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Case Report

Personalised Medicine for Dementia: Collaborative Research of Multimodal Non-pharmacological Treatment with the UK National Health Service (NHS)

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Abstract

The dominant narrative around dementia argues that progression cannot be halted or reversed. However, evidence on multimodal non-pharmacological treatments formulated around a 'personalised medicine' approach challenges this view. This paper reviews the current evidence for dementia prevention utilising such treatments and explains the logic of applying personalised medicine. The functional medicine treatment approach to 'root cause' analysis is presented as currently practiced with patients experiencing cognitive decline. We report six case reports including in-depth practitioner evaluations, recommendations and follow-ups. We cover the various presentations of memory and concentration problems and the screening process with advanced functional testing. The case reports appear in a table, followed by 11 key points, insights and findings. To our knowledge, this is the first paper reporting practitioner case reports documenting improvements in symptoms of memory

decline in patients from the UK, Greece and New Zealand. Four patients had initial presentations and follow-up improvements verified by standardised screening instruments and/or formal diagnosis. Two patients had symptom improvements verified through self-report and proxy-report. Practitioners reported improvements through biomarkers (normalisation of serum levels, folate and homocysteine, thyroid function, blood sugar levels), as well as weight loss, decreased blood pressure and reduction in medications. They also reported improved mental, physical, social, energetic, emotional and spiritual functioning. The next phase is an enhanced intervention alongside the existing UK National Health Service memory assessment pathway. This paper advocates for personalised medicine in the UK for persons living with memory problems and dementia, driven by this increasing evidence base.

Keywords
Personalised medicine; dementia; multimodal non-pharmacological treatment

1. Introduction

As many as one in three people born in 2015 in the UK will develop dementia in their lifetime [1], yet modifiable risk factors contribute to one-third of Alzheimer's cases [2, 3]. The dominant narrative around dementia argues that progression cannot be halted or reversed. Current treatment approaches, whether pharmacological or neuropsychological at best delay decline [4]. Explosive headlines such as dementia being a 'ticking time-bomb' and estimates of prevalence based on no change in treatment reinforce this account. However, evidence on multimodal non-pharmacological treatments (MM NPTs) formulated around a 'personalised medicine' approach challenges this view.

This paper introduces a novel approach to dementia treatment in the following sections:

- Dementia prevention - Current evidence on multimodal non-pharmacological treatments
- The logic of applying personalised medicine to dementia
- A Functional Medicine (FM) treatment approach – 6 Case Reports
- Discussion and Conclusion

To our knowledge, this paper contains the first case reports showing improved symptomatology of memory-impaired patients in the UK [3], as well as two in Greece and one in New Zealand. It also reports in some depth the approach to root cause analysis, including presentations, indications, evaluations, treatment recommendations, outcomes and follow-ups over time. The reports give variable depth and extent of patient information as determined by each practitioner. Research ethics approval was granted by the Faculty of Health and Medicine Research Ethics Committee [FHMREC17047].

2. Dementia Prevention – Current Evidence on Multimodal Non-Pharmacological Treatments

Rather than having a precise neurobiological cause, Alzheimer's and other dementias represent a heterogeneous state, determined by multiple factors and mechanisms that interact and

intervene throughout life [5, 6]. Reduction of modifiable risks is currently the preferred strategy to reduce future cognitive decline. Modifiable risks include depression, sleep disturbances, smoking, obesity, hyperlipidemia, diabetes and hypertension. Remedial actions include further education, social engagement, cognitive training, Mediterranean diet, exercise and physical activity [7, 8]. Primary prevention trials aim to reduce future prevalence by modifying such factors in healthy or at-risk populations [7]. In at-risk elderly people, interventions modifying more than one factor have improved or maintained cognitive functioning [9] and seem feasible, cost-effective and engaging [10].

Increasingly, studies investigate secondary or tertiary prevention and seek to interrupt cognitive decline or dementia that is already underway [11]. Once a person experiences measurable cognitive impairment and receives a diagnosis, treatment interventions could potentially be more effective, because the person retains insight. Such studies are promising, tend to show a benefit with the intervention group compared to the controls and tend towards higher reporting quality [12]. An example is the Body, Brain, Life for Cognitive Decline (BBL-CD) RCT providing a multidomain lifestyle intervention to people with subjective cognitive decline (SCD) and mild cognitive impairment (MCI) in Australian primary care [13]. The intervention included on-line education and personal sessions on exercise, diet, nutrition, cognitive engagement, brain training and physical activity. All the studies above utilised examples of therapies that are not pharmacological.

Non-pharmacological therapies (NPTs) are a 'useful, versatile and potentially cost-effective approach to improve outcomes and QoL' in Alzheimer's disease (AD) and related disorders for both the person with dementia and caregivers [14]. Single-domain interventions (nutritional supplements, cognitive training and physical activity) for individuals with positive biomarkers and cognitive impairment have been shown to be protective of cognitive decline [15]. Physical activity also appears to benefit various aspects of cognition including stabilization of MMSE scores, improved attention, memory and recognition [16, 17], the ability to perform ADLs and overall well-being [18]. For people with cognitive decline or early dementia, NPTs have successfully addressed sleep, yoga, exercise and nutrition [19-22] among other domains. Cognitive decline can be attenuated by factors such as improved nutrition, appropriate dietary supplementation, increased physical exercise, mental exercise and social activities [23].

Evidence from multimodal studies elucidates possible synergistic effects. Exercise, in combination with dietary factors has been demonstrated to affect molecular events related to the management of energy metabolism and synaptic plasticity [24]. Randomised controlled trials (RCTs) of multimodal interventions find that community-dwelling cognitively impaired elders benefit from combining physical, cognitive and social activities [25]. Evidence suggests that multiple therapeutic approaches (nutritional, botanical and stimulatory) targeting several dysfunctions at once may offer the most benefit with fewer adverse consequences than conventional medications [4]. In a 12-week intervention for people with MCI involving diet, omega-3 supplements, physical activity, cognitive stimulation, neurofeedback and meditation, 84% significantly improved cognitive function and 53% showed hippocampal growth [26]. The multimodal approach may thus be effective for improving cognitive function [27] and for maintaining or improving cognitive health [28], for persons with mild cognitive impairment (MCI) or dementia [29]. However, randomly assigned interventions to treat memory complaints with a multidomain intervention and polyunsaturated fatty acids, either alone or in combination,

revealed no significant effects on cognitive decline over 3 years [30], which may support arguments for a personalised approach.

