# Assessing and Improving Everyday Functioning in Older Adults

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## COVID Statement

Before presenting this programme of work, the impact of COVID-19 on the original research plan will be overviewed.

Originally the 12-week intervention study reported in Chapter 3 was planned to run as a face-to-face study. This included measurements of stress response, which encompassed cardiovascular reactivity measured used a Portapres, and saliva samples to measure secretory immunoglobulin A, as an indicator of immune response. Mobility measurements were also to be collected and blood samples to measure c reactive protein and nutritional biomarkers.

This study was planned to be running throughout the duration of the second year and part of the third year of my PhD. This would have made up the main body of my thesis. Due to COVID regulations in person research stopped in March 2020. Those who were already enrolled in the study completed their final visit online, meaning only questionnaire data could be collected.

It was decided to adapt the study to run as an online intervention, the procedure for this is outlined in full in Chapter 3. My data collection was stopped for 8 months during this initial period, as alternative measures were considered and I could access materials to do this, as all treatments and materials were still on campus. Data collection began again in December 2020 until September 2021, with over 200 participants completing the study during this time.

Although not how originally planned, I believe the adaptions made actually improved this programme of work and the reasons for this are considered throughout.

## Abstract

The ageing population has led to a range of societal issues, and research needs to identify ways to promote healthy ageing and independent living for longer. One such area of interest in this area is diet and supplementation, which has focused on improving aspects of psychological and psychical health in older adults. However, there have been clear methodological limitations within this research, including stringent inclusion criteria and no measure of dietary intake. Furthermore, nutraceutical research has focused on very specific outcome measures which do not have clear real-world applicability. This programme of work aimed to address these limitations, and further knowledge in the area by taking novel approaches to assess and improve everyday functioning in older adults.

The first experimental study reported in Chapter 2 aimed to explore older adults' own views of their perceived levels of everyday functioning and in which areas they would like to see improvements. It was identified through thematic analysis that older adults reported difficulties with a range of activities (such as recreational hobbies and household tasks) which stemmed from underlying health and mobility issues. Furthermore, the themes found within this study were used as a guide to design outcome measures for the subsequent intervention (Chapter 3), with the aim to undertake a participant-led approach to study design.

Chapter 3 reports an experimental, randomised, placebo-controlled, double blind parallel groups study, investigating the effects of a multivitamin supplement on everyday functioning in older adults. This trial was designed to improve on issues with previous trials, and to incorporate areas highlighted as important to older adults in Chapter 2. Results showed that 12-week multivitamin supplement improved feelings of friendliness in females and reduce measures of prolonged stress reactivity and emotional loneliness in males. Furthermore, a range of interactions were found between habitual dietary intake and multivitamin supplementation, indicating that supplementation may be more effective in those with lower nutritional intake.

Chapter 4 explored how habitual dietary intake before supplementation effected everyday function outcomes. The aim of this was to both add to the vast literature in this area and to fully understand interaction found within Chapter 3. Surprisingly results of this study showed that those below the mean intake of various vitamins and minerals (in this sample) performed more favourably on everyday function outcomes. Suggesting that there may be an inverted U shape curve in relation to vitamin and mineral intake and favourable outcomes in everyday functioning, which warrants further exploration.

Finally, Chapter 5 reports a naturalistic repeated measures design, exploring the effects of COVID-19 lockdown on everyday function in older adults. It was shown that the government lockdown in response to the COVID 19 pandemic had largely negative implications for wellbeing, mood, perceived stress and memory in older adults, but there were improvements in general health, physical activity and social interaction. There are clear applications going forward for ways to minimise harmful side effects of stressful situations in older adults.

Overall, this programme of work has clear and important implications. As well as implications already mentioned in this abstract, it highlights that multivitamin supplementation in older adults may have the potential to elicit positive effects on everyday functioning. With these effects being even more pronounced in those who have worse diet, suggesting supplementation should be recommended in older adults who do not consume adequate levels of vitamins and minerals.

