contact a member of the research team via the email addresses provided below. If you experience any distress following participation you are encouraged to contact the sources of support provided below. You will be contacted again in 6 months' time to arrange the follow up appointment.

Should you feel distressed either as a result of taking part, or in the future, the following resources may be of assistance:

If you have any concerns about gas or fire safety please contact:

West Midlands Fire Service
Headquarters
99 Vauxhall Road
Birmingham B7 4HW
Email: contact@wmfs.net
Safe and Well Tel: 0800 389 5525
Fire Control: 0121 3806860

If you would like a gas engineer to check your home appliances please contact:

Gas Safe Register
Email: https://www.gassaferegister.co.uk/
Tel: 0800 408 5500

If you have any queries or concerns relating to benefit entitlement/ help with making a claim, home security and safety, home maintenance and repairs, hand rails and other aids, Coventry City Council services, carer support, falls safety, help with heating or help with housing issues please contact:

Age UK Coventry Contact and Connect
Tel: 024 7625 8176
Email: contactandconnect@ageukcoventry.org.uk

If you have any concerns about your performance on any of the tasks, we advise you to seek medical advice from your GP.

Thank you again for your time and participation.

Ms Beth Cheshire b.cheshire@lancaster.ac.uk Tel: 07895494277
Prof Carol Holland c.a.holland@lancaster.ac.uk Tel: 01524 510436
Dr Trevor Crawford t.crawford@lancaster.ac.uk Tel: 01524 593761

A2.6 Fire Service Intervention

Health & Medicine | Lancaster University

Fire Service Intervention

Study Title: Neuropsychological impact of chronic low-level carbon monoxide exposure in older adults

Thank you for your continued participation in the study. You are being visited by the Fire Service in order for them to place the carbon monoxide (CO) data logger back in your home to continuously measure the CO levels again for 1 month ready for the follow up appointment with the researcher Beth Cheshire. The Fire Service will also check that the CO alarm they gave you at the beginning of the study is still working. As part of the 'CO programme' the Fire Service are providing health and safety information regarding CO sources, safety and prevention and the associated health risks in order to raise awareness and educate.

	Please initial each statement you agree with
1. I confirm that the Fire Service have gone through the CO health and safety advice in the safe and well booklet and have left this information with me.	☐
2. I confirm that I have been informed that my property did not have any 'unsafe' levels of CO during the month the data logger was in place and that the levels were all within the Safe Working Exposure Limits (SWELs).	☐
3. I confirm that I have been provided with a CO alarm from the Fire Service and that it has been checked during this visit to ensure that it is working.	☐

Participant name_____ **Signature**_____ **Date** _____

A2.7 General Information Questionnaire

Health & Medicine | Lancaster University

General Information Questionnaire

Participant ID:

Age:

Gender:

Education Level:

Ambient CO Level:

COHb Level:

Exhaled Breath CO Level:

B/P:

Smoking Status: smoker/ non-smoker

How many cigarettes do you smoke per day?

0 1-5 6-10 11-20 21-40 40+

How many cigarettes are smoked inside the home per day?

0 1-5 6-10 11-20 21-40 40+

Appliances in the home

	Yes	No
Gas boiler	☐	☐
Gas cooker	☐	☐
Gas fire	☐	☐
Open fire (wood or coal)	☐	☐
Other		

When was the last time you had your appliances serviced? (e.g. boiler serviced/ chimney swept).

Primary heating method: Electric/ Gas/ Coal/ Wood/ Other .....

Primary cooking method: Gas/ Electric

Do you have a working smoke alarm? Yes/ No

Do you have a working carbon monoxide detector? Yes/ No

Tenure:

- Owner ☐
- Rented- Council ☐
- Rented-Private ☐
- Rented- Housing association ☐

Property type:

- Detached house ☐
- Semi-detached house ☐
- Terraced house ☐
- Bungalow ☐
- Flat ☐
- Sheltered accommodation ☐