A recent systematic review on multimodal non-pharmacological interventions to improve cognition for people with dementia [31] noted that group studies used 2-3 modes of intervention and multiple methods to implement them. Interventions utilised included cognitive, physical, psychological and psychosocial, nutrition, fasting, gut health, sleep hygiene, stress reduction, detoxification, hormonal health and oxygen therapy. In 19 (90%) of the 21 group comparisons, participants were reported to have cognitive improvements, stability with their dementia or a delay in their decline. However, persons treated individually in the five case studies achieved the most clinically effective results. Each personalised patient treatment utilised in-depth assessments and prescribed up to nine different modes. In cases where cognitive outcomes were improved, studies leveraged recent advances in our understanding of the underlying causes of dementia and ways to disrupt these neurodegenerative mechanisms. Furthermore, personalised one-to-one interactions specific to each individual involving investigation and assessment by the clinician, helped to focus or fine-tune the intervention.

3. The Logic of Applying Personalised Medicine to Cognitive Decline and Dementia

Personalised medicine addresses chronic disease with a holistic lifestyle approach common to Eastern mind-body-spirit traditions, which emphasise prevention rather than treatment, and focus on the person instead of the disease [32]. Lifestyle recommendations include healthy eating, active living, healthy weight and emotional resilience. A sub-optimal lifestyle is associated with the development and prognosis of long-term conditions. An individual's health metrics (laboratory tests, functional biomarkers and other diagnostics) are used to design patient-specific prescriptions for diet, exercise, stress and environment. In this way, lifestyle medicine-oriented therapeutic strategies can improve individual health outcomes and manage chronic disease [33-35].

Underlying this approach is the bodily process of homeostasis whereby the body self-regulates to changes within or outside the system to maintain a dynamic state of equilibrium called health [36], also formulated as 'the ability to adapt and self manage' [37]. Normal mental function depends on a balance between synaptoblastic (synapse-making) and synaptoclastic (synapse-destroying) activity [38]. When maintenance is unbalanced by deficiencies or pollutants, cells cannot be replaced and synaptoclastic processes win, resulting in cognitive decline. By correcting the environment to support healthy growth and repair while reducing toxins and infections, cells can rejuvenate.

To illustrate this point, consider current findings concerning amyloid-beta protein (Aβ), the primary pathological biomarker of Alzheimer's disease. *Why* it accumulates is of growing interest. Studies suggest β-amyloid deposition is an early innate immune response to infections acting as an antimicrobial peptide [39]. This antimicrobial role suggests inflammation propagates AD neurodegeneration, and immune pathways mediate pathogen entrapment and protect against infection [40]. Amyloid protein may also be evidence of an innate response to destroy fungal colonization [41]. Furthermore, we have yet to solve the 'Amyloid Paradox', whereby senile plaques composed of Aβ contain substantially elevated levels of iron, copper and zinc which bind to the Aβ making it toxic to neurons. On the other hand, Aβ can reduce the neurotoxicity of metal

ions, suggesting that the interaction can under some circumstances be protective. In studies where iron or copper were combined with Aβ, the neurotoxicity of these metals was substantially reduced, assisting the antioxidant defense of the brain [42]. Efforts to support plaque removal need to be guided by a better understanding of its protective role, and the imbalance of Aβ production *versus* destruction [43]. This gives one more reason to promote neurogenesis by supporting the body's natural equilibrium.

A personalised and programmatic therapeutic approach called Metabolic Enhancement for Neurodegeneration (MEND) has demonstrated the reversal of cognitive decline in patients with early AD [44]. This comprehensive precision medicine approach used clinical information and metabolic profiling of AD individuals, and provided additional objective evidence that this programmatic approach to cognitive decline is highly effective and may enhance pharmaceutical efficacy [45]. In some patients, modifications to daily activities, diet, exercise, stress, sleep, etc. can mitigate dementia symptoms such that a clinical diagnosis of dementia is no longer justified [46]. From the perspective of patient and caregivers, this alone may greatly improve quality of life and wellbeing. Over 100 case studies have now reported improvement in cognition, with some cases presenting electrophysiology or imaging of morphological structure as well as recovery of functional neurocognitive status [47, 48].

Personalised multimodal medicine (aka holistic [49], natural [32] or FM [50] as a 'whole systems' approach [51] is therefore logically suited to address cognitive decline or dementia because it identifies individual causative factors through in-depth investigation and root cause analysis. The practitioner asks not "What?" but "Why?" and prescribes an intervention as a 'disease modifying therapy' (DMT) that targets change in the underlying disease process leading to cell death [52]. The mechanisms and determinants are many [53] and predominantly involve nutritional deficiency [54], inflammation [55], oxidative stress [56], mitochondrial dysfunction [57], impaired methylation pathways [58], impaired Aβ clearance [43], hormone imbalance [59], chronic stress [60], gut dysbiosis [61], insulin dysregulation [62], infections [40, 63-66], poor sleep [67], vascular disease [68], and toxicity [41, 60, 69, 70], including heavy metals [71-75].

Recommendations to address these include diet and nutrition [22, 76] with an emphasis on healthy diets such as the Mediterranean, DASH, MIND and plant-based diets, whole foods, vegetables and fruits, probiotics, antioxidants, nuts and seeds and Omega-3 fatty acids [77-79] and nutritional support [80-82]. Recent findings support a low carbohydrate, high fat diet in which saturated fats (olive oil, butter, coconut oil) are advised over manufactured fats and seed oils [83-85]. The ketogenic diet [86, 87] and medium-chain triglycerides (MCTs) are also recommended [87]. Further recommendations include exercise [88-90], stress reduction, fasting [91, 92], cognitive stimulation and sleep hygiene [67].