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## Author’s Declaration

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas, and contributions from the work of others. The author and supervisors worked together to design the methodology for each chapter, methodology for Chapter 3 was approved by the external sponsor. All data collection, statistical analysis and interpretation of results was the work of the author alone. For publications, the external sponsor has the right to proofread, approve journal of submission, and provide edits as to how they are referred to in text.

The authors, supervisors and external collaborators worked together to design the methodology for each experimental chapter. Any ethical clearance for the research presented in this thesis has been approved. Approval has been sought and granted for all studies presented throughout this thesis by the Faculty of Health and Life Sciences Ethics Committee at Northumbria University.

**I declare that the Word Count of this PhD thesis is 53,067.**

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# CHAPTER 1. INTRODUCTION

## 1.1 Nutraceutical research

Nutraceuticals are food, or part of food, that provide medical or health benefits. Their consumption should prevent disease and allow overall good health to be maintained (Chauhan et al., 2013). They are formed by many active substances extracted from vegetal or animal origin, with beneficial pharmaceutical activity beyond its nutritional value (Santini et al., 2017). Nutraceuticals are typically represented by vitamins, minerals, amino acids, and probiotic compounds, and can range from dietary nutrient supplements, herbal products, food groups such as fruits and vegetables, and processed foods like cereals (Makkar et al., 2020; Prakash & van Boekel, 2010). There is an extensive range of these products available, and a wealth of clinical research conducted with the aim to provide evidence of their positive health benefit and disease prevention, particularly in older adults (González-Sarrías et al., 2013).

Numerous studies have demonstrated the effects of nutraceuticals on disease prevention. Flavonoid rich fruits and vegetables, and polyphenol rich cocoa products have been associated with reductions in blood pressure and lower risk of cardiovascular mortality (Mastroiacovo et al., 2015; Ried et al., 2012; Wang et al., 2014). Links have also been suggested between B vitamins, in particular B6, B12 and folate, and the reduced risk of cardiovascular disease and stroke, due to lowering of homocysteine (McNulty et al., 2008; Yuan et al., 2021). Calcium and vitamin D have clear roles in prevention of osteoporosis, vitamin D may be linked to various cancers and diabetes (Gupta & Prakash, 2015; Singh et al., 2014). Full consideration of the links between nutraceuticals and disease will be discussed in Chapters 3 and 4.

When considering older adults, a large proportion of research in this area specifically focuses on cognitive function. This is likely due to the fact that the chance of developing mild cognitive impairment and/or dementia can be exacerbated by nutritional deficiency (Reay et al., 2013). Many approaches have been undertaken to look at the effect of nutraceuticals on cognition and cognitive decline, the research area is extensive, and it is not possible to collate all the evidence in this review. Therefore, a brief overview of RCTSs and meta-analysis of RCTs specifically focusing on older adults will be discussed. Curcumin has been shown to improve attention and working memory following acute administration (Cox et al., 2015), this has been further supported in meta-analysis showing curcumin is effective at improving cognitive functions in older adults (Zhu et al., 2019). Resveratrol supplementation, and foods containing high levels of resveratrol such as grape juice, have been shown to improve cognitive functions, particularly verbal memory and learning (Evans et al., 2017; Phillips, 2017). Blueberry extract has been shown to improve memory performance (McNamara et al., 2018; Whyte et al., 2018), and, aspects of the Mediterranean diet, such as whole grains, legumes, and nuts, are positively correlated with higher cognitive functions (Wengreen et al., 2013).

