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GENDER AND THE PREMATURE DEATHS OF PEOPLE WITH INTELLECTUAL DISABILITIES

A Review of Evidence

This review formed the basis of an international expert consultation. The review is presented here as sent to respondents in the study and does not incorporate feedback received from respondents regarding the topics covered

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This review has been funded by Public Health England. However, the findings and views expressed in this review are those of the authors and should not be attributed to Public Health England. 2019

Gender and the Premature Death of People with Intellectual Disabilities: A Review of Evidence

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[1] These sections or specific topics are optional in the online questionnaire based on this literature review and you will be given the option to miss them out if you wish

Introduction

A recent systematic review of early death and causes of death among people with intellectual disabilities found that standardized mortality rates (SMRs) showed a greater inequality for women than men (O'Leary et al., 2018). The majority of studies found that SMRs were higher for females with intellectual disabilities in comparison with males with intellectual disabilities. This indicates that the inequality in mortality rates between the population with intellectual disabilities and the general population is greater for females than males. The reason for this is unclear.

In this review, we consider the evidence regarding gender differences in mortality among people with intellectual disabilities. We also look at gender differences in health conditions (and external causes of death) related to mortality among people with intellectual disabilities. We include conditions that are important causes of death for people with intellectual disabilities, such as epilepsy and respiratory disease. We also look at gender specific issues such as testicular and cervical cancer. Each section regarding health conditions related to mortality presents evidence on gender differences in the risk of death from the condition, and evidence on gender differences in the prevalence or incidence of the condition. Overall, there is little evidence on gender differences in relation to the risk of death due to specific causes. Hence, evidence on gender differences in the prevalence or incidence of conditions related to common causes of death is important in beginning to understand gender differences in premature mortality. Where literature searches identified evidence on gender differences in health conditions related to mortality for specific syndromes, the evidence for each specific syndrome is presented in a separate section of the report.

Evidence is also presented on gender differences in relation to risk factors for common causes of death such as obesity, physical inactivity, and metabolic syndrome, which is the co-existence of several major risk factors for cardiovascular disease. The five leading global risks for mortality in the world are high blood pressure, tobacco use, high blood glucose, physical inactivity, and overweight and obesity (World Health Organization, 2009). For example, physical inactivity is estimated to cause around 21–25% of breast and colon cancer burden, 27% of diabetes and about 30% of ischaemic heart disease burden (World Health Organization, 2009). These risk factors form part of a causal chain for disease and have the potential for modification.

A commonly used figure in this review is the standardized mortality ratio (SMR) which is the ratio of number of observed deaths in the study group to number of deaths that would be expected based on death rates of a chosen standard population. This can be presented as either a ratio or a percentage. For consistency, where studies have presented the SMR as a percentage we have converted this to a ratio.

Mortality

Gender Differences in Mortality Compared to the General Population

A number of studies suggest that inequality in mortality rates between the population with intellectual disabilities and the general population is greater for females than males. These are summarised below.

- A study in Finland included all individuals who during 1996–2011 received a disability pension, disability allowance or care allowance due to a diagnosis of intellectual disabilities. Based on 5,171 deaths of people with intellectual disabilities, a SMR difference between genders was consistently observed with the exception of no significant difference by gender for those with mild intellectual disabilities aged 0-14 (Arvio et al., 2016). The overall SMR for

females with mild intellectual disabilities was 2.80 (95% CI: 2.60–3.01) and for males 2.01 (95% CI 1.88, 2.14) ($p < 0.001$), and for females with severe intellectual disabilities 5.24 (95% CI 4.99, 5.50) and for males 2.59 (95% CI 2.48, 2.72) ($p < 0.001$).

- In a study of 693 people with intellectual disabilities in Australia, a population-derived cohort based on a prevalence study via multiple agencies, the SMR for males was 4.1 (95% CI 2.4, 5.9) and for females was 6.2 (95% CI 3.3, 9.1) (Durvasula et al., 2002). The years of potential life lost (YPLL) ratio for males was 5.9 (95% CI 5.6, 6.3) and for females was 8.0 (95% CI 7.4, 8.6) (meaning that there were eight times more YPLL in women with intellectual disabilities than expected compared to women in the general population) (Durvasula et al., 2002).
- For 40,705 people with intellectual disabilities aged 5 to 69 in Australia in receipt of intellectual disability services, the relative mortality of females with an intellectual disability compared to their same-aged female population peers was significantly greater (SMR 4.26, 95% CI 3.83, 4.74) than it was for males (SMR 2.52, 95% CI 2.29, 2.77) (Florio and Trollor, 2015).
- Based on 31,943 people on Ireland's National Intellectual Disability Database (NIDD) which includes people with an intellectual disability who are eligible for or receive services, the overall SMR for females was 4.90 (95% CI 4.63, 5.17), which was larger than that for males of 3.09 (95% CI 2.93, 3.25) (McCarron et al., 2015).
- For 2,995 adults with moderate to profound intellectual disabilities on the Leicestershire Intellectual Disability Register which includes those who use intellectual disability services (those with mild intellectual disabilities were excluded from the study), the all cause SMR for males was 2.28 (95% CI 2.02, 2.56), and for females 3.24 (95% CI 2.83, 3.69) (Tyrer and McGrother, 2009).
- For patients on GP registers in England with a recorded intellectual disability (664 deaths), the SMR for women (SMR 3.40, 95% CI 3.02, 3.81) was higher than that for men (SMR 3.03, 95% CI 2.73, 3.35) (Glover et al., 2017). GP registers may miss those with mild to moderate intellectual disability and no associated syndromic cause.
- For 2,436 adults with moderate to profound intellectual disabilities on the Leicestershire Intellectual Disability Register which includes those who use intellectual disability services (those with mild intellectual disabilities were excluded from the study), SMRs were higher in women than men across all age groups (Tyrer et al., 2007).
- Based on data from both US state intellectual and developmental disabilities service system administrative data sets and de-identified state Medicaid claims, females with intellectual and developmental disabilities were found to experience greater inequalities in mortality rates compared to the general population than males with intellectual and developmental disabilities (Lauer and McCallion, 2015). Administrative data sets are likely to under-represent people with mild intellectual disabilities, higher socio-economic status and a high level of functioning in daily living activities.

The reason for the greater inequality in mortality rates reported for females with intellectual disabilities is unclear and one of the drivers for undertaking this review. It is interesting to note that in one study of 64,207 people with intellectual disabilities in the US in receipt of services, which specifically excluded people with intellectual disabilities who had physical disability, a degenerative or genetic condition (e.g. Down syndrome), serious medical condition, epilepsy or autism, the age- and sex-specific excess death rates (EDRs) and mortality ratios (MRs) were fairly comparable for males and females (Shavelle et al., 2014). It should also be noted that some conflicting results have been reported. For 16,666 adults with intellectual disabilities on general practice registers in

England (which may miss those with milder intellectual disabilities), a higher mortality risk among adults with intellectual disability was seen at all ages, and although the hazard ratio was higher among men than it was among women, the difference was not statistically significant after adjustment (Hosking et al., 2016). A recent study in Ontario, based on people with an intellectual and developmental disability coded encounter with the healthcare system (which may miss those with more mild intellectual disabilities), found that the SMR of males with intellectual and developmental disabilities (3.7, 95% CI 3.4, 4.1) was very similar to that of females with intellectual disabilities (3.6, 95% CI 3.3, 3.9) (Stankiewicz et al., 2018), suggesting that the disparities compared to people without intellectual disabilities were equivalent for males and females.

Summary

Whilst there are some conflicting results, the weight of evidence suggests that inequality in mortality rates between the population of people with intellectual disabilities and the general population is greater for females than males.

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Age Trends in Gender Differences in Mortality

A number of studies suggest that gender differences in mortality among people with intellectual disabilities when compared to the general population are mainly a feature of younger age groups. This evidence is summarised below.

- For 2,436 adults with moderate to profound intellectual disabilities on the Leicestershire Intellectual Disability Register which includes people receiving intellectual disability services (those with mild intellectual disability were excluded from the study), differences were particularly evident in the younger age groups. For people aged 20–29 years mortality was almost nine times higher in men (SMR 8.83; 95% CI 5.60, 13.25) and more than 17 times higher in women (SMR 17.22; 95% CI 9.64, 28.40). For ages 30-39 the SMR for men was 6.36 (95% CI 4.07, 9.46) and for women was 12.10 (95% CI 7.58, 18.32) (Tyrer et al., 2007). By age 70+ the SMRs were similar (men 1.39 (95% CI 1.03, 1.82); women 1.60 (95% CI 1.18, 2.12).
- Based on 31,943 people on Ireland's National Intellectual Disability Database (NIDD) which includes people with an intellectual disability who are eligible for or receive services, gender differences were particularly apparent at younger ages, with the SMR for those aged 0–19 years being more than four times higher in males (SMR 4.65, 95% CI 3.92, 5.49) and almost 11 times higher in females (SMR 10.77, 95% CI 8.99, 12.78) (McCarron et al., 2015).
- For patients on GP registers in England with a recorded intellectual disability (664 deaths), age specific data suggest higher death rates in women with intellectual disabilities are mostly a feature of younger age groups (Glover et al., 2017). GP registers may miss those with mild to moderate intellectual disability and no associated syndromic cause.
- A study in Finland included all individuals who during 1996–2011 received a disability pension, disability allowance or care allowance due to a diagnosis of intellectual disabilities. Based on 5,171 deaths of people with intellectual disabilities, the SMR difference between genders was particularly marked for younger people with severe intellectual disabilities (age 0-14 female SMR 21.35 (95% CI 16.58, 27.07), male SMR 8.22 (95% CI 5.92, 11.11); age 15-29 female SMR 20.47 (95% CI 17.10, 24.31), male SMR 5.85 (95% CI 4.95, 6.87)) (Arvio et al., 2016).
- For 4,812 adults with intellectual disabilities living in US households (i.e. only including respondents from the noninstitutionalized, civilian population and not those who have the most involved health and care needs and reside in a hospital or nursing home), females had higher mortality risk than males at younger ages, which decreased into middle age, was equivalent with males from ages 50 to 59, then lower than males in older age (Landes, 2017). Among those without intellectual disabilities, females consistently had lower mortality risk than males. At age 20, females with intellectual disabilities had an 18.44 higher odds ratio of mortality that decreased to 6.93 times higher by age 50, and was 2.60 times higher by age 80. In contrast, the odds ratio of mortality for males with intellectual disabilities was only 6.49 times higher at age 20, decreased to 3.65 times higher at age 50, and was 2.05 times higher at age 80. The disparity in mortality risk between those with and without intellectual disabilities was more severe for females from ages 20 to 49. The mortality disadvantage for men with intellectual disabilities was minimal at ages 20 to 29.
- For 18,362 people with intellectual disabilities aged 40 or more in institutions or community care in California who had received services from the Department of Developmental Services between 1980 and 1992, male mortality rates were about equal to females at age 40 but were nearly 50% higher by age 65 (Strauss and Kastner, 1996).

- A 35 year prospective cohort study in Finland of 2,336 people, who were identified by municipalities as having known or suspected intellectual disabilities, found that females formed the majority from 60 years of age onwards, whereas in the general population, the corresponding age was 35 years (Patja et al., 2000).
- A study in Australia included 19,362 people with intellectual disabilities who were registered users of disability services with intellectual disability as a primary or secondary diagnosis. The overall age standardised mortality rate (ASMR) for adult males with intellectual disabilities (12.5) was substantially higher than for adult females with intellectual disabilities (8.6), similar to the general population (Trollor et al., 2017). However, the impact of gender on ASMRs differed with age. In young and middle-aged adults, ASMRs of males and females with intellectual disabilities approximated one another, whereas in the corresponding age bands of the general population, ASMRs for males were approximately double those for females. The comparative mortality figure (people with intellectual disability compared to the general population) at ages 20-44 for males was 3.0 (95% CI 2.2, 4.0) and for females was 6.1 (95% CI 4.0, 9.5). For the entire age range of 20+ the figures were 1.4 (95% CI 1.1, 1.6) for males and 1.3 (95% CI 1.1, 1.6) for females.

Suggestions have been given as to underlying reasons for these age related differences in mortality risk. Landes (2017) suggests that the mortality disadvantage for men with intellectual disabilities was minimal at ages 20 to 29 as mortality risk for men in the general population is higher at younger ages due to violence, suicide, or car accidents and young men with intellectual disabilities may be sheltered from these causes of death (Landes, 2017) (see also the separate section on external causes of death below). A similar suggestion is given by Trollor et al (2017) who note that observed gender differences may be driven in part by a relative under-representation of deaths in young males with intellectual disabilities (compared to the general population), rather than an overrepresentation of deaths in young females with intellectual disabilities, with a low proportion of injury and poisoning deaths in males and females with intellectual disabilities compared with the general population (Trollor et al., 2017).

Landes (2017), commenting on the remarkable severity of the intellectual disability mortality disadvantage for females at younger ages, notes that per a heterogeneity of frailty explanation, this would indicate females with intellectual disabilities have increased health frailty at younger ages. The question is whether this is a physiological characteristic of this group, or related to possible differences in access to and utilization of needed health care (Landes, 2017). Some of the deaths experienced by adults with intellectual disabilities among younger age groups may actually be preventable were this population afforded health care access and support similar to that offered to the general population. Landes (2017) suggests that this may especially be true for females with intellectual disabilities who often do not receive needed gender related health care or health behaviour information at younger ages, resulting in poorer morbidity outcomes that could lead to earlier mortality.

Summary

The greater inequality in mortality rates for females with intellectual disabilities is mainly a feature of younger age groups.

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Age at Death

For age at death, females with intellectual disabilities appear to be more disadvantaged compared to females in the general population than males, with the gap in life expectancy between those with and without intellectual disabilities being greater for females. Evidence regarding this is summarised below.