Having first summarised the current evidence on MM NPTs we then explained the logic of applying personalised medicine to dementia. In what follows, we draw on 6 patient case reports to demonstrate how practitioners are operationalising this personalised FM approach to the treatment of their patients with cognitive decline, Alzheimer's and other dementias. To clarify, cognitive decline or cognitive impairment are terms used to describe symptoms that may or may not precede dementia. The evidence is inconclusive as to any correlation between such symptoms and dementia, as the standards of proof can never be ethically met [93]. However, in the following case reports, patients presented with some form of cognitive impairment, decline or memory issues, most of which had progressed to a dementia.

These case reports are novel in showing marked improvement in symptoms for what is currently by conventional medicine considered an irreversible condition. These reports are not case studies, ie, not research exercises with a specified treatment period, treatment protocol and target outcomes. They provide instead a brief description of the patient's clinical and demographic details, the diagnosis, any interventions and the outcomes as specified in the BMC Medical Research methodology [94] and the CARE [95] guidelines. Importantly, these findings shed new light on the possible pathogenesis of the disease which may, based on publication of these and similar early patient reports [47, 48], prove to be ultimately treatable with this novel 'root cause' analysis approach.

4. Functional Medicine (FM) Treatment Approach - 6 Case Reports

As with other personalised medicine (holistic, integrative or natural) treating the person is paramount to treating a particular problem. FM [96] is a systems biology–based approach that focuses on identifying and addressing the root causes of disease.

Practitioners use low-risk interventions that modify molecular and cellular systems to reverse the drivers of disease. The FM approach is particularly useful for treating a disorder like cognitive impairment, where one condition can be driven by many causes. Cognitive impairment is driven by inflammation, insulin resistance, gut dysbiosis, metabolic syndrome, nutrient deficiencies, toxicity, infections, and so on (Figure 1). The underlying causes are also interlinked and respond to similar mechanisms. So treating one of the causes may synergistically alter and improve another. www.ifm.org

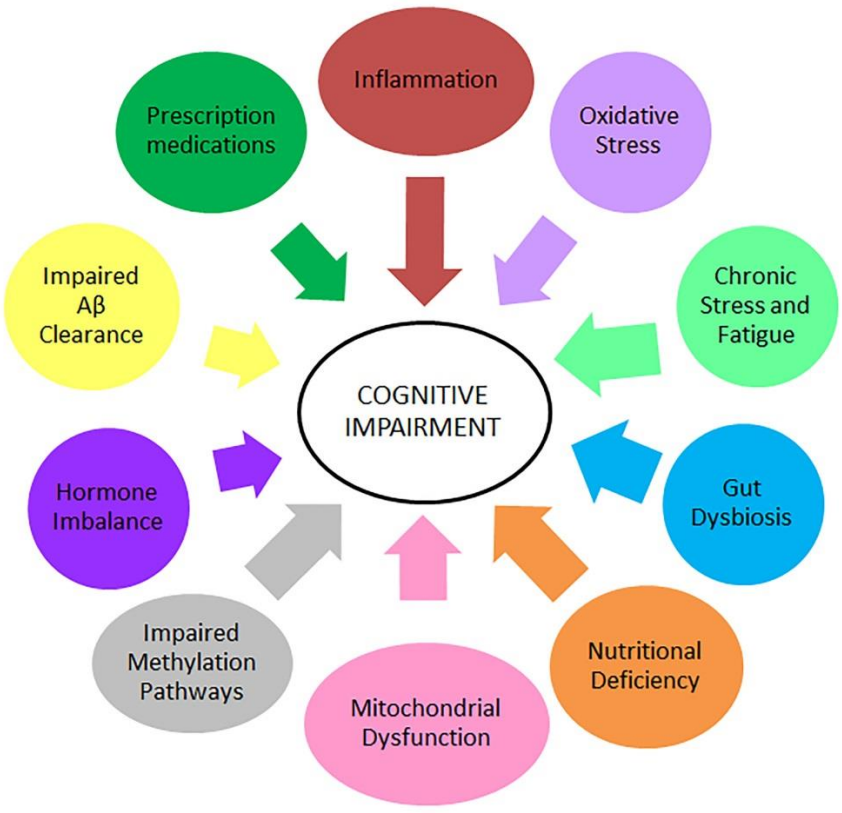

Figure 1 Identified drivers of cognitive impairment.

4.1 Presentation

Those with memory and concentration problems tend to belong to one of several categories of presentation:

- Many have *chronic fatigue* symptoms with both physical and mental fatigue (often described as 'brain fog'). As the brain consumes around 22% of the energy created by the body per day, anything leading to lack of energy production will inevitably impact on cognitive processing. This can be associated with unusual neurological symptoms such as blurred vision, tinnitus and pain syndromes / fibromyalgia.
- Some patients have cognitive dysfunction linked to *toxicity* - often due to genetic or acquired chemical processing issues. These can lead to severe side effects where other individuals with similar exposure may suffer no effects. Many of these patients have accompanying chemical sensitivities and are unable to tolerate volatile organics or even perfumes. Examples include those with ammonia overload (from trans-sulphuration pathway defects and bacterial overgrowth), and patients with exposures to heavy metals accompanied by poor metals elimination processing.
- Some have *endocrine dysfunction* which has not been recognised or adequately treated. Hypothyroidism is a common presentation – when untreated this leads to fatigue, low mood, poor concentration and metabolic syndrome.
- Some have specific *nutritional deficits* leading to poor metabolism and malfunctioning mitochondria, poor methylation capacity or neurological damage. Unrecognised B12 deficiency, folate deficiency and metabolic problems with folate and B12 are common causes of neuro-cognitive malfunction. This can lead to peripheral neuropathy, pain syndromes, low mood, poor concentration, insomnia and memory losses. Due to the difficulty of identifying B12 metabolism disorders in some patients, a course of B12 injections will be routinely trialled with any patient with neurocognitive dysfunction, fatigue or peripheral neuropathy. However, where possible they will be screened for serum B12, methylmalonic acid and homocysteine levels first.
- Other miscellaneous syndromes presenting with subjective cognitive dysfunction include those with *intractable insomnia*, *severe mood disorders* and specific drugs (opiates, anti-epileptics / nerve pain-killers).

Many of these categories will overlap (patients often have low B12, Vitamin D deficiency and Hypothyroidism for example). This indicates the importance of looking for all underlying contributing factors and addressing them to give the patient the best chance of recovery.