Focusing on specific vitamins and minerals, meta-analysis has shown there is limited evidence of a link between B-vitamin supplementation and cognitive performance (Ford & Almeida, 2019; Zhang et al., 2017). However, three-year supplementation with folic acid led to improvements in memory, information processing speed and sensorimotor speed (Durga et al., 2007). Long term supplementation with vitamin D in those with Alzheimer's disease showed improvements to cognitive performance such as digit span and picture arrangement (Jia et al., 2019). Short term supplementation with pine bark extract and vitamin C improved speed of response on spatial working memory and immediate recognition tasks (Pipingas et al., 2008). Studies of this type have been criticised for focusing on the concept of a single active ingredient, which may explain the limited efficacy observed in these studies (Howes et al., 2020). Studies looking at nutraceuticals in combination on cognitive performance have provided some promising evidence. Multivitamin supplementation has been shown to improve measures of processing speed, speed of response in spatial working memory tasks, and episodic memory (Harris et al., 2012; Macpherson et al., 2012; Small et al., 2014).

Despite extensive research into the impact of nutraceuticals on measures of health and cognitive function in older adults, there has been considerably less focus upon how transferable these outcomes are to the real world. Furthermore, there has been no consideration as to whether the outcomes being measured impact the research participants in any meaningful way. These studies are limited in what they assess based on the deductive nature of cognitive testing. Further work is therefore, needed in this area that encompasses a wider range of outcomes, will have direct implications on real world functioning, and will be meaningful to the population, such as everyday functioning.

## 1.2 Everyday functioning

Everyday functioning is the effective functioning in day-to-day life, which is dependent on an individual's ability to change and is reliant on their sensorimotor, cognitive, personality and social resources (Baltes & Lang, 1997). This can be categorised further into basic activities e.g., eating, dressing, and grooming, and higher-level activities e.g., cognitive domains and emotion regulation (Farias et al., 2006; Strine et al., 2006). Issues have been highlighted in the past with the measurement of everyday functioning, as individuals have previously been categorised as either completely "dependent" or "independent" in any given domain (Farias et al., 2006). Instead, everyday functioning should be considered as a multi-dimensional spectrum, where individuals could be placed at any point across multiple domains. There is some overlap with instrumental activities of daily living, which are complex tasks important for independent living such as cooking, housework and managing money (Feger et al., 2020). However, everyday functioning encompasses a wider range of domains and independent activities of daily living only focus on independent living, so there is a distinction between the two. Limited evidence in the area has shown everyday functioning can be affected in bipolar disorder (Depp et al., 2012), schizophrenia (Reichenberg et al., 2014) and HIV (Vance et al., 2013) but given the implications to day-to-day life, it is surprising that it has not been the focus of more research,

## 1.3 Everyday functioning and ageing

Perhaps the biggest factor which can impact everyday functioning is the ageing process. Rowe and Kahn (1987) were one of the first to conceptualise successful ageing as the absence of disease, lack of physical disability, good mental health, and good social engagement. Based on this there is clear overlap between successful ageing and everyday functioning. Detriments due to ageing are likely to lead to poorer everyday functioning and consequently increased dependence. It is well established that the proportion of older adults in the world's population is increasing and in 50 years' time there will likely be an additional 8.6 million people aged 65 years and over (Office National Statistics, 2018) in the UK. If population ageing occurs alongside a deterioration of health, this will lead to a large proportion of society being dependent, having functional problems, and receiving more health and care services and this will exacerbate impacts on public expenditure (Howdon & Rice, 2018). It first must be understood how the ageing process affects domains of everyday functioning before ways to improve this can be tested.

## 1.4 Successful ageing and everyday functioning

### 1.4.1 Absence of disease

The first aspect of successful ageing as outlined by Rowe and Kahn (1987) is the absence of disease. It is well established that the immune system changes with age, where the process of immunosenescence results in the declining function of the immune system (Stahl & Brown, 2015). This results in greater susceptibility to infectious disease and can contribute to the risk of degenerative diseases such as cancer, cardiovascular and autoimmune disease (Pawelec, 2018). The declining immune system is primarily attributed to T-cell and B-cell populations, which are involved in antigen specific immune response (Cano & Lopera, 2013; Crooke et al., 2019). B-cells are responsible for producing antibodies, which are essential for humoral-mediated immunity, whereas cell-mediated immunity depends on T-cells (Cano & Lopera, 2013). Due to these age-related changes, older adults exhibit increased susceptibility to infections such as influenza, pneumonia, and COVID-19 (Haynes, 2020). They are also more susceptible to complications during these infections (Keilich et al., 2019), for instance in England the highest death rate due to COVID-19 was in those aged over-65 (Aron & Muellbauer, 2020). Therefore, research should strive to discover approaches to overcome age-related declines in immunity, as this is a direct way to promote successful ageing.