- Based on 31,943 people on Ireland's National Intellectual Disability Database (NIDD) which includes people with an intellectual disability who are eligible for or receive services, whilst females with intellectual disabilities had a significantly higher average age of death than males (56 vs 53), they were more disadvantaged relative to women in the general population than males. Females in the general population outlived females with intellectual disabilities by an average of 21 years compared to 17 years longer for males in the general population compared to males with intellectual disabilities (McCarron et al., 2015).
- Based on 19,362 people with intellectual disabilities in Australia (registered users of disability services with intellectual disability as a primary or secondary diagnosis) there was no significant difference between the median age at death for males (55 years) and females (52 years) with intellectual disabilities. This compares to the median age at death in the comparison group of 78 for males and 84 for females (Trollor et al., 2017).
- The Confidential Inquiry into premature deaths of people with intellectual disabilities in the UK took a population-based approach to reviewing all known deaths of people with intellectual disabilities in a particular geographical area, which were identified via a wide-ranging notification system. A total of 247 deaths were reviewed and the median age of death was lower for females (63) than males (65) (Heslop et al., 2014). On average, male individuals with intellectual disabilities died 13 years earlier than the population of England and Wales, and female individuals died 20 years earlier (Heslop et al., 2014).
- For 15,289 people with intellectual disabilities aged 55 or more in Sweden identified via two National registers, one covering all specialist health-care visits (out-patient visits and hospitalisation) and the other covering people accessing social/support services, the median survival time for men was 68.8 years and 69.8 years for women. This compared with 75.2 years for men and 78.4 years for women in the control population. The gender gap in median survival was relatively small among Swedish older adults with intellectual disabilities compared with the control population (Ng et al., 2017).
- For patients on GP registers in England with a recorded intellectual disability (664 deaths), life expectancy at birth for men with intellectual disabilities was 63.8 years (57.7 to 69.9) and 66.7 years (63.4 to 70.0) for women. This represents a shortfall for people with intellectual disabilities compared to the general population of 19.7 years for men and 20.2 years for women (Glover et al., 2017). GP registers may miss those with mild to moderate intellectual disability and no associated syndromic cause.
- Based on data from around half of GP practices in England, in 2017-18 females with intellectual disabilities had a life expectancy 18 years lower than females without intellectual disabilities (65 years compared to 83 years) and males with intellectual disabilities had a life expectancy 14 years lower than males who did not have intellectual disabilities (66 years compared to 80 years) (NHS Digital, 2019).
- A 35 year prospective cohort study in Finland of 2,336 people with intellectual disabilities, who were identified by municipalities as having known or suspected intellectual disabilities, found that survival between sexes differed less than in the general population for all levels of intellectual disabilities (Patja et al., 2000).

- Based on 1,236 deaths of people with intellectual disabilities between 1970 and 2012 in Finland, identified via two district organizations responsible for intellectual disability services, the average age at death was 22 years younger for men (95% CI: -24 to -20) and 30 years for women (95% CI: -33 to -27) (Arvio et al., 2017). Unlike in the general population, female individuals with intellectual disability had similar lifespans to those of the men (Arvio et al., 2017).
- A large scale study in Germany involved over 24,000 people with intellectual disabilities who were receiving social aid for integration, the majority of whom lived in residential settings. As in the general population, women with intellectual disabilities had a higher survival rate than men with intellectual disabilities but gender differences were smaller than in the general population (Dieckmann et al., 2015).
- A study in the US used data from both state intellectual and developmental disabilities service system administrative data sets and de-identified state Medicaid claims. Females with intellectual and developmental disabilities were found to experience greater inequalities compared to the general population than males with intellectual and developmental disabilities, including greater differences in average age at death (19.1 year difference for females; 16.8 year difference for males) (Lauer and McCallion, 2015). Administrative data sets are likely to under-represent people with mild intellectual disabilities, higher socio-economic status and high level of functioning in daily living activities.
- For around 25,000 children and adults on the National Intellectual Disability Database of Ireland (NIDD), which includes people with an intellectual disability who are eligible for or receive services, gender did not have a significant effect on lifespan either for the sample as a whole or within each level of intellectual disability. This was in contrast to the general population in Ireland where males have a shorter life expectancy (73 years) than females (78.5 years) (Lavin et al., 2006).
- For 29,290 adult and child residents of residential centres in the Netherlands (which may thus underrepresent those with milder intellectual disabilities), there were no systematic differences in age specific life expectancy between women and men with intellectual disabilities (Maaskant et al., 2002).
- For adult service recipients of the Massachusetts Department of Developmental Services (DDS) in 2014, the average age at death was lower for women (60.1) than men (61.7) although in other years females lived slightly longer than males (by 2.1 years in 2012 and 3.7 years in 2013) (Lauer et al., 2015).

Overall, the evidence is consistent in indicating that whilst the life expectancy of females with intellectual disabilities may be equal to or higher than that of males with intellectual disabilities, females with intellectual disabilities face a greater disadvantage compared to females in the general population than males with intellectual disabilities compared to males in the general population.

Summary

The gap in life expectancy between those with intellectual disabilities and the general population is greater for females than males.

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Gender Differences in Health Conditions Related to Mortality (for specific syndromes see the relevant syndrome section)

Respiratory Disease

Respiratory disease is the leading cause of death for people with intellectual disabilities (46%-52%), with rates much higher than for the general population (15%-17%) (Thillai, 2010, Hollins et al., 1998, Puri et al., 1995, Douglas, 2010). Higher rates of asthma, chronic obstructive pulmonary disease and upper respiratory tract infections have been reported for people with intellectual disabilities (Emerson et al., 2011, Glover et al., 2012, Samele et al., 2006, Straetmans et al., 2007, Oeseburg et al., 2011). Despite being a leading cause of death, there is very little evidence regarding gender differences in relation to respiratory disease. The small amount of evidence identified is outlined below.

Risk of Death

A 35 year prospective cohort study in Finland of 2,336 people with intellectual disabilities, identified in a population based study as having known or suspected intellectual disabilities, examined specific causes of death in relation to 1,095 deaths (Patja et al., 2001). Men were at higher risk of death due to respiratory diseases than women in younger age groups (< 39 years), but at lower risk from 60 years of age onwards. A study including 2,995 adults with moderate to profound intellectual disabilities on the Leicestershire Intellectual Disability Register which includes those who use intellectual disability services (those with mild intellectual disabilities were excluded from the study), examined specific causes of death in relation to 503 deaths (Tyrer and McGrother, 2009). The SMR for bronchopneumonia was 6.46 (95% CI 4.52, 8.94) for males and 2.29 (95% CI 1.55, 3.28) for females. The SMR for other respiratory infections was 3.55 (95% CI 2.46, 4.96) for males and 6.04 (95% CI 4.10, 8.58) for females. The Confidential Inquiry into premature deaths of people with intellectual disabilities in the UK found that deaths from respiratory disorders occurred at an earlier age in people with intellectual disabilities than in the general population but with a similar gender gradient of women dying at a later age (male median age at death 65-69, female 70-75) (Heslop et al., 2013).

Incidence or Prevalence

For 1,371 adult group home residents in New York with intellectual disabilities aged between 40 and 79 years, results of logistic regression analysis indicate that respiratory disease was not associated with gender (Janicki et al., 2002). In an analysis of pooled data from three studies (including Janicki et al 2002) using the Rochester Health Status Survey, including a total of 4,449 older people with intellectual disabilities aged 40 or more, males in the combined cohort were less likely to have respiratory diseases (OR 0.25, 95% CI 0.06, 1.00; $p < 0.05$) than females (Robinson et al., 2010). A study of oral opportunistic pathogen (OOP) infections in 31 people with motor and intellectual disabilities in one residential setting found that there was higher number of OOP-positive patients among males than among females (72.7% of men and 33.3% of women and any OOP; OR 77.21, 95% CI 2.38 – 2506.02, p= 0.014) (Horie et al., 2014). However, the sample size is small and included only 10 females. Based on the primary care records of 1,097 adults (age 16 or more) with intellectual disabilities in Bristol, there was no significant difference between men and women in the overall prevalence of a diagnosis of asthma (Gale et al., 2009). Men diagnosed with asthma were significantly more likely to be current smokers (35.7%) than men who did not have asthma (17.7%) but the difference between women with (22.6%) and without (12.8%) asthma was non-significant.

Summary

There is not enough evidence to make conclusions about gender differences in the risk of death due to respiratory disease. Some evidence suggests that men aged over 40 with intellectual disabilities may be less likely to have respiratory diseases than women but further evidence is required to support this finding.

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Cancer

Please note that evidence regarding gender specific cancers (e.g. breast cancer, testicular cancer) is contained within separate sections that follow later in this review.

Cancer is a leading underlying cause of death among people with intellectual disabilities (O'Leary et al., 2018). The first population-based cohort study of intellectual disabilities and cancer ever published, based on 2,173 people with intellectual disabilities in Finland followed up between 1967 and 1997, found that the overall incidence of cancer among people with intellectual disabilities was comparable with the general population (Patja et al., 2001a). Evidence regarding gender differences in cancer among people with intellectual disabilities is summarised below (gender specific cancers are covered in individual sections later in this review).

Risk of Death

A 35 year prospective cohort study in Finland of 2,336 people with intellectual disabilities, identified in a population based study as having known or suspected intellectual disabilities, examined specific causes of death in relation to 1,095 deaths (Patja et al., 2001b). The relative risk of cancer was significantly lower at all levels of intellectual disability and in all age groups, with no reported gender differences. A study including 2,995 adults with moderate to profound intellectual disabilities on the Leicestershire Intellectual Disability Register which includes those who use intellectual disability services (those with mild intellectual disabilities were excluded from the study), examined specific causes of death in relation to 503 deaths (Tyrer and McGrother, 2009). No differences in death due to neoplasms were found between those with intellectual disabilities and general population, with no reported gender differences.

The Confidential Inquiry into premature deaths of people with intellectual disabilities in the UK found that deaths from cancer in those with intellectual disabilities occurred at a much younger age than in the general population, especially among women (median age of death for females 55–59 years, males 60-64) (Heslop et al., 2013). For patients on GP registers in England with a recorded intellectual disability (664 deaths), in relation to cause of death, colorectal cancer was more common in men than in women (men SMR 2.68 (95% CI 1.34, 4.80), women SMR 1.85 (95% CI 0.60, 4.32)) (Glover et al., 2017).

Incidence or Prevalence

A study of 811 people with intellectual disabilities in Hong Kong found that rates of cancer were higher for women than for men (men 0.9%, women 3.7%) but it is noted that the participants were a purposive sample from 18 select residential care facilities in Hong Kong and may not be a representative sample (Wong, 2011). For 1,371 group home residents with intellectual disabilities in New York aged between 40 and 79 years, cancer increased significantly with age ($p = 0.00001$) and was more likely to occur in females ($p = 0.018$) (Janicki et al., 2002). Based on 9,409 people with intellectual disabilities in Australia, the age-standardised incidence of stomach cancer was significantly higher among males with intellectual disabilities compared to males in the general population (SIR 3.19, 95% CI 1.29, 6.59), but this was not the case for females with intellectual disabilities (Sullivan et al., 2004). However, colorectal cancers were significantly more common among women with intellectual disabilities (SIR 3.10, 95% CI 1.42, 5.88), while men showed no significant increase in risk (Sullivan et al., 2004). The authors suggest that obesity may be one factor in the increased colorectal cancer rate among women with intellectual disabilities (Sullivan et al., 2004). However, a recent review concluded that evidence is insufficient to evaluate differences between women and men with intellectual disabilities in relation to colorectal cancer (Willis et al.,

2018). Females had a significantly higher age-standardised SIR for leukaemia (SIR 4.64, 95% CI 2.40, 8.11) than men (SIR 3.31, 95% CI 1.81, 5.56) (Sullivan et al., 2004).

For 50 to 64 year olds in Ontario, both men and women with intellectual and developmental disabilities were less likely to have received a faecal occult blood test (FOBT) for colorectal cancer than people in the general population, but being female was associated with higher odds of being screened for people with intellectual disabilities (Ouellette-Kuntz et al., 2015).

Summary

There is little evidence relating to gender and the risk of death due to cancer in people with intellectual disabilities. Some studies report no association with gender. Deaths from cancer in those with intellectual disabilities may occur at a younger age than in the general population, especially among women. Whilst gender differences have been reported with regards to the risk of specific types of cancer among people with intellectual disabilities, evidence is insufficient and further research is required to confirm these findings.

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Cardiovascular Disease

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease, congenital heart disease, and deep vein thrombosis and pulmonary embolism (World Health Organization, 2017). Globally more people die annually from CVDs than from any other cause (World Health Organization, 2017).

Risk of Death

A 35 year prospective cohort study in Finland of 2,336 people with intellectual disabilities, identified in a population based study as having known or suspected intellectual disabilities, examined specific causes of death in relation to 1,095 deaths (Patja et al., 2001). The relative risk of death due to vascular diseases was lower for men with intellectual disabilities than men in the general population in all groups and for most women except those with mild or moderate ID aged between 20 and 39 years. A study including 2,995 adults with moderate to profound intellectual disabilities on the Leicestershire Intellectual Disability Register which includes those who use intellectual disability services (those with mild intellectual disabilities were excluded from the study), examined specific causes of death in relation to 503 deaths. Deaths from ischaemic heart disease and other diseases of the circulatory system were more common in women with intellectual disabilities (SMRs 1.74 and 2.18 respectively) but not men (compared to those in the general population) (Tyrer and McGrother, 2009). The Confidential Inquiry into premature deaths of people with intellectual disabilities in the UK reviewed 247 deaths and found that deaths from heart and circulatory disorders were less prevalent in women (17%) than men (25%) and occurred at a younger age for both gender groups than in the general population (Heslop et al., 2013).

Incidence or Prevalence

Findings regarding gender differences in relation to the prevalence of cardiovascular disease (CVD) in people with intellectual disabilities are mixed. For people with intellectual disabilities aged 33 years or older living in institutions (n=614) or living with their family (n=514) in Taiwan, CVDs were more likely to occur in females ($p = 0.046$) (Wang et al., 2007). For 436 people with intellectual disabilities supported by one provider in the Netherlands in residential settings (aged 0-19 to 70+), 59 (14%) were found to have cardiac disease and 6 (1%) congenital heart defects (van den Akker et al., 2006). The prevalence of cardiac disease was higher in women than men (17% vs 10%). In logistic regression the adjusted odds ratio (female vs male) for cardiac disease was 1.64 (90% CI 1.01, 2.67). However, all kinds of conditions were included (congenital, hypertension, arterial and venous conditions) and it is noted that the difference was mainly due to higher prevalences in women of diseases of veins, lymphatic vessels and lymph nodes on the one hand, and on the other hand, diseases of arteries, arterioles and capillaries (van den Akker et al., 2006). Diseases of veins included phlebitis, thrombophlebitis, portal vein thrombosis, other venous embolism, and thrombosis, varicose veins of the lower extremities and other sites, haemorrhoids, oesophageal varices (van den Akker et al., 2006).