4.2 Screening

FM practitioners proceed with a detailed intake process and dietary analysis (captured in a lengthy, in-depth questionnaire). In addition to routine haematology, biochemistry, hormone levels, HbA1c and thyroid screen, some advanced functional testing is arranged to establish the potential contributors to cognitive decline. Patients with neuro-cognitive problems and/or fatigue are generally screened for:

- Hypothyroidism and T4 to T3 conversion disorder (T4 and T3 are hormones containing iodine, that are produced by the thyroid gland. The thyroid produces mainly T4, which is then converted to T3, in tissue and organs. T3 is the active hormone.)
- B12 and folate deficiencies / metabolism disorders
- All other B vitamin deficiencies
- Vitamin D deficiency
- Iron deficiency / overload / anaemia
- High ammonia / nitrogen overload
- Miscellaneous metabolic disorders (with organic acids)
- Possible contributing medications / supplements
- Risk factors for toxicity / heavy metals exposure (all screened for dental amalgam) / mold
- GI map genetic stool test and Small Intestine Bacterial Overgrowth (SIBO) breath test
- Home "burp" test to assess adequacy of stomach acid
- DUTCH (urine and saliva based) adrenal and hormone testing
- Yeast and bacterial overgrowth (organic acid testing)
- Chronic viral screen; Oral and nasal swabs; Candida questionnaire; Allergies
- Trauma

They may also consider testing salivary cortisol levels and ordering a hair analysis for heavy metals. Blood tests determine the need for vitamin support, blood glucose support and thyroid support. (Patients on warfarin are not given Vitamin D with K2.) A homocysteine blood test is used for B vitamin support with folate, B12 and B6. Adrenal support (fatigue, anxiety) and sleep support supplements depend on the questionnaire. After the first 8 weeks neurotrophic support can be added with Bacopa monnieri and Lion's mane mushroom. Detox support depends on the hair analysis. One must wait 2-3 months before detoxing.

Upon receiving test results the practitioner analyses these data to determine what processes are compromised by what mechanism or input. The aim is to identify the root causes of the disturbance and adjust the process through lifestyle and supplements, in order for the body to regain homeostasis.

4.3 Case Reports

Six case reports are given from four medical practitioners involving patients with cognitive decline and/or a formal diagnosis of a dementia. All patients gave informed consent to the practitioners for their data to be included. Patient reports are summarised in Table 1.

Table 1 Case reports of patients with cognitive decline or a dementia treated with FM.

Pt	Sex / Age	Presentation	Indications / Root causes from screening	Treatment	Outcomes
1	M mid 90s	•Cognitive decline for 7-8 yrs. •AD confirmed 5 years ago •Very frail physical health - needs help with all ADLs •Significantly impaired cognitive function - day to day living fully dependent on son with whom he lives •Son already started supplementation and dietary changes	***Serum*** •Vitamin B6 levels were above normal at 49.2 (LR 5.0-30.0) •Homocysteine elevated - 18.1 (optimal <7) •Vitamin D levels above range (at >70 which is high) •Interleukin 6 very elevated at 10.99 (normal <4.0) •Ferritin level (120.4) in upper limit of normal range (13-150) ***Thyroid function*** •TSH slightly elevated at 4.320 •T3 low at 2.24 (normal 3.98 - 6.54) •Zinc low at 44 (normal 70-150) •Copper higher end of normal at 124 (65-165) indicates high copper-zinc ratio. These showed a moderate amount of toxicity but not excessive. *Interestingly it did show considerably higher levels of thorium than I have seen in any other person – the patient had worked in the nuclear industry overseas for many years.*	•Diet (Ketogenic, low carb, hi fat) •Exercise (don't sit all day; HIIT - high intensity interval training) •Stress management (Cardio Coherence, Buddy App) •Address sleep quality ***Supplements*** •Multivitamin/mineral •R-Omega •Phyte Inflam •Vitamin B12 (methyl and adenosyl) sublingual •Methyl Factors •Probiotic fos-a-dophilus •Whole food Zinc •Thyroid Support	***Feedback at 6 months*** • *The more closely I follow the advice in the Bredesen [97] book the more success I have with my father* •*He is mostly bedridden, incredibly weak - he cannot stand* •*My father's brain continues to get better very slowly* •*Yesterday he asked me about something that had occurred 8 hours earlier. He has begun to thank me for looking after him.* •*I am now including five of Bredesen's [97] Indian herb supplements, as well as the ones you recommended. I think they are making a difference. Probably an important difference.* ***Feedback as 8 months*** •*Still making slow progress… generally a bit more awake, he said quite a few interesting things over the course of a couple of hours* •He now asks his son, '*What are you going to do about my dementia!?*' ***GP*** *– 'Previously this chap could spend days in a row asleep.'*
2	F 65	•Previously meditated, now unable to think clearly or remember	•Multiple amalgams •High carb diet with severe 'carb addiction'	•Weaned slowly off opiates then pregabalin •Supplemented with	•Able to meditate and think again – cognitive dysfunction lifted as drugs stopped (Pregabalin - main culprit)