Are you in receipt of benefits? Yes/ No

Do you have an existing diagnosis of any of the following medical conditions?	Yes	No
High Blood pressure	☐	☐
Coronary Heart Disease	☐	☐
Diabetes	☐	☐
Stroke	☐	☐
Chronic Obstructive Pulmonary Disease	☐	☐
Asthma	☐	☐
Arthritis	☐	☐
Osteoporosis	☐	☐
Cancer	☐	☐
Parkinson's	☐	☐
Dementia	☐	☐
Memory impairment	☐	☐
Organic brain syndrome	☐	☐
Depression	☐	☐
Anxiety	☐	☐
Bi-polar disorder	☐	☐
Schizophrenia	☐	☐
Obsessive compulsive disorder	☐	☐
Post-traumatic stress disorder	☐	☐
Personality disorder	☐	☐
Substance addiction/ dependence	☐	☐
Other (please record below)	☐	☐

Self-perceived health

Please rate how you see your health on the following scale:

Excellent	Very Good	Good	Fair	Poor
☐	☐	☐	☐	☐

Healthcare use

How many times have you visited your GP in the last 6 months?

How many planned and unplanned hospital admissions (not including outpatient appointments) have you had in the last 6 months?

How many outpatient appointments have you had in the last 6 months?

How many falls have you had in the last 6 months?

Social care use

Do you receive any care at home? Yes/ No

If yes, how many hours per week?

Time spent in the home

How many hours a day do you spend in the house?

Since the data loggers have been in your home, have you been on holiday or spent time away from the home visiting relatives?

Do you have any holidays planned in the next few weeks whilst the data loggers are in your home?

A2.8 Ethical approval

A2.7.1 Approval letter

Applicant: Beth Cheshire
Supervisor: Carol Holland
Department: Health Research
FHMREC Reference: FHMREC17082

02 July 2018

Dear Beth

Re: Neuropsychological impacts of chronic low-level carbon monoxide poisoning in older adults

Thank you for submitting your research ethics application for the above project for review by the **Faculty of Health and Medicine Research Ethics Committee (FHMREC)**. The application was recommended for approval by FHMREC, and on behalf of the Chair of the Committee, I can confirm that approval has been granted for this research project.

As principal investigator your responsibilities include:

- ensuring that (where applicable) all the necessary legal and regulatory requirements in order to conduct the research are met, and the necessary licenses and approvals have been obtained;
- reporting any ethics-related issues that occur during the course of the research or arising from the research to the Research Ethics Officer at the email address below (e.g. unforeseen ethical issues, complaints about the conduct of the research, adverse reactions such as extreme distress);
- submitting details of proposed substantive amendments to the protocol to the Research Ethics Officer for approval.

Please contact me if you have any queries or require further information.

Tel:- 01542 592838
Email:- fhmresearchsupport@lancaster.ac.uk

Yours sincerely,

Dr Diane Hopkins
Research Integrity and Governance Officer, Secretary to FHMREC.

A2.7.2 Ethics amendment and approval letter (version 2)

Faculty of Health and Medicine Research Ethics Committee (FHMREC) Lancaster University
Application for Amendment to Previously Approved Research

1. Name of applicant: Beth Cheshire

2. E-mail address and phone number of applicant: b.cheshire@lancaster.ac.uk 07530493418

3. Title of project: Neuropsychological impact of chronic low-level carbon monoxide poisoning in older adults

4. FHMREC project reference number: FHMREC17082

5. Date of original project approval as indicated on the official approval letter (July/2018):

6. Please outline the requested amendment(s)
   Note that where the amendment relates to a change of researcher, and the new researcher is a student, a full application must be made to FHMREC
   - The carbon monoxide level at which participants will be excluded from the study has been changed from ≥30 ppm to ≥20 ppm.
   - A question has been amended on the CASP-12 measure (appendix 12).

7. Please explain your reason(s) for requesting the above amendment(s):
   - West Midlands Fire service have amended their safe working exposure CO limits and incident reporting level to ≥20 ppm to comply with the new EU directive.
   - To correspond with the questionnaire on the CASP-12 website.

Guidance:

a) Resubmit your research ethics documents **(the entire version which received final approval, including all participant materials, your application form and research protocol)**, with all additions highlighted in yellow, and any deletions simply 'struck through', so that it is possible to see what was there previously.
b) This should be submitted as a **single PDF** to Becky Case. There is no need to resubmit the Governance Checklist.