A Canadian study comparing medical outcomes for 1,457 women and 1,951 men with intellectual and developmental disabilities newly initiating antipsychotic medication found that women were at higher risk for venous thromboembolism (HR 1.72, 95% CI 1.15, 2.59; cumulative incidence 10.5% v. 2.7%) and death (HR 1.46, 95% CI 1.02, 2.10; cumulative incidence 4.8% v. 3.2%), with thromboembolism risk remaining greater for women after covariate adjustment (aHR 1.58, 95% CI 1.05, 2.38) (Vigod et al., 2018). The authors suggest that the increased risk of venous thromboembolism should be considered in the clinical care of women newly starting antipsychotic medication (Vigod et al., 2018).

A number of studies report no difference in CVD by gender. A study of 811 adults with intellectual disabilities in Hong Kong found that rates of heart disease were similar for men and women (men 6.9%, women 8.7%) but it is noted that the participants were a purposive sample from 18 select residential care facilities in Hong Kong and may not be a representative sample (Wong, 2011). For 510 people with intellectual disabilities aged over 50 living in residential settings in the Netherlands, prevalence and incidence of atherosclerotic cardiovascular disease (myocardial infarctions (MI) and cerebrovascular accidents (CVA)) did not differ to a general population control group and there was no association with gender (Jansen et al., 2013). For 1,371 group home residents with intellectual disabilities in New York aged between 40 and 79 years, there was no association between gender and cardiovascular disease (Janicki et al., 2002). In an analysis of pooled data from three studies (including Janicki et al 2002) using the Rochester Health Status Survey, including a total of 4,449 older people with intellectual disabilities aged 40 or more, there was again no association between gender and cardiovascular disease (Robinson et al., 2010).

Heart rate variability (HRV) represents an autonomic function. Reduced HRV significantly increases cardiovascular mortality and has been related to ischemic heart disease and heart failure (Chang et al., 2012). Of 129 adults with intellectual disabilities in one Taiwanese institution who participated in annual examinations, HRV examination results in people with intellectual disabilities were significantly higher in men compared with women ($P < 0.05$) (Chang et al., 2012).

Summary

There is little evidence on gender differences in the risk of death from CVDs. Evidence regarding gender differences in the prevalence of CVDs is mixed, with some studies suggesting that women with intellectual disabilities are more at risk, and other studies finding no evidence of a gender difference. For those newly initiating antipsychotic medication, being female appears to be associated with a greater risk of venous thromboembolism.

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Dementia

Risk of Death

A study including 2,995 adults with moderate to profound intellectual disabilities on the Leicestershire Intellectual Disability Register which includes those who use intellectual disability services (those with mild intellectual disabilities were excluded from the study), examined specific causes of death in relation to 503 deaths. Deaths related to dementia were more common in men with intellectual disabilities (SMR 4.57, 95% CI 1.24, 11.70) but not women (SMR 0.88, 95% CI 0.02, 4.91) (Tyrer and McGrother, 2009).

Incidence or Prevalence

In the general population, females have a higher risk of Alzheimer's Disease (AD) than men (Li and Singh, 2014) whereas males are at greater risk of developing vascular dementia (Podcasy and Epperson, 2016). Studies suggest an increased risk of dementia among women with intellectual disabilities compared to men (Axmon et al., 2017). Based on 3,609 women and 4,327 men with intellectual disabilities aged 55+ in Sweden, women were more likely than men to have at least one diagnosis of dementia (odds ratio 1.40, 95% CI 1.06, 1.83) (Axmon et al., 2017). Based on 295 men and 295 women with intellectual disabilities living in community settings and referred to a specialist mental health service in South-East London, more women had a diagnosis of dementia than men (5.8% vs 1.7%) (Tsakanikos et al., 2006). Of 222 people with intellectual disabilities aged 60 or over assessed for dementia, 9.4% of men and 17.1% of women met criteria for dementia but gender differences in prevalence were not statistically significant (Pearson's chi square 2.92, p=0.087), although the authors acknowledge that the study may have lacked the power to make within group comparisons (Strydom et al., 2009). Of 134 people aged 65 or over living in Leicestershire, a greater proportion of women than men were assessed as having dementia (28.4% vs 14.9%, chi square 3.55, df 1, p = .050) (Cooper, 1997). For 8,655 adults aged 18+ years with intellectual and/or developmental disabilities in Canada, the prevalence of dementia identified via records was 7.2% for males and 9.2% for females (compared to 2.2% and 3.1% in the general population) although no statistics are presented relating to any gender difference in prevalence (Shooshtari et al., 2017).

Summary

There is very little evidence on gender differences in the risk of death related to dementia among people with intellectual disabilities. Women with intellectual disabilities appear to be at greater risk of having dementia than men with intellectual disabilities.

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Epilepsy

Risk of Death

We have identified only one study that considers gender in relation to the risk of death due to epilepsy. A 35 year prospective cohort study in Finland of 2,336 people with intellectual disabilities, identified in a population based study as having known or suspected intellectual disabilities, examined specific causes of death in relation to 1,095 deaths (Patja et al., 2001). Sixteen deaths were due to epileptic seizures. The mean age at death from epilepsy was 29.8 years and there was no significant variation by level of intellectual disability or gender.

Incidence or Prevalence

There is no strong evidence to suggest that overall the prevalence of epilepsy varies between men and women with intellectual disabilities. In a systematic review of the prevalence of epilepsy in people with intellectual disabilities, where male and female prevalence figures were given separately (nine studies), pooled estimates were 24.8% (95% CI 19.6, 30.8) for males and 22.2% (17.3, 28.1) for females (Robertson et al., 2015). However, a more recent study, based on a representative sample of 953 people with intellectual developmental disorders in Spain, found that women were more likely than men to experience epilepsy (men 29.1%, women 33.0%, OR 1.15 (95% CI not given)) (Folch et al., 2019). Further research is required to establish any difference in epilepsy prevalence between men and women with intellectual disabilities.

For adults with intellectual disabilities and epilepsy, one study based on the Leicestershire Intellectual Disability Register has reported the all cause standardised mortality ratio (SMR) to be higher for women (SMR 5.6 (95% CI 4.6, 6.7)) than for men (SMR 3.2 (95% CI 2.7–3.8)) (Kiani et al., 2014). Nearly two-thirds of adults who died from sudden unexpected death in epilepsy (SUDEP) in those both with and without intellectual disabilities were male (Kiani et al., 2014). The study also reports SMRs for SUDEP (probable or definite) for people with intellectual disabilities although this is based on only 26 deaths (17 of whom were men) and confidence intervals are wide (male SMR 37.6 (95% CI 21.9, 60.2); female SMR 52.0 (95% CI 23.8, 98.8)) (Kiani et al., 2014).

Summary Statement

The extremely limited evidence suggests that there are no gender differences in the risk of death due to epilepsy among people with intellectual disabilities. One study suggests that all cause mortality may be higher for women than men with intellectual disabilities who have epilepsy. Overall there is no strong evidence to suggest that the prevalence of epilepsy varies between men and women with intellectual disabilities.

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Digestive System

Risk of Death

A 35 year prospective cohort study in Finland of 2,336 people with intellectual disabilities identified in a population based study as having known or suspected intellectual disabilities, examined specific causes of death in relation to 1,095 deaths (Patja et al., 2001). Diseases of the digestive system as a primary cause of death were 2.5 times more common than in the general population and associated with profound intellectual disabilities and male sex (Patja et al., 2001). A study including 2,995 adults with moderate to profound intellectual disabilities on the Leicestershire Intellectual Disability Register which includes those who use intellectual disability services (those with mild intellectual disabilities were excluded from the study), examined specific causes of death in relation to 503 deaths (Tyrer and McGrother, 2009). Both men and women with intellectual disabilities were at higher risk of death due to digestive system diseases than the general population but there was no difference by gender with a SMR of 2.21 (95% CI 1.14, 3.86) for men and 2.57 (95% CI 1.17, 4.88) for women. For patients on GP registers in England with a recorded intellectual disability (664 deaths), in relation to cause of death, colorectal cancer was more common in men than in women (men SMR 2.68 (95% CI 1.34, 4.80), women SMR 1.85 (95% CI 0.60, 4.32)) (Glover et al., 2017).

Incidence or Prevalence

A study of 811 people with intellectual disabilities in Hong Kong found that rates of gastrointestinal disease were similar for men and women (men 1.4%, women 2.4%) but it is noted that the participants were a purposive sample from 18 select residential care facilities in Hong Kong and may not be a representative sample (Wong, 2011). For 1,371 group home residents with intellectual disabilities in New York aged between 40 and 79 years, a higher prevalence of gastro-intestinal disorders was seen among males (Janicki et al., 2002). In a similar study, for 1,373 adults aged 33 to 79 years with intellectual disabilities living in small group homes in New York State, male gender was found to be an independent predictor of gastroesophageal reflux but the reason for this was unknown (Henderson et al., 2009) and the relationship was not found in a previous study of a large cohort of institutionalized intellectually disabled individuals (Bohmer et al., 1999). In an analysis of pooled data from three studies (including Janicki et al 2002) using the Rochester Health Status Survey, including a total of 4,449 older people with intellectual disabilities aged 40 or more, gender was not associated with gastro-intestinal conditions (Robinson et al., 2010).

Summary

Evidence on gender differences in the risk of death due to diseases of the digestive system is limited and conflicting. There is also limited and conflicting evidence regarding gender differences in the risk of digestive system disorders among people with intellectual disabilities.

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Infectious Diseases

Risk of Death

A 35 year prospective cohort study in Finland of 2,336 people with intellectual disabilities identified in a population based study as having known or suspected intellectual disabilities, examined specific causes of death in relation to 1,095 deaths (Patja et al., 2001). Excess mortality was observed for infectious diseases but no gender related difference was reported.

Incidence or Prevalence

For 1,371 adult group home residents in New York with ID aged between 40 and 79 years, infectious diseases (including urinary tract infections, positive tuberculosis test, pneumonia, bronchitis, cellulitis and sinusitis) significantly increased with age ($P < 0.0001$), and occurred more often in females ($P = 0.008$) (Janicki et al., 2002). In an analysis of pooled data from three studies (including Janicki et al 2002) using the Rochester Health Status Survey, including a total of 4,449 older people with ID aged 40 or more, males in the combined cohort were less likely to have infectious diseases than females (OR 0.24, 95% CI 0.10, 0.57; $p < 0.01$) (Robinson et al., 2010). This may be related to an increased risk of urinary tract infections among women compared to men with intellectual disabilities, as found in the general population (Henderson et al., 2009)

Summary

The small amount of evidence on the risk of death from infectious diseases among people with intellectual disabilities shows no gender difference. The little evidence available suggests that older women with intellectual disabilities may be more likely to suffer from infectious diseases than men. This may be related to an increased risk of urinary tract infections. Further research is required to confirm these findings.

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Endocrine Disorders

In relation to endocrine disorders, diabetes is covered in a separate section below.

Risk of Death

There does not appear to be any evidence on gender differences in the risk of death due to endocrine disorders among people with intellectual disabilities.

Incidence or Prevalence

For 1,371 adult group home residents in New York with ID aged between 40 and 79 years, endocrine disorders were more common among females (p = 0.00001) (Janicki et al., 2002). In an analysis of pooled data from three studies (including Janicki et al 2002) using the Rochester Health Status Survey, including a total of 4,449 older people with ID aged 40 or more, males in the combined cohort were less likely to have endocrine diseases (OR 0.22, 95% CI 0.09, 0.53; p < 0.05) (Robinson et al., 2010). A recent study, based on a representative sample of 953 people with intellectual developmental disorders in Spain, found that women were more likely than men to suffer from thyroid disease (men 6.4%, women 13.7%, OR 2.28 (95% CI not given)) (Folch et al., 2019).

Summary

We are not aware of any evidence on gender differences in the risk of death due to endocrine disorders. Endocrine disorders have been reported to be more common among women than men with intellectual disabilities but the evidence is limited. There does not appear to be any evidence comparing the risk of endocrine disorders among men and women with intellectual disabilities to men and women in the general population.

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Diabetes

Globally, diabetes was the seventh leading cause of death in 2016 with an estimated 1.6 million deaths directly caused by diabetes (World Health Organization, 2018).

Risk of Death

We are not aware of any evidence on gender differences in the risk of death due to diabetes among people with intellectual disabilities.

Incidence or Prevalence

Worldwide, there has been a shift from an excess prevalence of diabetes in women in 1980, to a higher male prevalence in 2014 (NCD Risk Factor Collaboration, 2016). This shift in diabetes prevalence from women towards men might be due to men having higher prevalences of some risk factors for diabetes, such as smoking, or being at risk of diabetes at lower BMI levels than women (NCD Risk Factor Collaboration, 2016). European men in the general population are usually diagnosed with diabetes at an earlier age and at lower BMI than women, with the most prominent sex difference being at younger age (Kautzky-Willer et al., 2016).

For people with intellectual disabilities, this male preponderance in diabetes prevalence may be reversed. For 7,936 people with intellectual disabilities aged 55+ in Sweden, women were more likely to have a diagnosis of diabetes than women in the general population (Relative Risk (RR) 1.69, 95% CI 1.42, 2.01) (Axmon et al., 2017). This was particularly the case for a non-insulin dependent diagnosis (RR 1.67, 95% CI 1.39, 2.01) as opposed to an insulin dependent diagnosis (RR 1.16, 95% CI 0.84, 1.61)). However, this was not the case for men with intellectual disabilities whose likelihood of a diagnosis of diabetes did not differ from men in the general population (RR 0.96, 95% CI 0.83, 1.10) (Axmon et al., 2017). Within the general population cohort, a higher risk of diabetes mellitus diagnosis was found for men (RR 1.64, 95% CI 1.39–1.95). The same effect was not found in the intellectual disability cohort (RR 0.93, 95% CI 0.81, 1.08) (Axmon et al., 2017). A high prevalence of being overweight among women with intellectual disabilities may be an explanation for their higher prevalence of non-insulin-dependent diabetes mellitus (Axmon et al., 2017).