		recent events •Unknowingly becoming very repetitive •Severely low mood, feels she is going to die soon, hopelessness. Multiple comorbidities: •Prolapsed disc, severe pain •Lymphoedema •Worsening fatigue •Blood pressure dropping. Possible case of postural orthostatic tachycardia and hypotension (POTS). •Severely obese (BMI 40) •Worsening control of Type II diabetes, on Metformin and insulin •Arthritis •4 incidents of cancer •Hypertension •Fatty liver disease	•Increased intestinal permeability and poor protein digestion •B1 and B3 deficiency •Severe intracellular folate deficiency •High homocysteine •Vitamin D deficiency •Hashimoto's Hypothyroidism, TSH (3.29), TPO antibodies (44) •Multiple toxic insults (mercury exposure; chemo-therapy & radiotherapy twice) combined with poor methionine cycle functioning and nutritional deficits (PPIs and Metformin cause low B12), lead to poor metabolism of medications. •Probable longstanding 'subclinical hypothyroidism' may well have contributed to weight gain, metabolic syndrome and diabetes. •Opiates and Pregabalin added resulting in mitochondrial dysfunction with fatigue, cognitive dysfunction and inability to regulate autonomic nervous system	methylated B complex, vitamin D, Mineral complex with extra magnesium. •B12 injections (once B12 well replaced, started with titrated methylfolate up to 800mcg) •Switched to low carb, modified Medi diet (gluten free) •Regular blood sugar monitoring and insulin self-adjustment under guidance •Probiotic •Worked with GP to come off insulin as this was causing weight gain and carb cravings to worsen. •Likely to remain at risk of recurring cognitive impairment without continued attention to reducing metabolic syndrome and nutritional support for methylation. •Whether heavy metals detoxification strategies would reduce dementia risk at this stage is not known.	•Lost 1.5 stone in weight, down to 10 units insulin from 40 units •Off all painkillers except Ibuprofen •Only able to tolerate 2-3 weeks between B12 injections – any longer and worsening fatigue and memory problems start to come back. •Mood much improved, starting to feel hopeful for the future again. •Over last 18 mos continued to improve, energy and cognitive function now normal for her again •Meditates twice a day and able to attend weekend retreats and philosophy classes •Does Sudoku every day, back to reading novels again •Now looks after grandchildren 2 afternoons per week and occasional weekends. •Off insulin completely for 12 months
3	F 76	•Progressive cognitive decline •Features of Parkinson's Disease •Tentative diagnosis of	•MSQ (Medical Symptom Questionnaire) score was 69, mainly symptomatic in Mind, Emotions, Energy and Musculoskeletal domains	•Stepwise introduction of a therapeutic food plan, mitochondrial and strategic nutritional support and lifestyle measures	•Prior to receiving results, she was seeming a little brighter on the program •Progress was being made. Her mood was improved

		Lewy Body Dementia •Declining cognition •Neurological symptoms included anxiety, auditory hallucinations, difficulty with concentration, speech, memory, judgement •Significant symptomatology: fatigue, insomnia, night waking, nightmares and distorted sense of smell. •Paranoia, fearfulness, panic attacks and seizure activity •Needed assistance with ADLs and could not easily interact with her family •Noticeable resting tremor and expressionless face •MOCA score August 2017 14/30 with visuospatial, naming, language, attention and recall deficits •Atrial Fibrillation •Myocardial infarction (stented) •Dyslipidaemia	•Oral health suboptimal, many missing teeth, multiple amalgam restorations and considerable periodontitis •In AF clinically at a controlled rate of 72 bpm •Blood pressure 137/76 (R arm), 127/76 (L arm) •Colonic dysbiosis, evidence of enterocyte stress & inflammation •Low levels of beneficial bacteria •Nutrient deficiency - profoundly deficient in selenium, Vitamin D insufficiency, suboptimal Vit B5 & B6, Vit C •Mitochondrial dysfunction on organic acid analysis particularly affecting amino acid metabolism •Neurotoxic markers (quinolinic acid) •Total body water was significantly reduced ***Medications:*** 12 Rx including statins, antidepressant, ACE inhibitor, blood pressure medication and Parkinson's medication •Significant chemotoxic load including glyphosate, 2HIB, PGO, HEMA & NADB – petrochemical, agrochemical, styrene and rubber derivatives which are neurotoxic or	•Nutrition plan includes Paleo reset diet, fresh produce, good fats, vitamins & other supplements, hydration and fasting 12 hours a day •Lifestyle measures include: Stress reduction, Exercise, Oral hygiene, Regular elimination, Sleep hygiene, Breathing exercises •A letter was written to her GP with all of these details and a request to stop her statin to remove this as a cause of mitochondrial dysfunction. The GP stopped it for a month.	• Her family interactions were markedly improving, including going out for walks, being able to look after her grandchildren one afternoon with her husband •She was doing more in the house, helping with chores and her daughter, who was visiting from xxxx, saw a dramatic difference in her ability to interact and get out and about •MOCA score was 20/30 having increased from 14/30 in 4 weeks •At 14 weeks significant resolution of cognitive, emotional and musculoskeletal complaints - MOCA score was 24/30 •Improvement had occurred in the areas of visuospatial ability, memory, delayed recall, attention and orientation •This lady managed to travel to her daughter's home after her case review appointment - daughter reported a very significant improvement in her overall health and cognition •Tragically, this lady fell and died the following year.

		•Cerebrovascular events •Seizure activity •Depression & anxiety •Urinary leakage, constipation, incontinence •Moderate dyspnoea •Varicose veins	increase the risk of CV disease and cancer. Notably, this lady had looked after her family on a farm and whilst not working in direct contact with chemicals / machinery, she had handled and washed her husband's work clothes over the years.		
4	M 79	•Memory issues for 4 years •Formal diagnosis of AD 2 years ago; on donepezil •Living in a Mediterranean country •Very active - had been a sportsman •Excellent diet •No obvious environmental factors	•Extremely low folate, Vit B9 (1.4) •Elevated homocysteine (19.1) •Vit B12 (410) within 'normal' limits but prefer it to be >500 •Vit D (37.5) within 'normal' limits but need it optimally around 100 •No signs of insulin resistance and no significant inflammation •HbA1c (4.94), CRP, HS CRP & ESR all within normal range ***Hair Toxicology Test*** •Low lithium •Toxic levels of aluminium, arsenic and tin	***Diet*** •Low carbohydrate high-fat (LCHF) diet to allow cells to metabolise glucose more efficiently, reverse insulin resistance. •Fructose is metabolised by the liver; be careful not to inflame it, with negative impacts ***Supplements*** •Multivitamin / mineral (C0 q10 multi) •R-Omega •K2/D3 Vegan •Vitamin B12 (methyl and adenosyl) sublingual; •Probiotic fos-a-dophilus •Methyl Factors •Detox support •Lithium oratate •Chia seeds - excellent source of potassium	***Initial outcomes / Follow-up at 4 months*** "After discussion with my Mother and my brother we can say that there is some signs of slight improvement in his memory. For example some days ago he remembered that his favorite football Team xxxx lost that championship this year because the owner entered the football field with a gun in his waist in order to protest to the referee and of course the team was banned!" •Blood markers for folate and homocysteine had improved. ***Feedback at 6 months*** - He definitely had more energy and patches of improvement in memory ***Feedback at 8 months*** - Physically better but memory fluctuates - but stable overall **Feedback at 11 Months** - "I am writing you about my dad's condition. As I