Age is also a significant risk factor for several cancers (Cao et al., 2019), where altered functions to genomes due to changes in cell environment, inflammation, decreased immune function, and DNA damage are associated with ageing (Naylor et al., 2013). Age related changes in tumour microenvironment have also been identified as key contributors to cancer progression and response to treatment (Zabransky et al., 2022). Age is also a main risk factor for cardiovascular disease (CVD), including heart failure, stroke, and myocardial infarction (Gensous et al., 2017; Yazdanyar & Newman, 2009). Similarly, to all ageing pathophysiology, the high prevalence of CVD is attributed to inflammation and damage to cells, mainly degeneration and deterioration of myocardial muscle and cells (Curtis et al., 2018; Steenman & Lande, 2017). Links have also been made between ageing and lupus, multiple sclerosis, thyroid disease, and coeliac disease, with suggested roles for B-cell and T-cell irregularities (Roberta et al., 2018; Yang et al., 2015). Ageing is also associated with rheumatoid arthritis, an autoimmune disease, where multiple immune cells and signalling networks are impaired leading to maladaptive tissue repair processes, and damage predominately in the joints, but also in the lungs and vascular system (Weyand & Goronzy, 2021).

### 1.4.2 Lack of physical disability

Physical disability is the second facet of successful ageing suggested by Rowe and Kahn (1987).

Physical disability is defined as the difficulty in performing activities necessary for independent living, and loss of independence (Fried et al., 2004). Disability among older adults occurs as a result of health problems and interactions between health condition, activity and participation, personal and environmental factors (Connolly et al., 2017). Older age, compromised functional capacity, sleep quality, depression, and cognitive function have all been associated with physical disability (Chien & Chen, 2015). Symptoms of physical disability such as pain and stiffness have been found to affect mobility (e.g., walking, sitting, bending), daily activities (housework, dressing, working), and other activities (relationships and socialising, mood, sleep, and appetite) (Burbridge et al., 2020). Evidently, there are clear links between physical disability and everyday functioning.

Frailty, a geriatric state resulting from significant loss of physiological reserve (Pansarasa et al., 2019) is also closely linked to physical disability. This is characterised by fatigue, weight loss, and poor muscle strength, which increases the risk of adverse outcomes such as falls and disability (Clegg et al., 2013; Fried et al., 2001; Mulero et al., 2011). In fact, the terms frailty and disability were once used interchangeably due to similarity and high coexistence rate (Clegg et al., 2013; Fried et al., 2001; Walston et al., 2006). Aspects of frailty are interlinked, for instance having impaired balance, can lead to a fear of falling which in turn can cause reduced mobility (Dupuy et al., 2020; Seidel et al., 2011). It is linked to many aspects of everyday functioning and can even predict cognitive decline in older adults (Godin et al., 2017). Importantly, frailty is a dynamic state, which can transition from worse to better status over time (Gill et al., 2006), due to this, interventions can be put into place to target this, to slow the decline into disability and thus maintain good everyday functioning.

### 1.4.3 Good mental health

The third aspect of successful ageing is to maintain good mental health (Rowe & Kahn, 1987). Quality of life is dependent on both physical and mental components, and they both contribute to wellbeing in later life (Makovski et al., 2019). Within the context of older adults, mental health can encompass mood disorders (e.g., depression and anxiety), stress, and cognitive performance (Lin et al., 2022), all of which can be directly affected by physical disease (Lorem et al., 2017). According to the World Health Organization (2017), over 20% of older adults have suffered from a mental health disorder. In the UK the prevalence of depression was reported as 8.7% in 2007 (McDougall et al., 2007) and for anxiety, prevalence rates vary between 1.2-14% (Remes et al., 2016). Prevalence rates for mood disorders in this population are predicted to increase as this age group grows with population ageing (Sajatovic et al., 2015). Early research suggested there are five significant risk factors for depression in older adults, these being bereavement, sleep disturbance, disability, history of depression and being female (Cole & Dendukuri, 2003).