Based on a cohort of 28,567 people with intellectual and developmental disabilities between 30–69 years of age in Canada, women with intellectual and developmental disabilities had a higher prevalence of diabetes (17.5%; no differentiation given between type I and type II diabetes) than men with intellectual and developmental disabilities (15.3%), but the opposite was true for people without IDD (men, 11.9%; women, 9.6%) (Balogh et al., 2015). The adjusted prevalence ratio for males was 1.33 (95% CI 1.28, 1.37) and for women 1.77 (95% CI 1.70, 1.83) (Balogh et al., 2015).

A further study in Sweden included people with intellectual disability excluding Down syndrome (n = 11,785); Down syndrome (n = 1,282) and a general population comparison group (n = 1,996,140) (Wallén et al., 2018). For those with intellectual disabilities but not Down syndrome, diabetes was more likely in both men (OR 2.005, 95% CI 1.795, 2.240) and women (OR 2.403, 95% CI 2.113, 2.733) (Wallén et al., 2018).

Among people age 50-70 with intellectual disabilities receiving formal care or support in the Netherlands (n=611) diabetes was more common among women with intellectual disabilities than those aged 50-70 in the general population (15.5% (95% CI 11.3, 19.6) vs 8.0% (95% CI 6.4, 9.6)). However, there was no difference for men (men with intellectual disabilities 10.0% (6.7, 13.3) vs 10.2% (95% CI 8.3, 12.0)) (de Winter et al., 2012). A study of 811 people with intellectual disabilities in Hong Kong found that rates of diabetes were similar for men and women (men 4.1%, women

6.6%) but it is noted that the participants were a purposive sample from 18 select residential care facilities in Hong Kong and may not be a representative sample (Wong, 2011). However, for 291 adults with intellectual disabilities living in New York City, based on data from a review of medical records, a diagnosis of diabetes mellitus was less common among women with intellectual disabilities (adjusted odds ratio 0.38 (95% CI 0.10, 1.37)) (Sohler et al., 2009).

Summary

We are not aware of any evidence on gender differences in the risk of death due to diabetes among people with intellectual disabilities. Women with intellectual disabilities appear to have a higher prevalence of diabetes than women in the general population, particularly non-insulin dependent diabetes, but this has not been found for men with intellectual disabilities. A high prevalence of being overweight among women with intellectual disabilities may be an explanation for their higher prevalence of non-insulin-dependent diabetes mellitus.

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Bone health and fractures

Osteoporosis is a result of reduced bone mass and disruption of the micro-architecture of bone which leads to decreased bone strength and increased risk of fracture (Poole and Compston, 2006). Fragility fractures are associated with considerable disability, costs and an increased risk of mortality, which is particularly the case for fractures of the hip and vertebra (Sattui and Saag, 2014). Osteoporosis is generally thought of as a ''woman's disease'' because the prevalence of osteoporosis and the rate of fractures are much higher in postmenopausal women than in older men (Cawthon, 2011). However, older men still suffer poor health outcomes related to osteoporosis and fractures, and tend to have worse outcomes after fracture than women, being twice as likely to die after hip fracture than women (Cawthon, 2011). Further, a lower proportion of men at high risk of fracture are treated than women at high risk (Cawthon, 2011).

Risk of Death

A 35-year follow-up study of a nation-wide population of 2,369 people with intellectual disabilities in Finland found that among the elderly, women had an increased risk of fatal fracture compared to the general population (Patja et al., 2001).

Incidence or Prevalence

Studies indicate that people with intellectual disabilities may have an increased prevalence of osteoporosis and lower bone density than the general population (Tyler et al., 2000, Jaffe et al., 2005, Jaffe et al., 2001, Mergler et al., 2009, Center et al., 1998). There is some evidence that poor bone quality may be associated with being female among people with intellectual disabilities. A study of 768 persons with intellectual disabilities (aged 50 years or more) in the Netherlands used ultrasound to determine the prevalence of low bone quality (Bastiaanse et al., 2014). The prevalence of low bone quality was 43.9% and was associated with female gender (OR 2.37, 95% CI 1.44, 3.88). In Ireland, the prevalence of a doctor's diagnosis of osteoporosis for 753 people with intellectual disabilities aged 40 years and over was 8.1% and associated with female gender (OR 4.58, 95% CI 2.29, 9.17) (Burke et al., 2017). A large-scale population-based study in Greater Glasgow incorporating health assessments found an osteoporosis prevalence of 18.5% among 1,023 people with intellectual disabilities, with osteoporosis being more common in women (OR 2.34, 95% CI 1.64, 3.32) (Kinnear et al., 2018).

Being female has also been reported to be associated with fractures among people with intellectual disabilities. For 1,373 adults aged 33 to 79 years with intellectual disabilities living in small group homes in New York State, women were more likely than men to have osteoporosis ($p = 0.0001$) and fractures ($p = 0.046$) (Henderson et al., 2009). A study of people with intellectual disability and epilepsy found that fractures were more likely in women (32% of 121 participants) than men (20% of 142 participants) (Jancar and Jancar, 1998). A chart review of 93 women with intellectual disabilities found that the prevalence of fractures was very high with 32% (30/93) of the charts containing a history of an adult-onset fracture, with the average age of first fracture being 41.7 years (Schrager et al., 2007).

However, some studies indicate that osteoporosis and fractures may also be a significant issue for men with intellectual disabilities. Data from a 23-year longitudinal cohort registry of 1,434 people with severe and profound developmental disabilities found that gender was not a factor in fracture risk (Glick et al., 2005). Other studies have found male gender to be associated with low bone

density (Lohiya et al., 2004) and fractures (Lohiya et al., 1999, Vanlint and Nugent, 2006) in people with intellectual disabilities.

An increased risk of poor bone health or fractures in males with intellectual disabilities has been reported compared to the general population. An analysis of femoral fractures and of other fractures in 17,880 people with developmental disabilities (mainly people with intellectual disabilities and also some people with other disabilities) identified in a large health claims database in Germany found that for those age 20 or more, compared to the general population the age standardized incidence ratio was 4.80 for women (95% CI 3.44, 6.72) and 7.06 for men (95% CI 5.70, 8.74) (Büchele et al., 2017). A study including 30,522 individuals with intellectual and developmental disabilities between the ages of 40 and 64 years of age in the United States found that the rate of low-trauma fractures was approximately three times greater than in adults without intellectual disabilities (Balogh et al., 2017). The highest ratio was found when comparing the rates between men with to those without intellectual and developmental disabilities (RR 3.64, 95 % CI 2.97, 4.47), but the ratio was also higher for women (RR 2.56, 95% CI 2.11, 3.09) and the crude low trauma fracture rate was greater for women with intellectual and developmental disabilities (78.99 per 10,000 population) than men (61.32). After adjusting for covariates, females with intellectual and developmental disabilities were 2.6 times more likely than males to receive a bone mineral density test post fracture (95 % CI 1.1, 5.9). Men with intellectual and developmental disabilities may be neglected when it comes to bone mineral density testing because female sex has been identified as a risk factor for osteoporosis in the general population which may influence clinical decision making (Balogh et al., 2017).

Summary

Older women with intellectual disabilities may be more at risk of fatal fracture than women in the general population. Poor bone health and fractures appear to be more common among women with intellectual disabilities than men. However, men with intellectual disabilities are also at increased risk of poor bone health and fractures compared to the general population.

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Death from External Causes

Adult males without intellectual disabilities often die in accidents and other violent circumstances, whilst deaths from accidents, suicides or violence are not as prevalent in young men with intellectual disabilities (Tyrer et al., 2007). The resulting difference in the mortality pattern leads to better survival of adult males with intellectual disabilities (Patja et al., 2001a). For example, for 2,995 adults on the Leicestershire Intellectual Disability Register accidental deaths were more common in women with intellectual disabilities (SMR 4.10), but not men compared to those in the general population (Tyrer and McGrother, 2009). Based on a subgroup of young adults aged 20-44 from 19,362 people with intellectual disabilities in Australia (registered users of disability services with intellectual disability as a primary or secondary diagnosis), the proportion of deaths from injury and poisoning was low for both males (9%) and females (10%) (Trollor et al., 2017). In contrast, the proportion of such deaths in a comparison cohort was much higher, and higher in males (52%) than females (30%).

Whilst less common among people with intellectual disabilities than in the general population, suicidality and completed suicides do occur among those with intellectual disabilities (Hurley, 2002). Based on 2,369 people with intellectual disabilities in Finland who were followed up over 35 years, women with intellectual disabilities had an equal suicide risk to Finnish women in general, while men with intellectual disabilities had only one-third of the population risk (with suicide being more common among men than women in the general population) (Patja et al., 2001a). In a related study examining specific causes of death, in age groups younger than 40 years, the relative disease mortality (i.e. excluding external causes) excess was larger for men than women with intellectual disabilities, but not thereafter (Patja et al., 2001b). Men with intellectual disabilities were at the highest risk of dying of disease in their first two decades, but at the same time, their risk of accident was only one tenth that of the general population (Patja et al., 2001b). Ageing increased the accident risk for both sexes with intellectual disabilities, particularly for women. Among older people, women with intellectual disabilities had an increased risk of fatal fracture compared to the general population, while for men with intellectual disabilities increased risk of external cause of death was caused by the higher suicide rate (Patja et al., 2001b). The difference between sexes in cause-specific mortality was smaller for people with intellectual disabilities than in the general population.

A further study of adults on the Leicestershire Intellectual Disability Register found that on excluding deaths from external injury, the mortality differences between younger men and women with intellectual disabilities narrowed (but still remained), particularly for those aged 20-29 where the male to female ratio of 1:1.95 lowered to 1:1.17 on excluding external causes of death (SMR 19.47 for men and SMR 22.71 for women) (Tyrer et al., 2007). Whilst deaths from accidents, suicides or violence are not as prevalent in young men with intellectual disabilities as in men in the general population, these results suggest that the disadvantages faced by women compared with men with intellectual disabilities cannot be wholly explained by external injury (Tyrer et al., 2007).

Summary

Men with intellectual disabilities are at less risk of death from external causes than men in the general population. However, the limited available evidence suggests that the mortality disadvantage of females with intellectual disabilities cannot be completely attributed to the differential pattern of mortality in relation to external causes of death.

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Specific Syndromes[1]

Specific syndromes: Down syndrome[1]

People with Down syndrome appear to have an increased mortality risk compared to other people with intellectual disabilities. For 15,289 people with intellectual disabilities aged 55 or more in Sweden (Ng et al., 2017), the overall HR for those with intellectual disabilities was 4.14 (95% CI 3.98, 4.31) but for those with Down syndrome when separated out the HR was 25.4 (95% CI 21.3, 30.4).

There may be a relative survival advantage for males with Down syndrome. A study on the survival of people with intellectual disabilities in Western Australia from 1953 to 2000 found that males had a shorter median lifespan (66.7 years) compared with females (71.5 years) (Bittles et al., 2002). However, in a related study whilst the survival disadvantage was again found for males with intellectual disabilities, it was reversed in those with Down syndrome, with a median age of survival of 61.1 years for males and 57.8 years for females indicating a comparative survival advantage for males with Down syndrome (Glasson et al., 2003).

Other studies suggest that the survival advantage seen for females in the general population is not evident among people with Down syndrome. For 14,781 people with Down syndrome in the US, mortality rates did not differ by gender (Day et al., 2005). A study of a cohort of 917 children with Down syndrome born in Italy between 1978 and 1984 and studied for survival through the age of 8 years found no differences in survival by gender (Mastroiacovo et al., 1992). For 389 Irish children with Down syndrome, born between 1 January 1980 and 31 December 1989 and followed up to 1992, gender had no impact on survival (Hayes et al., 1997).

For 2,046 young people with Down syndrome aged 1-29 years hospitalised in Tennessee between 1997 and 2008, male deaths constituted 71–73% of all deaths in the age groups before age 20, but males then constituted less than half (47%) of all deaths during the 20–29-year age group, with a disadvantage for females beginning to emerge in the 20-29 year group (Miodrag et al., 2013). Significantly more females (57%) than males (43%) died from cardiac-related diseases and females who did die from heart problems were more often young adults supporting a suggestion that cardiac problems might partly account for the mortality disadvantage reported for women with Down syndrome (Miodrag et al., 2013). Cardiovascular disease is considered in detail below.

Cardiovascular Disease

Based on data from 4,081 people with Down syndrome and 16,324 without Down syndrome who had been hospitalized in Australia, Down syndrome was associated with a greater risk of incident cerebrovascular events (first admission for ischemic or hemorrhagic stroke, or transient ischemic attack) (Risk Ratio (RR) 2.70, 95% CI 2.08, 3.53) especially among females (RR 3.31, 95% CI 2.21, 4.94) (Sobey et al., 2015). Down syndrome was associated with a 40–70% reduced risk of any coronary event (first admission for myocardial infarction or angina) in males (RR 0.58, 95% CI 0.40, 0.84) but not in females (RR 1.14, 95% CI 0.73, 1.77) (Sobey et al., 2015). In males, Down syndrome was associated with a greater risk of any cerebrovascular event (RR 2.32, 95% CI 1.63, 3.30), stroke (RR 2.51, 95% CI 1.70, 3.69), ischemic stroke (RR 2.63, 95% CI 1.42, 4.87) or haemorrhagic stroke (RR 4.02, 95% CI 2.00, 8.10). In females, the magnitude of the associations were larger than in males for cerebrovascular events (RR 3.31, 95% CI 2.21, 4.94), stroke (RR 3.52, 95% CI 2.27, 5.45), and ischemic stroke (RR 5.84, 95% CI 2.93, 11.64) (Sobey et al., 2015). Results suggest that Ischemic stroke risk in Down syndrome appears mostly driven by cardioembolic risk. The greater risk of haemorrhagic stroke and lower risk of coronary events (in males) with Down syndrome remain unexplained.

A study in the US estimated atherosclerotic burden in 52 community residing adults with Down syndrome compared to a control group via a noninvasive intima-media thickness (IMT) assessment of the carotid artery (Draheim et al., 2010). The mean IMT of adults with Down syndrome was significantly lower than the mean IMT of the matched control group and was predicted by male gender and physical activity but the model only predicted 33% of variance (Draheim et al., 2010).