				Exercise - sitting a long time is very harmful; high intensity interval training has particular health benefits over and above other exercise regimes. ***Stress reduction*** – *Bhuddify* app; diaphragmatic breathing ***Sleep*** – excessive; possibly due to low folate levels	have already told you he was here in UK during January and February when he started his detoxification. Here he had the chance to have sauna something that unfortunately can't do back home. My mother and my brother that are watching his behavior both say that his cognitive status seems to be steady or even slightly better than before he started the detoxification."
5	F 71	•AD diagnosis 2017 on the basis of memory symptoms and CT findings •She had no insight into her symptoms •Gradual decline over four years since retirement (technical author) – decreased energy, short-term memory and cognitive processing with more recent confusion & disorientation •MoCA score was 14/30 •Examination findings in keeping with hypothyroidism;	•Hypothyroidism from 1995; on thyroxine •Hypertension from 2001, on ACEi; beta-blocker and diuretic added in 2014 *(shortly before the start of cognitive decline)* •Extensive dental work with mercury amalgams in situ •Ex-smoker, significant past exposure to pesticides and chemicals •Low vit D and folate •Suppressed TSH with very high T4 but low T3 •Raised homocysteine •Early insulin resistance - from high carbohydrate (CHO) diet (contributes to inflammation) •Requirement for digestive support •Low levels of *Helicobacter pylori* (*H. pylori*) without virulence factors •Low levels of beneficial bacteria, some opportunistic bacterial overgrowth (would impact ability to	***Diet*** •Remove gluten, dairy & processed foods •Reduce alcohol & caffeine intake •2 litres clear fluid/day •Balance blood sugar with healthy fats, protein & slow-release carbs at each meal •Organic produce •Water filter •Remove non-stick cookware •Sleep hygiene advice •Daily walk 30-60 mins before noon (when UV exposure supports circadian rhythm) •Brain HQ program, daily piano playing, daily relaxation listening to music, social interaction at least 2x week •Thyroid medications changed to NDT	***Initial follow-up at 3 months*** •MoCA score improved by 3 points to 17/30 and patient was noticeably more engaged with conversation although short-term memory remained poor •Thyroid now functioning normal clinically and biochemically •Remained hypertensive and bradycardic •ECG showed sinus bradycardia •Agreed with GP to reduce beta-blocker dose by half ***Further progress*** •Further cognitive improvement and engagement since reducing the beta-blocker dose •Interestingly, there was a decrease in blood pressure •Stopped the beta blocker completely

		bradycardic and hypertensive •Father had inflammatory bowel disease and vascular dementia but lived to 96.	extract nutrients from food) •Adrenal testing revealed adequate production but rapid metabolism of cortisol •Low melatonin and likely low levels of all neurotransmitters (probably from low protein intake, low stomach acid & low digestive enzymes) •High MTBE levels (high toxic load) •Low glycine and glutathione (would impair detox pathways) •Low selenium and zinc (would impact thyroid function) •Lack of trophic factors was the main issue, indicates this is likely Type II AD (atrophic) according to Bredesen classification [97] •Fibroids and ovarian cysts. •Toxic load (mercury, pesticides, lab chemicals, smoking, ETOH) with likely poor detox pathways is also a contributor.	***Initial supplements*** •Omega-3, curcumin (anti inflammatory), multivitamin, B12/folate, magnesium ascorbate (antioxidant support), Magnesium threonate (crosses blood brain barrier effectively), digestive enzymes and apple cider vinegar before each meal, probiotics, MCT oil, NAC with antioxidants, D3 plus K2, ashwagandha (adaptogen that supports adrenals), glycine (glutathione precursor), EPO. ***Follow-up at 3 months*** •Supplements continued with the addition of magnesium glycinate before bed •Advised to further reduce (preferably stop) ETOH.	•Patient has now read The End of Alzheimer's by Dr Dale Bredesen [97] as well as her initial clinical reports, is able to make insightful comments and suggestions •This is a vast improvement from our initial meeting •The latest report from her husband is that it seems that "the lights have been turned back on!" This is less than 5 months after starting the interventions •Patient has been suffering from Type II or Atrophic AD due to under-treated hypothyroidism, decreased cerebral perfusion due to too much beta blocker medication, and lack of several key nutrients •More work to do regarding toxic load •Look at genetics of methylation and detoxification pathways to inform long term management.
6	F early 70s	•First symptoms of memory loss 3 yrs prior •Diagnosed with AD 2 yrs prior •Taking memantine •No significant previous history and no social or environmental	***Serum levels*** •Very low vitamin D (12.1) •Raised Interleukin 6 (marker of inflammation) 4.7 •Some degree of insulin resistance but not in formal prediabetes range •B12, HbA1c and Folate B9 did not show any identifiable features but	***Diet*** •Low carbohydrate high-fat (LCHF) diet to reverse insulin resistance, allow cells to metabolise glucose more efficiently. ***Fasting*** •Not eating after 7pm and delaying breakfast allows the body to reset its	•Physically stronger, more energy, brighter in herself but slight decline in memory. •At this stage neurotrophic supplements and lithium supplementation added.

		history of note.	already taking supplements. •Hair testing indicated high-ish levels of aluminium, arsenic, mercury and lead •Hair testing indicated low levels of lithium	fuel metabolism and lower insulin resistance. ***Exercise*** - Prolonged sitting is very harmful. •High intensity interval training has particular health benefits beyond other exercise regimes. ***Stress reduction*** •*Bhuddify* app, diaphragmatic breathing. ***Supplements*** Multivitamin/mineral (C0 q10 multi); R-Omega; Phyte Inflam; K2/D3 Vegan; Vitamin B12 (methyl and adenosyl) sublingual; Organic Vitamin B Complex; Probiotic fos-a-dophilus; Magnesium threonate ***Detox*** Liposomal Glutathione; Detox Support; Toxaprevent Pure	