The evidence therefore suggests that older adults may be at risk of a range of mood disorders. While these disorders have their own negative implications, they may also impact upon everyday functioning in older adults. Depressive symptoms in older adults can lead to a number of detrimental symptoms such as reduced concentration, fatigue, sleep issues, loss of interest in enjoyable activities, and issues carrying out usual work or social activities (Miller et al., 2019). Furthermore, those with higher depressive symptoms also report worse physical and cognitive function, which may be driven by inflammation levels (Derry et al., 2022). Older adults with depression have been shown to have a fourfold likelihood of also having frailty (Soysal et al., 2017), which, as previously outlined, can also impact upon everyday functioning. Depressive symptoms have also been associated with declines in subjective memory and sleep disturbance (Kiyoshige et al., 2019; Ryu et al., 2016; Smagula et al., 2016).

In line with depression prevalence, around half of over 55s have reported experiencing anxiety, and both anxiety symptoms and disorders are relatively common in older adults (Bryant et al., 2008; NHS England, 2017). Anxiety has been shown to be a significant predictor of a range of everyday functioning outcomes. Those with anxiety have consistently reported higher levels of physical disability and lower quality of life (Ribeiro et al., 2020; Sousa et al., 2017). It is also a significant predictor of poorer cognition, social restriction, instrumental activities of daily living limitations and worse everyday function (Divers et al., 2021; Norton et al., 2012). It is clear that good mental health is critical for successful ageing and if disrupted this can have severe consequences on everyday functioning.

Stress is often indicated in the development of anxiety and depression in older adults, with the dysfunction of neural circuits due to chronic stress or trauma leading to pathological symptom expression (Craske, 2012; Moitra et al., 2008). Recent evidence reporting increased levels of perceived stress in older adults during the COVID-19 pandemic (Whitehead, 2021), further demonstrates the need to understand the impact of stress during the ageing process. Many older adults also have caregiving responsibilities, and this additional chronic stress burden leads to dysregulation of the HPA axis and declined immune response in older adults (Lovell & Wetherell, 2011), giving rise to the wide range of health implications discussed earlier in this section. Higher levels of stress have consistently been linked to greater cognitive decline and memory problems (Neupert et al., 2006; Rickenbach et al., 2014) and there is a negative correlation between stress and instrumental activities of daily living (Kim et al., 2016). Self-reported pain, sleep difficulties, and poor self-rated health are also associated with higher levels of perceived stress (Luchesi et al., 2016).

The final factor relating to mental health in older adults as outlined by Lin et al. (2022) is cognitive function. The association between ageing and cognitive decline has been addressed extensively since the 1980s (Jessen et al., 2020). Cognitive decline increases with age and is almost universal, so is to be expected in the majority of older adults (Park et al., 2003). It is potentially the costliest aspect of an ageing population, in terms of financial, personal, and societal burdens (Deary et al., 2009). These changes to cognition are attributed to structural and function changes in the brain, including decline in grey and white matter in the prefrontal cortex and hippocampal volume declines, both of which underlie memory function (Hedden & Gabrieli, 2004). When cognitive function drops to a lower threshold, beyond which impairment of everyday functions is considered severe, then dementia may be diagnosed (Tucker-Drob, 2019).