People with congenital heart disease (CHD) are at risk of premature CVD (Lui et al., 2014). CHD is a leading cause of death for people with Down syndrome (O'Leary et al., 2018). Down syndrome is a risk factor for congenital heart disease, occurring in 40-60% of people with Down syndrome (Diogenes et al., 2017). A meta-analysis and systematic review found that female gender is a risk factor for the presence of congenital heart disease in people with Down syndrome (OR 1.514, CI 1.207, 1.899) (Diogenes et al., 2017). Atrioventricular septal defects (AVSD) alone also showed a higher frequency in female gender (OR 1.376, CI 1.206, 1.570) (Diogenes et al., 2017). Overall, there appears to be a higher prevalence of congenital heart disease, particularly AVSD, in females with Down syndrome (Diogenes et al., 2017). The results of this review and meta-analysis are supported by findings from a recent study of 230 infants with Down syndrome in Italy which found congenital heart defects to be more common in females, with the exception of Tetralogy of Fallot for which male gender was predominant (Santoro et al., 2018). For severe CHDs (CHDs with a higher risk of mortality), for those without Down syndrome there was a higher risk for males, but for those with Down syndrome there was a higher risk in females (RRR 0.38; 95% CI 0.25, 0.57) (Santoro et al., 2018).

A study of hospitalizations in adults with Down syndrome and congenital heart disease in the United States found that Down syndrome was associated with higher in-hospital mortality (OR 1.8, 95% CI 1.4, 2.4), especially in women (OR 2.4, 95% CI 1.7, 3.4), with women with Down syndrome being at higher risk for death relative to women without Down syndrome than men were (Baraona et al., 2013). Women with Down syndrome were at significantly higher risk for dying during hospitalization than men with Down syndrome (OR 1.7, 95% CI 1.1, 2.8; multivariate OR 2.3, 95% CI 1.2, 4.5). The reasons for these gender related differences are unclear. Among patients without Down syndrome, men and women had equivalent rates of in-hospital death (OR 0.9, 95% CI 0.7, 1.1; multivariate OR 1.1, 95% CI 0.8, 1.5).

Cancer

A study by Patja et al (2001) found no cancer cases in women with Down syndrome, producing a significantly reduced risk of cancer for these individuals (SIR 0, 95% CI 0.0, 0.9), whilst men with Down syndrome shared the same risk as the general population (SIR 1.1, 95% CI 0.2, 3.3) (Patja et al., 2001). There has been more research directed at cancer among people with Down syndrome than among people with intellectual disabilities as a whole. Gender related differences from studies relating to Down syndrome are noted below.

An early review of cancers in people with Down syndrome suggested that there was a marked preponderance of males that was definitely proven for megakaryoblastic leukaemias and was probable for lymphomas, germ cell tumours, and retinoblastomas (Satgé et al., 1998). For people with Down syndrome in Israel between 1948 and 1995 a significant excess of gastric cancer was found in institutionalised males born before 1979 (Boker et al., 2001). Based on 1,298 people with Down syndrome in Western Australia, the rates for solid (non-leukaemia) tumours were significantly lower for males in the Down syndrome cohort compared to the general population (age-standardized incidence ratio (SIR) 0.21, 95% CI 0.03, 0.75), but this was not the case for females (SIR 0.70, 95% CI 0.26, 1.53) (Sullivan et al., 2007). SIRs for leukaemia were significantly higher for both

males and females with Down syndrome (Sullivan et al., 2007). For 2,814 people with Down syndrome in Denmark, the SIR for solid tumours was significantly lower in females (SIR 0.26, 95% CI 0.10, 0.53) than in males (SIR 0.82, 95% CI 0.48, 1.32) (Hasle et al., 2000). This was partly due to an absence of breast cancer in women with Down syndrome, whereas 7.3 cases were expected (Hasle et al., 2000).

For 3,581 people with Down syndrome in Finland followed up for a mean of 17.7 years, the SIR for leukaemia in women across all ages (SIR 18.4, 95% CI 10.5, 29.8) was higher than in men (SIR 10.5, 95% CI 6.6, 15.8), and remained significantly high until age 39 (Patja et al., 2006). However, a study of 4,872 people with Down syndrome in Sweden and Denmark found that the risks of leukaemia and solid tumours did not differ by gender (data not presented) (Hill et al., 2003).

A study on acute leukaemia in children with Down syndrome in the Nordic countries found that, of 136 children with Down syndrome diagnosed with acute leukaemia, for acute myeloid leukaemia (AML) there was a strong female predominance (ratio female:male 2.27 vs. 1.06 in non-DS patients) (Zeller et al., 2005). However, the authors highlight conflicting studies and note that whether the considerable female predominance represents a real epidemiological difference is an open question (Zeller et al., 2005). A study of 120 patients with Down syndrome (DS) and childhood acute lymphoblastic leukemia (ALL) found that there were more girls than boys (p.027) (Arico et al., 2008).

Dementia

For people with Down syndrome, few studies have examined the risk of dementia separately for men and women and future research should address this issue (Schupf et al., 2018). An early review found that the few studies that had presented results separately for men and women found conflicting results (Schupf and Sergievsky, 2002). An early small scale study reported that females with Down syndrome had earlier onset of dementia than males (mean age: 48.8 +/- 1.9, vs. 53.6 years; s.e.m. +/- 1.3; p = 0.05) and a more severe form of AD (Raghavan et al., 1994). Another study reported that there was a higher risk of AD among men than women with Down syndrome, with earlier age of onset (Schupf et al., 1998), although one possibility for the higher prevalence of dementia among men in the study is that the behavioural manifestations of early dementia in men with Down syndrome may have been more disturbing and obvious than they were in women (Lai et al., 1999). For 100 adults with Down syndrome (ages 35 to 79 years) assessed longitudinally, the incidence of AD was greater in women than in men (OR for males 0.32, 95% CI 0.13, 0.78; p = 0.01) although by age 65, the cumulative incidence of dementia was approximately the same in men and women (Lai et al., 1999).

Studies are consistent in showing that early age at menopause and low levels of endogenous bioavailable estradiol in postmenopausal women with Down syndrome are associated with earlier age at onset and overall risk for dementia (Schupf et al., 2018). Reductions in estrogen following menopause may contribute to the cascade of pathological processes leading to AD in women with Down syndrome (Zhao et al., 2011). For women with Down syndrome, early age at menopause is associated with a 1.8 fold increased risk of dementia (Hazard Ratio (HR): 1.82 (95% CI 1.31, 2.52) and with risk of death (HR 2.05 (95% CI: 1.33, 3.16) (Coppus et al., 2010). Similarly, based on 163 postmenopausal women with Down syndrome, women with early onset of menopause (46 years or younger) had earlier onset and increased risk of Alzheimer's disease (AD) compared with women with onset of menopause after 46 years (rate ratio, 2.7; 95% CI 1.2, 5.9) (Schupf et al., 2003).

Diabetes

A study in Sweden included people with intellectual disability excluding Down syndrome (n = 11,785); Down syndrome (n = 1,282) and a general population comparison group (n = 1,996,140) (Wallén et al., 2018). When adjusted for age, women with Down syndrome were more likely to have diabetes than women in the general population (Odds Ratio (OR) 1.783 (95% CI 1.167, 2.725) but this was not the case for men with Down syndrome (OR 0.704 (95% CI 0.424, 1.171). For those with intellectual disabilities but not Down syndrome, diabetes was more likely in both men (OR 2.005, 95% CI 1.795, 2.240) and women (OR 2.403, 95% CI 2.113, 2.733) (Wallén et al., 2018).

Bone Health and Fractures

Contributory factors to developing osteoporosis include earlier-than-average age at menopause for women (Petty et al., 2016) and this is an issue for women with Down syndrome. A study of 23 postmenopausal women with Down syndrome, with bone mass densities measured at three sites, found that nearly all of the women (87%) had osteopenia or osteoporosis in at least one of the three sites measured (Milberger et al., 2002). They also had higher relative risk for fracture when compared with women in the general population of the same age and ethnicity, with 30% already having a history of a fractured or broken bone that occurred during adulthood.

However, for men with Down syndrome poor bone health is also a significant issue. A study in Hong Kong which used scans to assess bone health in 128 people with Down syndrome found that for men with Down syndrome, the overall prevalence of osteopenia and osteoporosis at lumbar spine was 40% and 8% respectively, with the figures for women being 23% and 8% (Tang et al., 2019). Based on DXA scans from 234 adults with Down syndrome aged 20-69, adults with Down syndrome have lower bone mineral density compared to the general population and they experience a steeper decline with age and men with Down syndrome had a lower bone mineral apparent density (BMAD)[1] than women (Carfì et al., 2017). The authors suggest that this finding might be related to the role of androgens in the pathogenesis of osteoporosis in men with Down syndrome given the high prevalence of hypogonadism and hypoandrogenism that characterizes this condition.

Summary

Limited evidence suggests that the survival advantage for females seen in the general population might not be evident for females with Down syndrome. Evidence is consistent in indicating that females with Down syndrome are more likely to have congenital heart disease than males. Further evidence is required regarding gender and cancer in people with Down syndrome. Few studies have examined the risk of dementia separately for men and women with Down syndrome. Women with Down syndrome may be at increased risk of diabetes. Poor bone health and fractures are common among women with Down syndrome and this is also a significant issue for men with Down syndrome.

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[1] Bone mineral apparent density (BMAD) refers to volumetric BMD and was used in order to correct for anthropometric differences between those with Down syndrome and the general population.

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Specific syndromes: Rett Syndrome[1]

Rett syndrome is a genetic disorder that almost exclusively affects females and causes severe cognitive and physical impairments (Cianfaglione et al., 2015). The approximate incidence is 1:10,000 (Strydom et al., 2019). It represents the second most common cause of intellectual disabilities in females and the most common cause of intellectual disabilities caused by a gene mutation (De Felice et al., 2012).

Mortality

Survival among people with Rett syndrome is lower than among the general population. For 396 people with Rett syndrome followed up over 20 years, survival to the age of 20 years was 78.5% with 59.8% surviving to age 37 (Anderson et al., 2014). The most common cause of death was lower respiratory tract infection (36.8% 21/57), followed by aspiration/asphyxiation (31.6% 18/57), respiratory failure (14.0% 8/57) and seizure related illness (5.3% 3/57) (Anderson et al., 2014). A study of 1,189 people with Rett syndrome estimated that at least 95% of the classic Rett syndrome population survive until age 20, 80% survive until age 35, and more than 70% survive until age 50 (Tarquinio et al., 2015). The main cause of death was presumed or confirmed cardiorespiratory issues, often due to aspiration (Tarquinio et al., 2015). Based on 102 girls with Rett syndrome in Serbia, it was concluded that Serbian Rett syndrome patients have an increased risk for early death when compared to patients in more developed countries, most commonly due to pneumonia (Sarajlija et al., 2015).

For people with Rett syndrome, gastrointestinal problems, respiratory dysfunction such as hyperventilation, breath holding and apnoea, sleep disturbance, spinal curvature and epilepsy are common comorbidities (Anderson et al., 2014). Clinical and health data on 91 girls and women with Rett syndrome indicated that epilepsy, underweight, gastrointestinal and bowel problems were common co-occurring health issues (Cianfaglione et al., 2015).

Epilepsy

The majority of people with Rett syndrome have epilepsy, with reported rates of 60–80% (Cianfaglione et al., 2015). In the largest cohort studied, 68.1% of 1,248 females with Rett syndrome presented with epilepsy, with uncontrolled seizures in 32.6% of the people with epilepsy (Nissenkorn et al., 2015). In one study only 17.3% (71/411) had never experienced seizures and 64% were taking AEDs at the time of data collection (Anderson et al., 2014). Seizures were classified as drug resistant in 36.1% (95/263) of those experiencing epilepsy (Anderson et al., 2014). Constipation was also highly prevalent (83%) and many experienced bloating (53%) (Anderson et al., 2014). Biliary dyskinesia, inflammation or infection of the gallbladder was reported for 20 women (5%) and of those 13 had undergone gallbladder surgery. Other frequently reported medical conditions included urinary tract infections, pneumonia and other respiratory conditions (Anderson et al., 2014).

Respiratory Disorders

People with Rett syndrome are vulnerable to lower respiratory tract infections requiring hospitalization, which occurs more frequently in Rett syndrome than in the general population (MacKay et al., 2018). Scoliosis affects three-quarters of individuals with Rett syndrome by 15 years of age and this can impair posture and mobility as well as digestive and respiratory functioning (MacKay et al., 2018). Aspiration during or after seizures can also increase vulnerability to respiratory infection (MacKay et al., 2018). There may also be unrecognised lung disease. A study of 27 females with Rett syndrome which used high resolution CT scans of the thorax found that

pulmonary lesions, respiratory bronchiolitis-associated interstitial lung disease-like lesions, were present on imaging studies in about half of the participants (De Felice et al., 2010).

Cardiovascular Disease

Autonomic nervous system dysregulation may make those with Rett syndrome vulnerable to sudden death, with those with Rett syndrome being susceptible to sudden cardiac deaths attributable to underlying autonomic dysfunction (Kumar et al., 2017, Guideri et al., 2004, Guideri et al., 1999). Patients affected by Rett syndrome present a 300-fold increased risk of sudden cardiac death due to fatal arrhythmias (De Felice et al., 2012). A study of 92 patients with Rett syndrome (72 typical and 20 atypical Rett syndrome) gives echocardiographic evidence for a previously unrecognized subclinical systo-diastolic biventricular myocardial dysfunction in typical and atypical Rett syndrome patients (De Felice et al., 2012).

Episodes of autonomic arousals closely mimic seizures and contribute to significant parental anxiety and unnecessary use of antiepileptic drugs (Kumar et al., 2017). The heart rate variability (HRV) has emerged as the most valuable noninvasive test to measure the balance between the sympathetic and parasympathetic components of the autonomic nervous system (Kumar et al., 2017). A high variability in heart rate is a sign of good adaptability, whereas lower variability indicates insufficient adaptability of the autonomic nervous system (Kumar et al., 2017). Among 24 girls with Rett syndrome in India, compared to controls, girls with Rett syndrome exhibited significant cardiovascular autonomic dysfunction in the form of sympathetic overactivity, parasympathetic underactivity, and sympathovagal imbalance (Kumar et al., 2017). This study and other similar studies suggest that autonomic dysfunction is prevalent significantly in patients with Rett syndrome across diverse ethnic and geographic backgrounds compared with age-matched control subjects (Kumar et al., 2017).