Abbreviations – **ACEi** (acetylcholinesterase inhibitors); **AD** (Alzheimer's Disease); **AF** (Atrial fibrillation); **BMI** (Body Mass Index); **Brain HQ** (online brain fitness from Posit Science); **CHO** (High carbohydrate diet); **ECG** (Electrocardiogram); **EPO** (Erythropoietin); **ETOH** (Ethanol); **MoCA** (Montreal Cognitive Assessment); **MSQ** (Medical Symptom Questionnaire) [MSQ lists 71 possible symptoms in 15 domains. Scores from 0–284; lower score = less symptoms]; **MTBE** (toxin, Methyl tert-butyl ether); **2HIB** (toxin, 2-Hydroxyisobutyric Acid); **HEMA** (toxin, monomer used to make various polymers); & **NADB** (rubber toxin); **TSH** (cholera toxin); **T3** (thyroid hormone triiodothyronine); **T4** (thyroid hormone thyroxine); **NAC** (N-acetylcysteine); **NDT** (Natural Dessicated Thyroid); **CRP** (C-reactive protein); **HS** (High-sensitivity); **ESR** (Erythrocyte sedimentation rate); **CRP & ESR** (markers of inflammation).

4.4 Key Points, Insights and Findings

The 11 key points below summarise some insights gained, and tentative findings from these six case reports. By looking at cognitive impairment as one small piece of a larger puzzle these key points further illustrate the unique and potentially beneficial aspects of this treatment approach.

1. Not just a memory problem – Dementia is not a solitary problem of memory but is often one of a mixture of conditions and part of wider health issues. Lifestyle appropriate for addressing dementia has positive side-effects on other conditions.

2. Never too late to start – [CS1 – Case Study 1] A male in his mid 90s is very weak and frail, cannot walk and requires 24-hour assistance with all ADLs from a son with whom he lives. After an in-depth investigation by the FM practitioner, the son initiated dietary changes, further supplements and an exercise regime. "He has begun to help me a bit more than before when I ask him to move an arm or lift a leg or bend forward. If his brain is slowly waking up it must be difficult for him - to more fully realise his circumstances. He improves most after a fasting episode."

3. Success requires family support – [CS1] "Bananas brought on a relapse a month ago when I gave him banana every day for about a week - it ended with him not recognising me." "Relapses occur when I get tired of trying to help him or when I try too hard." "Exercise is very important. As well as exercising his legs with a Reck MOTOmed I have now got him a Motovator Medidrive - which bicycles his hands and arms. He has been using that for a week and the difference is noticeable." "I have been trying to take him swimming as often as I can, but the last time was two weeks ago. The sheer effort of it puts me off - but it is very good for him. Best would be every day...!" "I am now including five of Bredesen's [97] Indian herb supplements, as well as the ones you recommended. I think they are making a difference. Probably an important difference."

4. Nutrient deficiencies – Each case had abnormal nutrient levels with implications for brain health. "Profoundly deficient in selenium (red cell analysis), Vitamin D insufficiency 39ng/ml (optimum 50-80ng/ml), suboptimal vitamins B5 & B6, Vitamin C."[CS3] "PPIs (proton pump inhibitors) & Metformin cause low B12."[CS2] There is a role therefore, for B12 injections to be started right away with all memory problems. Patients can easily be taught to self-inject. Nutritional support is also needed for methylation, or run the "risk of recurring cognitive impairment" [CS2]. "Curcumin is anti-inflammatory. Magnesium ascorbate provides antioxidant support, and Magnesium threonate crosses the blood brain barrier effectively." [CS5].

5. Prescription medications – "Opiates and Pregabalin may result in mitochondrial dysfunction with fatigue, cognitive dysfunction and inability to regulate autonomic nervous system."[CS2] Pregabalin side effects include sleepiness, confusion and memory impairment. Statins cause mitochondrial dysfunction. PPIs (proton pump inhibitors) reduce acid formation in the stomach to prevent ulcers, but long term PPI use has been linked to dementia and vitamin B12 deficiency. Beta blockers (beta-adrenergic blocking agents) block adrenaline from binding to beta receptors on nerves; act to reduce heart rate/blood pressure by dilating blood vessels) (see CS5 about dropping these).

6. Mis/undiagnosed/untreated/under-treated thyroid function – "Probable longstanding 'subclinical hypothyroidism' may well have contributed to weight gain, metabolic syndrome and diabetes."[CS2] "Type II or Atrophic AD is due to under-treated hypothyroidism, decreased cerebral perfusion due to too much beta blocker medication, and lack of several key nutrients."[CS5] "Low selenium and zinc would impact thyroid function."[CS4].

7. Toxicity, heavy metals, pesticides, infection – Mercury exposure from dental amalgams was evident in half of the cases, whereas chemotherapy [CS4] or other chemotoxic loads (pesticides, lab chemicals, smoking, ETOH, glyphosate, petrochemicals, agrochemicals) or heavy metals (mercury, aluminium, tin, arsenic) were evident in all cases. "Oral health was suboptimal with many missing teeth, multiple amalgam restorations and considerable periodontitis and hard and soft plaque." [CS4]; "Low glycine and glutathione would impair detox pathways."[CS5]

8. Connection to diabetes – "Worked with GP to come off insulin as this was causing weight gain and carb cravings to worsen."[CS2] "Early insulin resistance - from high carbohydrate (CHO) diet contributes to inflammation."[CS5].

9. Gut-Brain connection – stomach acid and beneficial bacteria – Low stomach acid and low digestive enzymes [CS5]; There is a requirement for digestive support for low levels of beneficial bacteria, as some "(o)pportunistic bacterial overgrowth would impact ability to extract nutrients from food."[CS5].

10. Dehydration and fasting – [CS1] "(my father) improves most after a fasting episode." "Total body water was significantly reduced at 32.8 l (predicted optimal 36-43 l)"[CS5].

11. Metabolic syndrome presents continued risk for cognitive impairment – *"*Likely to remain at risk of recurring cognitive impairment without continued attention to reducing metabolic syndrome and nutritional support for methylation."[CS2].