Applicant electronic signature: B. Cheshire Date: 17/08/2018

Student applicants: please tick to confirm that you have discussed this amendment application with your supervisor, and that they are happy for the application to proceed to ethical review ☑

Project Supervisor name (if applicable): Prof Carol Holland Date application discussed: 16/08/2018

You must submit this application from your Lancaster University email address, and copy your supervisor in to the email in which you submit this application.

Applicant: Beth Cheshire
Supervisor: Carol Holland
Department: Health Research
FHMREC Reference: FHMREC17116

20 August 2018

Dear Beth

Re: Neuropsychological impact of chronic low-level carbon monoxide poisoning in older adults

Thank you for submitting your research ethics amendment application for the above project for review by the **Faculty of Health and Medicine Research Ethics Committee (FHMREC).** The application was recommended for approval by FHMREC, and on behalf of the Chair of the Committee, I can confirm that approval has been granted for the amendment to this research project.

As principal investigator your responsibilities include:

- ensuring that (where applicable) all the necessary legal and regulatory requirements in order to conduct the research are met, and the necessary licenses and approvals have been obtained;
- reporting any ethics-related issues that occur during the course of the research or arising from the research to the Research Ethics Officer at the email address below (e.g. unforeseen ethical issues, complaints about the conduct of the research, adverse reactions such as extreme distress);
- submitting details of proposed substantive amendments to the protocol to the Research Ethics Officer for approval.

Please contact me if you have any queries or require further information.

Tel:- 01542 593987
Email:- fhmresearchsupport@lancaster.ac.uk

Yours sincerely,

Becky Case
Research Ethics Officer, Secretary to FHMREC.

A2.7.3 Ethics amendment and approval letter (version 3)

Health & Medicine | Lancaster University

Faculty of Health and Medicine Research Ethics Committee (FHMREC) Lancaster University
Application for Amendment to Previously Approved Research

1. Name of applicant: Beth Cheshire

2. E-mail address and phone number of applicant: b.cheshire@lancaster.ac.uk 07530493418

3. Title of project: Neuropsychological impact of chronic low-level carbon monoxide exposure in older adults

4. FHMREC project reference number: FHMREC17082

5. Date of original project approval as indicated on the official approval letter (July/2018):

6. Please outline the requested amendment(s)
Note that where the amendment relates to a change of researcher, and the new researcher is a student, a full application must be made to FHMREC

   - The frailty index information (number of prescribed medications, exhaustion, activities of daily living, BMI/waist to hip ratio and the measures of physical robustness and mobility (grip strength, sit to stand, walking speed)) have been removed from the study. The questionnaire has been updated (see appendix 12).
   - The Katz index of independence in activities of daily living and the Lawton instrumental activities of daily living questionnaires have also been removed from the study.

7. Please explain your reason(s) for requesting the above amendment(s):
   - The tasks and assessments are taking an hour longer than the estimated completion time of 2.5 hours. Following these amendments the total time should be around the 2.5 hours.

uidance:

) Resubmit your research ethics documents **(the entire version which received final approval, ncluding all participant materials, your application form and research protocol),** with all additions ighlighted in yellow, and any deletions simply 'struck through', so that it is possible to see what was here previously.
) This should be submitted as a **single PDF** to Becky Case. There is no need to resubmit the overnance Checklist.

pplicant electronic signature: B. Cheshire Date: 25/10/2018

tudent applicants: please tick to confirm that you have discussed this amendment application with our supervisor, and that they are happy for the application to proceed to ethical review ☑

roject Supervisor name (if applicable): Prof Carol Holland Date application discussed: 22/10/2018

Applicant: Beth Cheshire
Supervisor: Carol Holland
Department: Health Research
FHMREC Reference: FHMREC18027

07 November 2018

Dear Beth

Re: Neuropsychological impact of chronic low-level carbon monoxide exposure in older adults

Thank you for submitting your research ethics amendment application for the above project for review by the **Faculty of Health and Medicine Research Ethics Committee (FHMREC).** The application was recommended for approval by FHMREC, and on behalf of the Chair of the Committee, I can confirm that approval has been granted for the amendment to this research project.

As principal investigator your responsibilities include:

- ensuring that (where applicable) all the necessary legal and regulatory requirements in order to conduct the research are met, and the necessary licenses and approvals have been obtained;
- reporting any ethics-related issues that occur during the course of the research or arising from the research to the Research Ethics Officer at the email address below (e.g. unforeseen ethical issues, complaints about the conduct of the research, adverse reactions such as extreme distress);
- submitting details of proposed substantive amendments to the protocol to the Research Ethics Officer for approval.