Rett syndrome is characterized by disturbed breathing and heart rate during sleep (Rohdin et al., 2007). Cardiorespiratory dysregulation during wakefulness has also been found during breathholds as well as during "normal" breaths and during breaths before and subsequent to breathholds (Weese-Mayer et al., 2006). In a study of breathing and heart rate during the night among 47 girls with Rett syndrome aged 2–7 years and matched controls, girls with RS had faster, deeper, and more erratic breathing as well as heart rate dysregulation during sleep when compared to matched controls and when compared to wakefulness (Weese-Mayer et al., 2008).

Bone Health and Fractures

Rett syndrome is associated with compromised bone quality and fractures. A study of fracture incidence in 234 girls and young women with Rett syndrome in Australia found a rate of 43.3 episodes per 1000 person-years, which was nearly 4 times greater than the population rate (Downs et al., 2008). An earlier study of 101 girls with Rett syndrome in Australia based on hand radiographs found that their bone quality was compromised and fractures had occurred in one-third of cases, with it being estimated that just over 40% of girls would sustain a fracture by the age of 15 years (Leonard et al., 1999). A case control study in Denmark found that 61 females with Rett syndrome sustained significantly more low-energy fractures from an early age compared with controls, even though overall fracture occurrence was not apparently increased (Roende et al., 2011).

Summary

Rett syndrome almost exclusively affects females. Survival for those with Rett syndrome is lower than for those in the general population. Respiratory related conditions are the main cause of death. They are vulnerable to lower respiratory tract infections requiring hospitalization. Epilepsy is highly prevalent and may be uncontrolled. A high prevalence of epilepsy and scoliosis may increase vulnerability to respiratory infections. Autonomic nervous system dysregulation makes those with Rett syndrome vulnerable to sudden cardiac death. There may be subclinical myocardial dysfunction and unrecognised lung disease. Poor bone health and fractures are common among people with Rett syndrome.

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Specific Syndromes: Fragile X Syndrome[1]

Fragile X Syndrome (FXS) is the second most common cause of intellectual disability after Down syndrome and the most prevalent cause of intellectual disability in males, affecting 1:5000–7000 men and 1:4000–6000 women (Ciaccio et al., 2017). However, a systematic review and meta-analysis suggests lower estimated frequencies of individuals with the full mutation allele of approximately 1:7,000 for males and 1:11,000 for females (Hunter et al., 2014). It is the leading inherited cause of intellectual disability (Arvio, 2016).

As is typical of X-linked disorders, the most severe manifestations are seen among males with FXS (Arvio, 2016). Females tend to be less severely affected owing to compensation by a typical X chromosome, with not all females who carry a full mutation allele exhibiting intellectual disability (Hunter et al., 2014). A 20 year follow up of 34 males with FXS in Finland found that almost one third died during the follow-up period, many of them at a young age (Arvio, 2016). One study found that male children with fragile X syndrome had higher rates of obesity (31%) when compared with typically developing same-aged peers (18%) but this was not the case for females or adult males with FXS (Raspa et al., 2010).

Epilepsy is an important co-occurring condition with FXS, although prevalence is lower than for people with intellectual disabilities as a whole, with reports suggesting a prevalence of seizures among FXS children of 10–20% in boys and 5–10% in girls (Ciaccio et al., 2017). Females with FXS are less likely to have epilepsy than males with FXS (Leung and Ring, 2013). Most patients control their seizures with antiepileptic drugs (AEDs), with only 7% of a sample of males with FXS and epilepsy needing more than one AED (Musumeci et al., 1999).

Summary

Females with Fragile X syndrome tend to be less severely affected than males, for example they are less likely to have epilepsy. However, there is little specific evidence comparing the health and mortality of males and females with Fragile X syndrome.

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Specific Syndromes: Prader Willi Syndrome[1]

Prader Willi syndrome (PWS) is characterized by severe hypotonia and feeding problems in early infancy (Sinnema et al., 2011). In childhood and adolescence, this is followed by hyperphagia and, without strict dietary control, extreme obesity (Sinnema et al., 2011).

A study of people with Prader Willi Syndrome including 486 deaths found that males had a significantly higher risk of early mortality compared with females ($\chi^2 = 5.0$; $P < 0.025$; hazard ratio 1.2; 95% CI 1.0, 1.5), with a lower average age at death among males (28 ± 16 years) than among females (32 ± 15 years) (Butler et al., 2017). Cardiopulmonary and BMI-related mortality factors predominated among females, whereas males were more likely to experience accidents, choking, and infection at a young age. The disproportionate impact of accidental and/or hyperphagia-related deaths among younger males may possibly be due to increased activity and/or impulsive characteristics (Butler et al., 2017). In a related article, there was a gender specific increase in the risk of respiratory failure in females with PWS (females HR 2.0; 95% CI 1.4, 2.8; males HR 1.1; 95% CI 0.76, 1.5) and a gender specific increase in the risk of accidental death in males (males HR 2.2; 95% CI 1.2, 4.0 males; females HR 0.8; 95% CI 0.34, 1.8 females) (Manzardo et al., 2018). Prior to 2000 there was an increased risk of deaths in females due to cardiac failure (HR 1.8; 95% CI 1.3, 2.6), but not in deaths since 2000, which may be attributable to earlier diagnosis and proactive interventions to prevent morbid obesity (Manzardo et al., 2018).

A study of 180 children with Prader Willi Syndrome found that congenital heart defects were more frequent in girls ($P = .030$), with 7 cases among 87 girls (8%), and 1 case among 93 boys (1%) (Torrado et al., 2013). No difference by gender has been found in the general population. No suggestions are given in the article as to the reasons underlying this gender difference in children with Prader Willi syndrome. A study of 154 patients (68 men/86 women) with PWS in France found that gender differences in comorbidities were minor (data not presented) (Laurier et al., 2015).

A study of 155 people with PWS in Denmark found that the risk of venous thromboembolisms was higher for males compared to the general population (RR 19.7, 95% CI 5.7, 67.9) than females (RR 5.3, 95% CI 1.3, 21.8) (Hedgeman et al., 2017). There was no difference for myocardial infarction. However, the sample size is small and the results should be interpreted with caution.

Summary

Males with Prader Willi syndrome may be at higher risk of early mortality than females. Males may be more at risk of accidental death and choking. Cardiopulmonary and BMI-related mortality factors may predominate among females.

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Gender Specific Health Conditions

Male Specific: Testicular Cancer

Risk of Death

The little available evidence suggests that men with intellectual disability may be at greater risk of death due to testicular cancer than men in the general population. One study gives the SMR for testicular cancer among men with Down syndrome as 12.5 (95% CI 1.5-45.1) (Sasco et al., 2008b) and a further study gives the SMR for testicular cancer among men with Down syndrome as 25.2 (95% CI 3.0-90.9) (Hill et al., 2003). However, both studies are based on only two observed deaths where the cause was testicular cancer. Recent analysis of NHS Hospital Episode Statistics for England suggests that men with intellectual disabilities are far more likely to die from testicular cancer than the general population, with a 1 in 10 chance of dying from the cancer, as opposed to a 1 in 36 chance in the general population (Afshar et al., 2017). Explanations given for this include the possibility that men with intellectual disabilities are not so good at self-examination, going to the doctor, and then following through with any treatment (Afshar et al., 2017). It could also be that difficulty obtaining consent from these patients affects the treatment they receive (Afshar et al., 2017). However, a further explanation may be that services are discriminatory.

Incidence or Prevalence

Considerably less attention has been drawn to the need for screening for sex-specific cancer in men with intellectual disabilities than has been the case for women (Hogg and Tuffrey-Wijne, 2008). Epidemiological studies suggest that men with intellectual disabilities may be at increased risk of testicular cancer compared to men in the general population (Sasco et al., 2008a). Down syndrome is undoubtedly associated with an increased risk of testicular cancer (Sasco et al., 2008a), with an excess of testicular germ cell tumours (TGCT) in individuals with Down syndrome and with some cases occurring very early in fetal life (Satgé et al., 1997). For example, a Finnish study found that the standardised incidence ratio (SIR) for testicular cancer among men with Down syndrome was 4.8 (95% CI 1.8, 10.4) (Patja et al., 2006). It has been suggested that an excess of luteinizing hormone and follicle-stimulating hormone gonadotropins and over-expression of the Ets-2 gene through gene dosage effect could predispose patients with Down syndrome to the development of TGCT (Satgé et al., 1997). Among men with Down syndrome testicular cancer is more often identified at a late stage (Sasco et al., 2008a).

Cryptorchidism (CO), or undescended testis (UDT), affects approximately 3% of all male live births, making it one of the most common congenital disorders (Banks et al., 2013). Despite a high rate of spontaneous resolution during the first year of life, CO is firmly established as the primary risk factor for subsequent development of testicular germ cell tumours (TCGT) (Banks et al., 2013). In males with Down syndrome there is an excess of undescended testis compared with the general population (Satgé et al., 1997). However, chromosome 21 gene expression might predispose to testicular cancer development independent of undescended testes (Hill et al., 2003). In a study of 102 people with PWS, it was found that for males, a history of cryptorchidism or absent testicles was almost universal (48 of 49 males) with 28 having undergone surgery (Sinnema et al., 2011). Early identification of UDT is important but late identification has been raised as an issue in relation to teenage boys with severe intellectual disabilities (Haire et al., 2015).

Testicular microlithiasis (TM) is a rare condition characterized by asymptomatic calcification of seminiferous tubules and is considered as a precursor of testicular germ cell tumours (Cebeci et al., 2015). Men with Down syndrome have a high prevalence of TM (Cebeci et al., 2015, Pedersen et al.,

2016) although a systematic review found that there seemed to be no relation between TM and development of testicular cancer in males with Down syndrome (Pedersen et al., 2016).

Summary

The little available evidence suggests that men with intellectual disability may be at greater risk of death due to testicular cancer than men in the general population. Men with intellectual disabilities may be at increased risk of having testicular cancer, particularly those with Down syndrome. Among men with Down syndrome testicular cancer is more often identified at a late stage. Men with intellectual disabilities who have testicular cancer are far more likely to die than men with testicular cancer in the general population.

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Male Specific: Prostate cancer

Risk of Death

We are not aware of any evidence on the risk of death due to prostate cancer among men with intellectual disabilities.

Incidence or Prevalence

The incidence of prostate cancer among men with intellectual disabilities appears to be lower than that of men in the general population. Based on 9,409 people with intellectual disabilities in Australia, the incidence of prostate cancer was lower in men with intellectual disabilities than in the general population (SIR 0.23, 95% CI 0.03, 0.82) (Sullivan et al., 2004). Based on 2,173 people with intellectual disabilities in Finland followed up between 1967 and 1997 there was a very low incidence of prostate cancer (SIR 0.2, 95% CI 0.0, 0.5) which the authors suggest may be related to a lack of screening and other types of diagnostic activity (Patja et al., 2001). For 3,581 people with Down syndrome in Finland followed up for a mean of 17.7 years, there were no observed cases of prostate cancer (two expected) which may be due to the lower life expectancy of people with Down syndrome and the fact that prostate cancer is a cancer of old age (Patja et al., 2006).

Summary

We are not aware of any evidence on the risk of death due to prostate cancer among men with intellectual disabilities. The small amount of evidence available suggests that the incidence of prostate cancer among men with intellectual disabilities may be lower than that of men in the general population. However, it is not clear to what extent this reflects a lack of screening among men with intellectual disabilities.

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Female Specific: Breast Cancer

Risk of Death

Evidence from England suggests that death rates from breast cancer in women with intellectual disabilities do not differ from those in the general population (Glover et al., 2017). Data from Massachusetts (cited in Wilkinson et al 2011), whilst based on small sample sizes, suggests that although the rate of breast cancer among women with intellectual disabilities was similar to the general population, they seem to have higher mortality rates from breast cancer (30.9 per 100,000 women with intellectual disabilities vs 24.2 per 100,000 women in the general population of women in Massachusetts since 2002) (Wilkinson et al., 2011).

Incidence or Prevalence

The incidence of breast cancer among women with intellectual disabilities may be similar to that of the general population (Patja et al., 2001, Trétarre et al., 2017, Sullivan et al., 2004), although evidence is inconsistent with some reports of lower incidence among women with intellectual disabilities (Willis et al., 2008). However, women with intellectual disabilities are less likely to receive breast screening than other women (General Practice Extraction Service (GPES), 2016/17, Glover et al., 2014, Osborn et al., 2012, Cobigo et al., 2013, Lai et al., 2014, Sullivan et al., 2003, Wilkinson et al., 2011, Xu et al., 2017). The only study identified regarding breast cancer characteristics at diagnosis in women with intellectual disabilities was conducted in France (Satgé et al., 2014). Women with intellectual disabilities presented at an earlier age, with tumours of a higher American Joint Committee on Cancer (AJCC) stage than controls despite no significant differences in tumour grade and histological type, which may be attributable to delayed diagnosis (Satgé et al., 2014).

The risk of breast cancer may be lower in women with Fragile X syndrome (Schultz-Pedersen et al., 2001) and Down syndrome (Martel-Billard et al., 2016, Chicoine et al., 2015). One study found that the SMR for breast cancer in women with Down syndrome was 0.6 (95% CI 0.1, 2.1) (Sasco et al., 2008). The risk of breast cancer may be higher in certain genetic conditions associated with intellectual disabilities. For example, for women with neurofibromatosis 1 in one area of England, the standardised incidence ratio (SIR) for breast cancer at age <50 years was 4.9 (95% CI 2.4, 8.8) suggesting they should be considered for mammography from 40 years of age (Sharif et al., 2007). A US study found that death from breast cancer was three times as common among women with cerebral palsy (mainly with intellectual disabilities) than the general population and it is suggested that diagnosis and/or treatment of the disease may be worse in this group than in the general population (Strauss et al., 1999). French data indicates that obesity was twice as frequent in women with intellectual disabilities with breast cancer compared to those without (42.9% vs. 18.7%) (Trétarre et al., 2017). Overall, further research is required regarding breast cancer risk and risk factors for women with intellectual disabilities.

For women with intellectual disabilities, knowledge of breast cancer including associated risks, preventative factors and signs and symptoms may be extremely limited (Truesdale-Kennedy et al., 2011). Women with intellectual disabilities may not easily communicate their symptoms and may be at risk of delayed diagnosis (Trétarre et al., 2017). Risk factors for breast cancer in women in the general population include: alcohol intake, smoking, low levels of physical exercise, overweight and obesity, not having children, and not having breastfed (Cancer Research UK). Whilst women with intellectual disabilities may be less likely to drink alcohol and smoke than women in the general

population, they are more likely to be overweight or obese, engage in low levels of physical activity (Emerson and Hatton, 2013) and to have not had children.