Performance of instrumental activities of daily living rely on cognitive function (Brewster et al., 2017), therefore it is logical that this would also extend to everyday functioning. Worsened cognitive function has been linked to a range of debilitating outcomes such as poor driving behaviour and worse performance on a range of everyday functions (Vance et al., 2011). Further longitudinal research showed the largest effects were found for daily activities such as cleaning, large scale shopping, and using public transport, which was mainly explained by decline in processing speed, and this predicted worse functional decline overall (Classon et al., 2016). Other daily activities affected by cognitive decline include keeping appointments, remembering current events, managing finances, and organising and completing activities (Aretouli & Brandt, 2010). Most of the research in this area has related to daily activities, however research has made clear links between cognitive decline and mortality, depression, anxiety, lower sleep quality and duration, and general health (Lee et al., 2017; Salthouse, 2012).

#### 1.4.4 Good social engagement

The final facet related to successful ageing is good social engagement (Rowe & Kahn, 1987). A range of terms encompass social engagement, including social networks, social support, social activity, social integration, and social participation (de Leon, 2005). The relationship between social engagement and health in older adults is not a new concept, one of the earliest studies on the topic showed aspects of social engagement predicted mortality independent of physical health and health behaviours (Berkman & Syme, 1979). The positive relationship between social engagement and better health has been explained through both physiological and psychological mechanisms (de Leon et al., 2001; Everard et al., 2000). Predominately the physiological effects of social isolation, which can result in reduced resistance to infection and increased vulnerability to disease (Berkman & Syme, 1979; Glass et al., 1999).

Although a range of terms are used to describe social engagement, there are clear distinctions between some of these constructs. Social engagement is defined as the performance of a meaningful social role for either leisure or productive activity (Glass et al., 2006). It has been shown that older adults who participate in social activities, especially in one’s community, receive beneficial effects on wellbeing and fewer depressive symptoms (Adams et al., 2011; Chiao et al., 2011). Research has demonstrated a range of positive outcomes associated with social engagement, including lower mortality rates (Aroogh & Shahboulaghi, 2020), lower stress levels (Mackenzie & Abdulrazaq, 2021), better independent activities of daily living (Dombrowsky, 2017) and better health related quality of life (Hajek et al., 2017). Clearly social engagement is important for successful ageing and everyday functioning. Furthermore, a lack of social engagement can lead to both social isolation and loneliness (Victor & Scharf, 2005), which in themselves pose potential risks to successful ageing.

Social isolation and loneliness are often discussed in combination; however, they are distinct concepts (Perissinotto et al., 2019). Social isolation is an objective measure of the lack of social relations or infrequent social contact with others, whereas loneliness is a subjective negative feeling of being isolated (National Academies of Sciences & Medicine, 2020). A wealth of research has explored the effects of social isolation in older adults, with this growing exponentially during the COVID-19 pandemic when isolation was enforced, especially in this age range. There have been clear health implications shown with links between social isolation and the cardiovascular and neuroendocrine systems, and an increased risk of frailty (Bhatti & ul Haq, 2017; Chen et al., 2015; Mehrabi & Béland, 2020),. This may be due to reduced physical activity in those who are socially isolated (Sepúlveda-Loyola et al., 2020), longitudinally this is associated with poorer physical performance, such as worsened balance and slower walking speed (Philip et al., 2020).

As well as the negative health implications there are also negative psychological consequences of social isolation. It has consistently been shown that being socially isolated leads to higher anxiety and depression, and worse mood outcomes such as panic and emotional disturbance in older men and women, even when controlling for confounding factors (Best et al., 2021; Seifert et al., 2022; Sepúlveda-Loyola et al., 2020). Social isolation has been linked to cognitive decline in a number of domains such as comprehension, memory, attention, abstract thinking and perception, as well increased levels of psychological stress (Bhatti & ul Haq, 2017; Evans et al., 2018; Sepúlveda-Loyola et al., 2020; Zhang & Ma, 2020). Sleep problems have also been reported, including deficiency and poor-quality sleep (Bhatti & ul Haq, 2017; Hawkley & Capitanio, 2015; Sepúlveda-Loyola et al., 2020), with neural, hormonal, genetic, emotional, and behavioural mechanisms being suggested (Bhatti & ul Haq, 2017).