Please contact me if you have any queries or require further information.

Tel:- 01542 593987
Email:- fhmresearchsupport@lancaster.ac.uk

Yours sincerely,

Becky Case
Research Ethics Officer, Secretary to FHMREC.

A2.7.4 Ethics amendment and approval letter (version 4)

Health & Medicine | Lancaster University

Faculty of Health and Medicine Research Ethics Committee (FHMREC) Lancaster University
Application for Amendment to Previously Approved Research

1. Name of applicant: Beth Cheshire

2. E-mail address and phone number of applicant: b.cheshire@lancaster.ac.uk 07530493418

3. Title of project: Neuropsychological impact of chronic low-level carbon monoxide exposure in older adults

4. FHMREC project reference number: FHMREC17082

5. Date of original project approval as indicated on the official approval letter (July/2018):

6. Please outline the requested amendment(s)
Note that where the amendment relates to a change of researcher, and the new researcher is a student, a full application must be made to FHMREC

   - The RAD-57 pulse carbon monoxide-oximeter measurement (COHb) has been removed from the study. The ethics application and participant information sheet has been amended (see appendix 2).
   - The CO data loggers have been programmed to continuously record the ambient CO concentrations with average levels taken and stored every 5 minutes.

7. Please explain your reason(s) for requesting the above amendment(s):
   - The RAD-57 equipment has been giving extremely inconsistent readings and at times, has not been working at all. It was purchased around 9 years ago, and after returning it to the Fire Service to fix they contacted the manufacturers who advised that the equipment would not be providing provide reliable or accurate readings due to its age. The RAD-57 readings are also affected by factors such as temperature and perfusion index and have previously been found to give false positive and negative readings. A replacement RAD-57 would be extremely expensive and the CO breathalyser that is being used in the research also gives a COHb reading, so no measurement is being lost by discontinuing the use of the Rad-57. The CO breathalyser also provides more precise readings.
   - The Rad-57 also provides information on oxygen saturation level and perfusion index, following discussion with the clinical lead on the research it was decided that it would be best to use the CO breathalyser only, as this equipment only provides information on CO levels. After combining information from numerous sources and advice from the clinical lead, it has been agreed that the COHb level at which the participant is advised to seek advice from their GP is: non-smokers >2%; smokers >5%. Any participants who have a COHb reading of ≥10%, NHS 111 will be contacted or 999 when needed.
   - The Fire service have programmed the data loggers to store average readings every 5 minutes rather than every 15 minutes, this will provide more data for analysis.

Guidance:

a) Resubmit your research ethics documents **(the entire version which received final approval, including all participant materials, your application form and research protocol),** with all additions highlighted in yellow, and any deletions simply 'struck through', so that it is possible to see what was there previously.
b) This should be submitted as **a single PDF** to Becky Case. There is no need to resubmit the Governance Checklist.

Applicant electronic signature: B. Cheshire Date: 30/01/2019

Student applicants: please tick to confirm that you have discussed this amendment application with your supervisor, and that they are happy for the application to proceed to ethical review ☑

Project Supervisor name (if applicable): Prof Carol Holland Date application discussed: 25/01/2019

You must submit this application from your Lancaster University email address, and copy your supervisor in to the email in which you submit this application.

Lancaster University

Applicant: Beth Cheshire
Supervisor: Carol Holland
Department: Health Research
FHMREC Reference: FHMREC18054

05 February 2019

Dear Beth

Re: Neuropsychological impact of chronic low-level carbon monoxide poisoning in older adults

Thank you for submitting your research ethics amendment application for the above project for review by the **Faculty of Health and Medicine Research Ethics Committee (FHMREC).** The application was recommended for approval by FHMREC, and on behalf of the Chair of the Committee, I can confirm that approval has been granted for the amendment to this research project.

As principal investigator your responsibilities include:

- ensuring that (where applicable) all the necessary legal and regulatory requirements in order to conduct the research are met, and the necessary licenses and approvals have been obtained;
- reporting any ethics-related issues that occur during the course of the research or arising from the research to the Research Ethics Officer at the email address below (e.g. unforeseen ethical issues, complaints about the conduct of the research, adverse reactions such as extreme distress);
- submitting details of proposed substantive amendments to the protocol to the Research Ethics Officer for approval.