There is a lack of research or practice guidelines at every stage of the breast cancer care pathway for women with intellectual disabilities which may arguably lead to late diagnosis, suboptimal treatment and management and overall survival rates for this group (Collins et al., 2014). The optimal care of breast cancer relies on early diagnosis (Satgé et al., 2014). Participation in screening should be enhanced in women with intellectual disabilities as they may not easily communicate their symptoms and may be at risk of delayed diagnosis (Trétarre et al., 2017). Barriers to accessing breast screening included literacy problems, consent issues and physical health; practical barriers such as transport and timing of appointment; and barriers attributed to healthcare professionals, including staff attitude and lack of awareness and training (McIlfatrick et al., 2011). Other reported barriers include lack of information and embarrassment (Truesdale-Kennedy et al., 2011). Information and support related to breast cancer and mammography may not meet the needs of some people with intellectual disabilities (Truesdale-Kennedy et al., 2011). Paid-carers play a key role in terms of support, information and as a potential influence in determining participation in breast screening (Willis, 2016).

Summary

There is little evidence on the risk of death due to breast cancer among women with intellectual disabilities. Evidence on the incidence of breast cancer is inconsistent. Women with intellectual disabilities may be at risk of delayed diagnosis which can adversely affect outcomes. Risk factors for breast cancer are common among women with intellectual disabilities but they are less likely to be in receipt of breast screening. Women with Down syndrome and Fragile X syndrome are at lower risk of breast cancer than other women. Women with other genetic conditions associated with intellectual disabilities, including neurofibromatosis 1, may be at increased risk of breast cancer.

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Female Specific: Cervical Cancer

Risk of Death

We are not aware of any evidence on the risk of death from cervical cancer among women with intellectual disabilities.

Incidence or Prevalence

Very little is known about the prevalence of cervical cancer in women with intellectual disabilities. The available evidence suggests that the prevalence of cervical cancer is lower in women with intellectual disabilities than other women (Sullivan et al., 2004, Patja et al., 2001, Sullivan et al., 2010, Parish et al., 2018). However, whilst lower, the risk of cervical cancer is not negligible (Wood and Douglas, 2007) and cervical cancer can be a cause of avoidable death in women with intellectual disabilities (Sullivan et al., 2010). Evidence from a number of countries consistently indicates that women with intellectual disabilities are less likely to receive a cervical screening test than other women (Reynolds et al., 2008, General Practice Extraction Service (GPES), 2016/17, Glover et al., 2014, Sally-Ann et al., 2018, Osborn et al., 2012, Cobigo et al., 2013, Huang et al., 2012, Parish et al., 2013, Sullivan et al., 2010, Xu et al., 2017) and more likely to be ceased from screening (not receive invitations for screening) than other women (Reynolds et al., 2008). Girls with intellectual disabilities may be less likely to receive the human papilloma virus (HPV) vaccine (MacLeod and Tuffrey, 2014). Some women with intellectual disabilities have been denied access to cervical screening on the basis of their assumed lack of sexual activity (Heslop et al., 2013). Even among women who have had a pregnancy, and are therefore known to have been sexually active, women with intellectual and developmental disabilities are less likely to be screened than other women (Brown et al., 2016).

Summary

We are not aware of any evidence on the risk of death from cervical cancer among women with intellectual disabilities. The prevalence of cervical cancer is lower in women with intellectual disabilities than other women but the risk is not negligible. Women with intellectual disabilities are less likely to receive a cervical screening test than other women, sometimes on the basis of their assumed lack of sexual activity.

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Female Specific: Ovaries and Uteri Cancer

Risk of Death

One study reports the risk of death due to cancer of the ovaries and uteri among women with intellectual disabilities on GP registers in England (which may miss those with mild to moderate intellectual disability and no associated syndromic cause). Malignant neoplasms of female genital organs accounted for nine deaths (expected 4.0, SMR 2.3, 95% CI 1.0, 4.3), almost equally divided between cancers of the uterine body, where this represented a statistically significantly high number, and of the ovary, where it did not (Glover et al., 2017).

Incidence or Prevalence

Evidence regarding the incidence of cancer of the ovaries and uteri among women with intellectual disabilities is mixed. Based on 9,409 people with intellectual disabilities in Australia, females had a significantly higher incidence of cancer of the corpus uteri than women in the general population (SIR 2.98, 95% CI 1.29, 5.87) (Sullivan et al., 2004). Based on 2,173 people with intellectual disabilities in Finland followed up between 1967 and 1997 the incidence of cancers of the uterine trunk and ovaries did not differ significantly from women in the general population (Patja et al., 2001). For people with Down syndrome in Israel between 1948 and 1995, a non-significant excess of cancer of the ovaries in females was found (Boker et al., 2001). However, a study of people with Down syndrome found no cases of death due to cancer of the ovary and other uterine adnexia (SMR 0.0, 95% CI 0.0, 4.7) (Sasco et al., 2008).

Summary

There is very little evidence on the risk of death due to cancer of the ovaries and uteri among women with intellectual disabilities. Evidence regarding the incidence of cancer of the ovaries and uteri is mixed, with some evidence suggesting that incidence may be higher among women with intellectual disabilities than women in the general population, but other evidence indicating no difference.

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Female Specific: Contraception[1]

Whilst not a specific cause of death, some forms of contraception may increase the risk of other health conditions. For example, Depo-Provera® reduces bone mineral density and causes weight gain (Jeffery et al., 2013).

Women with intellectual disabilities have markedly different patterns of contraceptive use to women in the general population with greater use of long term methods such as depot injection, oral contraceptive, intrauterine device or sterilisation and significantly less use of barrier methods (McCarthy, 2009b, Servais, 2006). A small scale survey found the most widely used form of contraception was a contraceptive implant (46%), followed by the combined (oestrogen and progesterone) contraceptive pill (24%) and the progesterone only contraceptive pill (7%) (Ledger et al., 2016). For those with severe or profound intellectual disabilities contraception was prescribed at an earlier age (38% prior to age 16 compared to 7% of those with mild or moderate intellectual disabilities), with management of menstruation being the most common reason for the introduction of contraception (50%) compared to 13% amongst women with mild or moderate levels of intellectual disability (Ledger et al., 2016).

Women with intellectual disabilities may be prescribed contraception even when they are not sexually active or are past child bearing age (McCarthy, 2009b). A study of nine UK women with intellectual disabilities who had been sterilized for contraceptive purposes found that none were reported to have been sexually active during a 20 year follow up period (Roy, 2010). Contraceptives may be prescribed to women with intellectual disabilities who are not sexually active 'just in case' or to manage menstruation (Ledger et al., 2016). GPs may prescribe depot medroxyprogesterone acetate (DMPA or Depo-Provera®) due to concerns that women with intellectual disabilities may not be reliable users of methods which rely on the user such as the pill (McCarthy, 2011). For those with severe or profound intellectual disabilities management of menstruation was the most common reason for the introduction of contraception (Ledger et al., 2016). An older study in Finland found that of 255 women with intellectual disabilities, 67.5% had at least once in their life received lynestrenol for therapeutic amenorrhea (Huovinen, 1993). No long term strategies exist to completely suppress menstruation without the possibility of adverse consequences (Albanese and Hopper, 2007). For example, Depo-Provera® reduces bone mineral density and causes weight gain (Jeffery et al., 2013). This may be a particular concern in relation to bone mineral density when Depo-Provera® is prescribed at a young age (McCarthy, 2011). Evidence suggests that women with intellectual disabilities are not given sufficient information and are not fully involved in decisions about contraception (McCarthy, 2009b, McCarthy, 2010, McCarthy, 2009a, Ledger et al., 2016), with the decision to take contraception being made for them (Ledger et al., 2016).

Summary

Women with intellectual disabilities have different patterns of contraceptive use to women in the general population, with greater use of long-acting contraception such as contraceptive implants or injections. There is a disproportionate use of Depo-Provera® among women with intellectual disabilities which may reduce bone mineral density and cause weight gain. Women with intellectual disabilities may be prescribed contraception when they are not sexually active 'just in case' or to manage menstruation.

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Female Specific: Pregnancy and Childbirth[1]

There has been increased recognition of the rights of people with intellectual disabilities to 'an ordinary life', including the right to be parents, with people with intellectual disabilities becoming more likely to develop relationships and form their own families (Working Together with Parents Network, 2008). As such, pregnancy and childbirth is an issue for women with intellectual disabilities. Indeed, a large study of fertility in women with intellectual and developmental disabilities in Canada found that age specific fertility rates were similar in young women with and without intellectual and developmental disabilities (Brown et al., 2016b).

Risk of Death

We are not aware of any evidence on the risk of death in relation to pregnancy and childbirth for women with intellectual disabilities.

Incidence or Prevalence

Women with intellectual disabilities experience poorer maternal wellbeing and pregnancy outcomes compared to the general population (Homeyard et al., 2016). Studies have reported poorer outcomes for women with intellectual disabilities including: increased rates of pre-eclampsia, venous thromboembolism, pre-term birth, delivery by caesarean section, low birth weight, and low Apgar scores (McConnell et al., 2008, Parish et al., 2015, Brown et al., 2017a, Brown et al., 2016a, Mitra et al., 2015, Höglund et al., 2012, Akobirshoev et al., 2017). Smaller scale research in England found no difference between women with and without intellectual disabilities for pre-eclampsia, caesareans or Apgar scores (Goldacre et al., 2015).

Data also suggest that women with intellectual disabilities have higher rates of postpartum hospital admissions and emergency department visits. A population based study in Canada on postpartum acute care utilization included 3,803 singleton live births to women with intellectual and developmental disabilities and 378,313 births to other women in Ontario (Brown et al., 2017b). Women with intellectual and developmental disabilities, compared to women without, had increased risk for postpartum emergency department visits for medical reasons (0-42 days postpartum) (15.8% vs. 7.8%; 41.9 vs. 19.5 visits per 10,000 person-days, adjusted Hazards Ratio (aHR) 1.80, 95% CI 1.66, 1.96). The most common reasons were puerperal infection/sepsis, abdominal/pelvic pain, and postpartum haemorrhage. A subsequent study looking at the first postpartum year among women with and without intellectual and developmental disabilities in the United States included 1,104 deliveries to mothers with intellectual and developmental disabilities and 778,409 deliveries to mothers without intellectual and developmental disabilities (Mitra et al., 2018). Women with intellectual and developmental disabilities had markedly higher rates of postpartum hospital admissions and emergency department visits during the critical postpartum periods after a childbirth (within 1–42, 43–90, and 91–365 days). These findings were robust and persisted even after controlling for many social, demographic, and clinical characteristics.

Perinatal mortality has been found to be higher in babies born to women with intellectual and developmental disabilities in the US (Mitra et al., 2015), with the odds ratio for stillbirth in one US study being 2.40 (95% CI 1.70, 3.40) (Akobirshoev et al., 2017). In one UK study combining stillbirths and infant deaths, rates per 1000 were 27.9 for babies of mothers with intellectual disabilities and 13.4 for other babies (borderline significant at $p = 0.07$), but larger UK studies are needed to determine whether stillbirth and infant death rates are higher (Goldacre et al., 2015).

Pregnant women with intellectual disabilities are less likely to seek or attend regular antenatal care (Homeyard et al., 2016), and struggle to understand antenatal information communicated during

pregnancy which is often text based (Homeyard et al., 2016). In one small scale study in the UK, no women with intellectual disabilities had been given easy-read pregnancy and birth information by maternity practitioners (although some had received this from other sources) (Malouf et al., 2017). Mothers with intellectual disabilities in the United Kingdom had less positive perceptions of their maternity care than nondisabled women, for example fewer felt that they were always spoken to in a way they could understand (66% vs. 84%) (Redshaw et al., 2013). Midwives may lack training in relation to supporting women with intellectual disabilities, and time constraints may mean that they are unable to spend the necessary time with the women to meet their pregnancy needs (Castell and Stenfert Kroese, 2016). Finally, for women with intellectual disabilities a safeguarding process (child protection) may be an inevitable part of their pregnancy experience (Castell and Stenfert Kroese, 2016).

Summary

We are not aware of any evidence on the risk of death in relation to pregnancy and childbirth among women with intellectual disabilities. Women with intellectual disabilities experience poorer maternal wellbeing and pregnancy outcomes compared to the general population. This includes increased rates of pre-eclampsia, venous thromboembolism, pre-term birth, delivery by caesarean section, and higher rates of postpartum hospital admissions and emergency department visits. Services may not offer appropriate support to meet the needs of pregnant women with intellectual disabilities.

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Female Specific: Menopause[1]

Whist not a direct cause of death, menopause is associated with increased health risks, for example cardiovascular disease greatly increases after the menopause when estrogen levels reduce (Newson, 2018). The long-term consequences of premature or early menopause include adverse effects on, cardiovascular and bone health, as well as an increased risk of early mortality (Faubion et al., 2015). What little evidence there is suggests that women with intellectual disabilities, and in particular women with Down syndrome, tend to have earlier menopause than other women (Schupf et al., 1997, Carr and Hollins, 1995). Studies are consistent in showing that early age at menopause and low levels of endogenous bioavailable estradiol in postmenopausal women with Down syndrome are associated with earlier age at onset and overall risk for dementia (Schupf et al., 2018). For example, for women with Down syndrome early age at menopause has been found to be associated with an increased risk of dementia (Hazard Ratio (HR) 1.82 (95% CI 1.31, 2.52) (Coppus et al., 2010). Early menopause has also been associated with risk of death (HR 2.05 (95% CI 1.33, 3.16) in women with Down syndrome (Coppus et al., 2010).

Summary

Women with intellectual disabilities, and in particular women with Down syndrome, tend to have earlier menopause than other women. In women with Down syndrome, early age at menopause has been found to be associated with an increased risk of dementia and with risk of death.