5. Discussion

These observations provide further support to the growing body of case reports describing reversal of cognitive decline in patients with early Alzheimer's or other dementias. To our knowledge, this is the first paper reporting practitioner case reports documenting improvements in symptomatology of memory decline in patients from the UK, Greece and New Zealand. Four patients had their initial presentations and follow-up improvements verified by MoCA and/or a formal diagnosis, and two patients had symptom improvements verified through self-report and proxy-report.

Improvements were shown through biomarkers, such as normalisation of serum levels, folate and homocysteine, thyroid function, blood sugar levels, as well as weight loss, decreased blood pressure and reduction in medications (beta-blockers, statins, insulin, metformin, pregabalin and painkillers).

Improvements were also reported in: cognitive function, memory, visuospatial ability, delayed recall, attention, orientation, overall health, physical strength, communication, clarity, mood, emotions, feeling hopeful for the future, lifting of brain fog, energy levels, a bit more awake, reading, ability to meditate, doing Sudoku, going out, socialising, looking after grandchildren, going for walks, helping with chores, visiting family, interacting, engagement in conversation and making insightful comments and suggestions.

A small but growing body of evidence illustrates through N-of-1 case studies or case reports the process, practice and progress of patients presenting with cognitive decline. This paper has contributed a few more. Limitations are many. The particular analyses and interventions are not uniform across the practitioners, nor were consistent measures taken at baseline and beyond. There was no uniformity of diagnoses, except that a clear presence of cognitive decline was reported, measured or diagnosed. Further limitations of case reports include sample size (n=1)

and lack of control or randomisation. In the case of any treatment for dementia, 'usual care' spells ultimate decline [98, 99] acting as a control whereby any stability in symptoms or delay in decline can be interpreted as improvement [100, 101]. Furthermore, as this is a multimodal intervention involving a wide range of treatments, it is impossible to correlate improvement with any one mode. As this is not mono-therapy drug research, there is no need or intention to isolate any particular intervention. If a mono-therapy could treat dementia it would be marketed already. The multi-domain nature of dementia and the multimodal treatments of IM practitioners advocate for a medical paradigm shift towards an ecological model where health is determined by a complex interaction of factors at different levels, including the realms of energy [102] and intent [103].

There is also an epistemological argument to be made whereby empiricism concerns only knowledge gained through sense experience. Most energy medicine operates beyond the narrow bandwidths of human sensing and is often dismissed as scientifically impossible simply because modern empirical science, and therefore conventional medicine fails to understand it. This is blaming a fish for not being able to ride a bicycle. But this is slowly changing as technology evolves to record, measure and verify the body's energy field or 'biofield' [104]. The biofield is a 'multilevel organizational concept in which information flows within and between the various levels of the organism' [103]. Biofield therapy [104] is non-invasive and involves practitioner interactions with the client's biofields, interacting fields of energy and information both within and around living systems [105-107], capturing an "aspect of healing beyond limited implication of medicine as a treatment for illness," [103] but also in clinical studies reducing pain, negative behavioural symptoms in dementia and anxiety in hospitalised populations [108, 109]. The possibilities are staggering - "The ability to understand and control shape in its most general form offers the opportunity to address a wide range of biomedical problems and restore complex structures damaged by injury, cancer, disease or age." [105.]

With these case reports, regardless of which mode was most efficacious, an outcome of improvement for the patient is our optimal concern. These findings lend further supportive evidence to silence the dominant narrative that dementia is incurable and irreversible.

5.1 Future Directions

We advocate for personalised medicine within the UK National Health Service (NHS) for persons living with memory problems and dementia [110]. Approaching a chronic multifactorial condition in this manner is relatively new to the UK, but attracting attention elsewhere [111]. A 'root cause' FM approach to cognitive decline or dementia is not available through the NHS, nor is it clear as to the extent of global availability. Practitioners are being trained around the world and starting private practice, but we are unaware of any present government health service provision. The availability of FM practitioners motivates resourceful individuals to implement multiple difficult lifestyle changes, subsequently contributing data to case reports, as above.

There is a pressing need for interventions that can modify the disease process and affect measurable improvement in cognition and associated benefits to quality of life for patients and caregivers. We therefore aim to draw upon the latest evidence, learn from existing projects worldwide and develop the next phase of the work: a logistically practical, affordable, holistic, enhanced intervention alongside the existing NHS memory service pathway. However, lifestyle change can be difficult for older people as it may involve changing or relinquishing cherished

habits and routines, as well as challenging long-held perceptions and beliefs around dementia, its causes and the possibility of change through treatments. Crucially, in designing the intervention protocol, we aim to assist participants and their caregivers to overcome the major physical, emotional, environmental and psychological hurdles associated with behaviour change [112]. To facilitate this goal, substantial engagement with people with early-stage dementia, caregivers and practitioners is ongoing.

6. Conclusions

Existing evidence and workable protocols emerging from personalised medicine regarding the arrest and reversal of cognitive decline in symptomatic individuals opens a new window for research and care practice. The suitability of this approach to dementia is evident given the multiple causative factors identified to date. Personalised multimodal medicine provides a potent cocktail targeting several individual causative factors through in-depth investigation and root cause analysis, resulting in the disruption of neurodegenerative mechanisms. Although this systems approach seems novel and ground-breaking, it merely reinforces ancient mind-body-spirit traditions of treating the person, not the disease, by way of energy that contributes information for a person's mental, emotional, physical, and spiritual wellbeing [107]. Such practices continue to sustain lives around the world today.

The window of opportunity for intervention is when subjective impairment or early-stage dementia renders the person both aware of their circumstance and cognitively able to address it. A proposed collaborative project between Lancaster University and the NHS in the UK will offer an enhanced level of intervention alongside the existing NHS memory assessment service pathway. Support for lifestyle change will be perhaps the most critical factor in success for these patients - helping them to overcome the major physical, emotional, environmental and psychological hurdles they will face.

Beyond the paradigm of 'living well with' dementia, existing treatment protocols are facilitating a future whereby people with dementia and their loved ones can 'live well beyond' diagnosis.

Author Contributions

SD, DM, RW and LW provided patient case reports and treatment protocols. GC conducted the research and drafted the paper. CM and JS are the PI and Co-I on this project respectively. Both have been involved in the running of the project, data analysis and reading and commenting on drafts of the paper.

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Competing Interests

The authors have declared that no competing interests exist.

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