Please contact me if you have any queries or require further information.

Tel:- 01542 593987
Email:- fhmresearchsupport@lancaster.ac.uk

Yours sincerely,

Becky Case
Research Ethics Officer, Secretary to FHMREC.

A2.7.5 Ethics amendment and approval letter (version 5)

Health & Medicine | Lancaster University

Faculty of Health and Medicine Research Ethics Committee (FHMREC) Lancaster University
Application for Amendment to Previously Approved Research

- Name of applicant: Beth Cheshire
- E-mail address and phone number of applicant: b.cheshire@lancaster.ac.uk 07530493418
- Title of project: Neuropsychological impact of chronic low-level carbon monoxide exposure in older adults
- FHMREC project reference number: FHMREC17082
- Date of original project approval as indicated on the official approval letter (July/2018):
- Please outline the requested amendment(s)
  Note that where the amendment relates to a change of researcher, and the new researcher is a student, a full application must be made to FHMREC
- Fire safety officers will re-visit all of the properties prior to the follow up (rather than just the homes with the higher levels of CO) to provide health and safety information to the participants regarding CO sources, safety and prevention, and the associated health risks (intervention; see appendix 15).

Please explain your reason(s) for requesting the above amendment(s):

- By carrying out the intervention in all of the homes rather than only those with higher CO levels will mean that the participants won't know which group they fall into. If participants were informed or thought that they were part of a group of homes with slightly higher CO levels they might become distressed and possibly alter their behaviour at the follow up testing point. All the CO levels collected so far are within the safe working exposure level guidelines that the Fire Service follow. During the intervention participants will be informed that none of the homes had CO concentrations above the guidelines or that are considered 'unsafe' and that the Fire Service are providing health and safety information regarding CO sources, safety and prevention, and the associated health risks to all homes whilst putting the loggers back out as part of the 'CO programme' to raise awareness and educate. Fire Officers will also remind participants that the research is only looking at low levels of CO, all below levels that would trigger a CO alarm, and that the CO alarm is given to them to keep them safe from higher CO concentrations. The CO alarm will also be checked during the visit.

idance:

Resubmit your research ethics documents **(the entire version which received final approval, luding all participant materials, your application form and research protocol),** with all additions

highlighted in yellow, and any deletions simply 'struck through', so that it is possible to see what was there previously.

b) This should be submitted as a **single PDF** to Becky Case. There is no need to resubmit the Governance Checklist.

Applicant electronic signature: B. Cheshire Date: 21/05/2019

Student applicants: please tick to confirm that you have discussed this amendment application with your supervisor, and that they are happy for the application to proceed to ethical review ☑

Project Supervisor name (if applicable): Prof Carol Holland Date application discussed: 17/05/2019

You must submit this application from your Lancaster University email address, and copy your supervisor in to the email in which you submit this application.

Applicant: Beth Cheshire
Supervisor: Carol Holland
Department: Health Research
FHMREC Reference: FHMREC18086

13 June 2019

Dear Beth

Re: Neuropsychological impacts of chronic low-level carbon monoxide exposure in older adults

Thank you for submitting your research ethics amendment application for the above project for review by the **Faculty of Health and Medicine Research Ethics Committee (FHMREC).** The application was recommended for approval by FHMREC, and on behalf of the Chair of the Committee, I can confirm that approval has been granted for the amendment to this research project.

As principal investigator your responsibilities include:

- ensuring that (where applicable) all the necessary legal and regulatory requirements in order to conduct the research are met, and the necessary licenses and approvals have been obtained;
- reporting any ethics-related issues that occur during the course of the research or arising from the research to the Research Ethics Officer at the email address below (e.g. unforeseen ethical issues, complaints about the conduct of the research, adverse reactions such as extreme distress);
- submitting details of proposed substantive amendments to the protocol to the Research Ethics Officer for approval.

Please contact me if you have any queries or require further information.

Tel:- 01542 593987
Email:- fhmresearchsupport@lancaster.ac.uk

Yours sincerely,

Becky Case
Research Ethics Officer, Secretary to FHMREC.