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Risk Factors for Mortality[1]

Risk Factors: Overweight and Obesity[1]

Both overweight and obesity are associated with the incidence of multiple co-morbidities including type II diabetes, cancer and cardiovascular diseases (Guh et al., 2009). Female gender has been found to be the strongest risk factor for overweight/obesity status in individuals with intellectual disabilities (Ranjan et al., 2018). Studies have consistently shown that the prevalence of obesity and morbid obesity among women with intellectual disabilities is significantly higher than among women without intellectual disabilities (Ranjan et al., 2018). For example, a study of 1,450 people with intellectual disabilities in the US found that morbid obesity (BMI ≥ 40) was twice as common among women with intellectual disabilities than among women in the general population (10.9% vs. 5.4%), but it was similar for men (4.5% vs. 3%) (Hsieh et al., 2014). There was a significantly higher prevalence of obesity among women (43.2%) with intellectual disabilities compared with men with intellectual disabilities (34.3%) (Hsieh et al., 2014), with figures for both men and women being higher than for the general population (general population women 27.7%, men 28.3%).

A study in Stockholm included people with intellectual disability excluding Down syndrome (n = 11,785); Down syndrome (n = 1,282) and a general population comparison group (n = 1,996,140) (Wallén et al., 2018). Both women (13.6%) and men (8.7%) with intellectual disabilities but without Down syndrome were more likely to be obese than the general population (women OR 3.048 (95% CI 2.805, 3.312), men OR 3.409 (95% CI 3.131, 3.712) (Wallén et al., 2018). This was also the case for women (14.4%) and men (8.1%) with Down syndrome (women OR 3.299 (95% CI 2.618, 4.156), men OR 2.998 (95% CI 2.273, 3.956) (Wallén et al., 2018).

Summary

Female gender has been found to be the strongest risk factor for overweight/obesity status in individuals with intellectual disabilities. The prevalence of obesity and morbid obesity among women with intellectual disabilities is significantly higher than among women without intellectual disabilities.

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Risk Factors: Hypertension[1]

Hypertension is a risk factor for CVD (Axmon et al., 2017). There is a well-established gender difference in the prevalence of hypertension in the general population such that men have a higher prevalence of hypertension compared with women prior to the onset of menopause, after which women display a more rapid increase in the prevalence of hypertension relative to men such that hypertension rates in women eventually exceed those seen in men (Ramirez and Sullivan, 2018), with males having a higher incidence of hypertension compared to females of the same age until the sixth decade of life (Gillis and Sullivan, 2016).

For nearly 8,000 people with intellectual disabilities aged 55+ in Sweden, both men and women with intellectual disabilities were less likely to have a diagnosis of hypertension than people in the general population (for men and women combined RR 0.55 (95% CI 0.50–0.60) (Axmon et al., 2017). People with intellectual disabilities may be underdiagnosed with respect to hypertension. However, the study did not include primary care diagnoses, only diagnoses made during inpatient care and at outpatient specialist visits.

A study in Stockholm included people with intellectual disability excluding Down syndrome (n = 11,785); Down syndrome (n = 1,282) and a general population comparison group (n = 1,996,140) (Wallén et al., 2018). Both men (OR 0.181 (95% CI 0.102–0.318)) and women (OR 0.256 (95% CI 0.152, 0.432)) with Down syndrome were less likely to have hypertension than the general population. For those with intellectual disabilities but not Down syndrome there was no difference in hypertension for women but an increased risk for men (OR 1.215 (95% CI 1.099, 1.344)) (Wallén et al., 2018).

Among 685 people aged 50-70 with intellectual disabilities receiving formal care or support in the Netherlands, hypertension (ascertained via testing rather than recorded diagnoses) was less common among men with intellectual disabilities than men in the general population (men with intellectual disabilities 45.4% (95% CI 40.3, 50.5) vs 55.1% (95% CI 52.1, 58.0)). However, hypertension was more common among women with intellectual disabilities than among women in the general population (women with intellectual disabilities 53.9% (95% CI 48.5, 59.4) vs 44.0% (95% CI 41.1, 46.8)) (de Winter et al., 2012). It should be noted that hypertension may be underdiagnosed. In this study, 385 people with intellectual disabilities met criteria for hypertension, of whom 191 (50%) had not been previously diagnosed with hypertension (de Winter et al., 2012).

A study on multimorbidity in 753 persons with intellectual disabilities aged 40 years and over in Ireland found that women were almost two times more likely to be multimorbid than males, regardless of age, and to have higher levels of reported hypertension diagnoses, although figures relating to hypertension are not presented (McCarron et al., 2013). A study of 213 people with intellectual disabilities in the Netherlands, which measured blood pressure, found no association between hypertension and gender (van de Louw et al., 2009). However, the sample size was small and confidence intervals were wide (male hypertension prevalence 15.0% (95% CI 8.45, 21.64), female 20.0% (95% CI 12.16, 27.84)) (van de Louw et al., 2009). Of 291 adults with intellectual disabilities living in New York City, based on data from a review of medical records, females were less likely to have hypertension than males (adjusted Odd Ratio 0.61 (95% CI 0.32, 1.15)) (Sohler et al., 2009). A study of 811 people with intellectual disabilities in Hong Kong found that rates of hypertension were similar for men and women (men 6.9%, women 8.7%) but it is noted that the participants were a purposive sample from 18 select residential care facilities in Hong Kong and may not be a representative sample (Wong, 2011).

Summary

Both men and women with intellectual disabilities have been reported to be less likely to have a diagnosis of hypertension than men and women in the general population. However, hypertension may be underdiagnosed in people with intellectual disabilities. Further studies involving assessing participants for hypertension rather than relying on recorded diagnoses are required.

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Risk Factors: Physical Inactivity[1]

A recent systematic review and meta-analysis of physical activity levels among people with intellectual disabilities included 15 studies consisting of 3,159 participants (Dairo et al., 2016). Only 9% of participants met minimum physical activity guidelines. Gender was independently significantly correlated with the number of participants achieving physical activity guidelines, with the proportion of males being correlated to the number of participants achieving physical activity guidelines (Dairo et al., 2016). In the largest study included in the review, which included 1,542 adults with intellectual disabilities living in supported accommodation in Northern England, women were at significantly greater risk of physical inactivity (OR 1.9, 95% CI not given) (Emerson, 2005). A more recent study including 8,636 people in the US with intellectual and developmental disabilities found that more males met physical activity guidelines (14.9%) than females (11.7%) (chi square = 18.83 (df 1, N = 8,602), $p < 0.001$) as was the case for the general population (Stancliffe and Anderson, 2017). A recent study of 527 adolescents and young people with mild/moderate intellectual disabilities found that females with intellectual disability were more disadvantaged in relation to participation in sport and exercise (compared to females without intellectual disability) than males (Robertson et al., 2018).

Summary

Women with intellectual disabilities are less likely to take part in physical activity than men with intellectual disabilities and for both men and women the number meeting physical activity guidelines is extremely low.

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Risk Factors: Smoking[1]

Among people with intellectual disabilities, men are more likely to smoke cigarettes than women as is the case in the general population (Steinberg, 2009), and substance use and misuse more generally among people with intellectual disabilities is associated with being male (Huxley et al., 2018). A recent study appears to be the first to specifically examine the influence of gender on tobacco use among people with intellectual and developmental disabilities (IDD) (Eisenbaum et al., 2018). Among 13,714 Special Olympics athletes, tobacco use prevalence was greater among men (8.1%) than among women (3.8%) (Eisenbaum et al., 2018). Based on a sample of 527 adolescents and young adults with mild to moderate intellectual disability compared to those without intellectual disability, males with intellectual disability (aged under 18) were at significantly greater risk of having ever smoked (28% versus 22%) and of smoking 6+ cigarettes a week (17% versus 11%) than males without intellectual disability (Robertson et al., 2018). Females with intellectual disability were at significantly less risk of having ever smoked than females without intellectual disability (22% versus 30%).

Summary

Men with intellectual disabilities are more likely to smoke than women with intellectual disabilities. Further research is needed to compare smoking rates among men and women with intellectual disabilies to smoking rates among the general population. Internationally, cultural differences are likely to influence smoking rates.

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Risk Factors: High Cholesterol[1]

An early study of 325 people with intellectual disabilities aged 17-72, based on blood tests, found that females with intellectual disabilities both with and without Down Syndrome had better lipid profiles than their male counterparts and appeared to have a lower risk of coronary heart disease (CHD) as a result of higher HDL-C and lower LDL-C values (Rimmer et al., 1992). More recently, among 611 people aged 50-70 with intellectual disabilities receiving formal care or support in the Netherlands, high cholesterol (determined via a blood test) was less prevalent in men and women compared to the general population (men with intellectual disabilities 15.6% (95% CI 11.7, 19.6) vs 36.2% (95% CI 33.4, 39.1); women with intellectual disabilities 28.9% (95% CI 23.7, 34.1) vs 40.2% (95% CI 37.3, 43.0)) (de Winter et al., 2012). In multivariate logistic regression for a larger sample including those aged over 70 (n=724), being female was associated with high cholesterol in people with intellectual disabilities (OR 1.8 (95% CI 1.1, 2.8)) (de Winter et al., 2012), with the rate of high cholesterol for men with intellectual disabilities being 16.5% (95% CI 12.8, 20.3) compared to 30.1% (95% CI 25.3, 34.9) for women (de Winter et al., 2012).

A study of 811 people with intellectual disabilities in Hong Kong found that rates of recorded high cholesterol were similar for men and women (men 1.4%, women 1%) but it is noted that the participants were a purposive sample from 18 select residential care facilities in Hong Kong and may not be a representative sample (Wong, 2011). Of 291 adults with intellectual disabilities living in New York City, based on data from a review of medical records, 77 (26.5%) had high cholesterol and females were less likely to have high cholesterol than males (adjusted Odd Ratio 0.42 (95% CI 0.24, 0.75)) (Sohler et al., 2009).

Summary

There is little evidence regarding gender differences in relation to high cholesterol in people with intellectual disabilities. Studies based on recorded diagnoses present conflicting findings but high cholesterol is likely to be underdiagnosed. More studies based on blood testing are required to clarify any gender differences and the age related nature of any differences.

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Risk Factors: Metabolic Syndrome[1]

Metabolic syndrome is a condition characterized by the co-existence of several major risk factors for cardiovascular disease (CVD) including high blood pressure, hyperglycaemia, and dyslipidaemia (reduced high density lipoprotein cholesterol or raised triglycerides) (Han and Lean, 2015). The International Diabetes Federation estimates that one quarter of the World's population has metabolic syndrome (O'Neill and O'Driscoll, 2015). In persons with metabolic syndrome, the risk of developing type II diabetes is five times greater and the risk of stroke and myocardial infarction is three times higher as compared to normal/healthy persons (Zafar et al., 2018). Metabolic syndrome is associated with significantly higher risk of cardiovascular complications such as coronary and peripheral arterial diseases, arrhythmias, congestive cardiac failure, and stroke (Zafar et al., 2018). Metabolic syndrome has also been associated with other clinical conditions, such as hepatic steatosis and non-alcoholic fatty liver disease (NAFLD), hypogonadism, polycystic ovary syndrome (PCOS), obstructive sleep apnoea, vascular dementia, Alzheimer's disease, and carcinomas, especially pancreatic and colorectal cancers (Zafar et al., 2018).

In the general population, the prevalence of metabolic syndrome differs by gender and age, being slightly higher in men below the age of 50 but reversing after that age to a female preponderance (Zafar et al., 2018). Among 492 people aged 50-70 with intellectual disabilities receiving formal care or support in the Netherlands, metabolic syndrome was less prevalent in men with intellectual disabilities (27.5% (95% CI 22.2, 32.9) compared to men aged 50-70 in the general population (44.8% (95% CI 41.8, 47.8)). It was more prevalent in women with intellectual disabilities (46.2% (95% CI 39.6, 52.7) than in women aged 50-70 in the general population (36.6% (95% CI 33.8, 39.4)) (de Winter et al., 2012). In multivariate logistic regression for a larger sample including those aged over 70 (n=584), being female was associated with metabolic syndrome in people with intellectual disabilities (OR 2.8 (95% CI 1.9, 4.1)) (de Winter et al., 2012), with the rate of metabolic syndrome for men with intellectual disabilities being 36.5% (95% CI 31.2, 41.8) compared to 54.3% (95% CI 48.3, 60.2) for women (de Winter et al., 2012). Of 164 adults with intellectual disabilities in one Taiwanese institution, metabolic syndrome prevalence was 8.0% for men and 17.2% for women (Hsu et al., 2012). Of 129 adults with intellectual disabilities in one Taiwanese institution who participated in annual examinations, prevalence of metabolic syndrome was 9.6% in men and 16.1% in women (Chang et al., 2012).

Summary

The small amount of evidence suggests that metabolic syndrome may be more common among women than men with intellectual disabilities. Metabolic syndrome may be more common among older women with intellectual disabilities than among older women in the general population, but lower among older men with intellectual disabilities than among older men in the general population. Further research is required to confirm this.

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Low and Middle Income Countries

Whilst some evidence exists regarding mortality among people with intellectual disabilities in LAMI countries (e.g. Lakhan and Kishore, 2016), we have identified scant information regarding gender and mortality in LAMI countries. However, it is clear that issues relating to mortality may be qualitatively different in LAMI countries than those in high income countries. For example, parasitic infections, caused by intestinal helminths and protozoan parasites, are among the most prevalent infections in humans in developing countries and cause a significant morbidity and mortality in endemic countries (Haque, 2007). Of 200 people with intellectual disabilities in Egypt, 87 (43.5%) were infected with intestinal parasites, 46.7% of males and 38.5% of females (non significant), most commonly cryptosporidium (23.5%) and and microsporidia (15%) (Shehata and Hassanein, 2015). Mortality is also elevated in comparison to high income countries. Congenital heart disease (CHD) was found to be a major cause of death among 543 children with Down syndrome in India, and the first year survival rate for infants with CHD was 44%, and 79% for those without CHD (Nahar et al., 2013). This compares to first year survival of those with Down syndrome without CHD approaching 100% in developed countries, and 71.7 % for those with CHD. The high mortality rate found is likely to be due to lack of adequate and timed cardiac care (Nahar et al., 2013). Based on 102 girls with Rett syndrome in Serbia, it was concluded that Serbian Rett syndrome patients have an increased risk for early death when compared to patients in more developed countries, most commonly due to pneumonia (Sarajlija et al., 2015). Further research is required to identify any gender differences in relation to the mortality of people with intellectual disabilities in LAMI countries.

Summary

Mortality for people with intellectual disabilities is likely to be elevated in low and middle income (LAMI) countries compared to high income countries. Qualitative differences in issues related to mortality are likely to exist between LAMI and high income countries. Further research is required to identify any gender differences in relation to the mortality of people with intellectual disabilities in LAMI countries.

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