Although distinct concepts, those who are socially isolated are more likely to report being lonely (Freak-Poli et al., 2022). Therefore, many of the consequences of loneliness on everyday functioning also overlap with those already outlined. It is well established that the consequences of loneliness are profound, especially on health and wellbeing (Prohaska et al., 2020). In terms of health, loneliness is associated with an increased risk of developing cardiovascular disease, coronary heart disease, stroke and type two diabetes (Christiansen et al., 2021; Valtorta et al., 2018). The pooled effects of loneliness on general health outcomes have shown medium to large effect sizes in meta-analysis (Park et al., 2020). Aside from physical health, loneliness is associated with depression, anxiety, sleep problems and quality, cognitive decline, and an overall increased risk of dementia (Lara et al., 2019; Malhotra et al., 2021; McHugh & Lawlor, 2013; Park et al., 2019; Santini & Koyanagi, 2021).

## 1.5 Sex differences in everyday functioning and nutrition needs

Everyday functioning gives a direct indication of functional health and ability, which can be influenced by the markers of successful ageing discussed, but there are also sex differences. It has been well evidenced that females live longer than males (Austad & Fischer, 2016), yet have disadvantages for several measures of health. Women have higher levels of frailty, and arthritis, worse self-reported health, and a greater number of comorbidities (Ahrenfeldt et al., 2019; Crimmins et al., 2011). It is proposed that this is due to a combination of biological, behavioural, and social factors, which include sex difference in health reporting behaviour (Oksuzyan et al., 2010; Schünemann et al., 2017). Women also have higher rates of depression and anxiety disorders compared to males (Crimmins et al., 2011; Vasiliadis et al., 2020). Given that these are all associated with everyday functioning, as evidenced throughout this introduction, it is not surprising that there are also sex differences in everyday functioning. Studies focusing on independent activities of daily living as a marker of everyday function have consistently found there to be disadvantages in females, with the likelihood of having difficulties around twofold higher (Crimmins et al., 2019; Scheel-Hincke et al., 2020). Despite these sex differences, studies that have explored the role of nutritional supplementation in improving specific aspects of everyday functioning have tended to overlook sex differences. The importance of considering sex differences is further indicated by the different nutritional needs of men and women.

## 1.6 Summary of thesis aims

Nutraceutical research has largely focused on very specific outcomes in older adults which has limited applicability to the real world. Further work is needed to address broader outcome measures with clearer implications for older adults, namely, everyday functioning. There are four main domains associated with successful ageing, all of which impact everyday functioning. Natural changes due to the ageing process can lead to detriments in these markers of successful ageing which can be severe and debilitating and can result in reduced independent living in the ageing population. This increased demand consequently has societal impacts, putting pressure on different services, in particular healthcare services. Given these consequences, there is a clear need for targeted interventions to tackle the underlying biological systems which underpin these declines. This thesis aims to address these issues

Firstly, the issue with previous work in the field only focusing on a limited number of outcomes was addressed in Chapter 2. This was achieved through exploring the views of older adults using qualitative research to understand which aspects of everyday function they themselves felt had detriments, and in which areas they would like to improve. This allowed subsequent outcome measures to be derived from the population of interest. This overcame limitations in previous work, allowing outcome measures to be created using a person-centred approach and keeping study participants at the heart of the research.

Following on from the qualitative work in Chapter 2, the emerging issues were used to develop the outcome measures utilised in Chapter 3, 4, and 5. The next stage of this thesis addressed the need for targeted interventions to improve these markers of everyday functioning. Given the importance of nutrition and nutraceutical research, an age targeted multivitamin supplement was trialled in this chapter to improve everyday functioning. The links between nutrition and everyday function have been briefly covered in this introduction but will be covered in more detail in Chapters 3 and 4. Furthermore, as there are sex differences in both nutritional needs, health, and everyday functioning, which are often not acknowledged in nutraceutical research, Chapter 3 will consider sex differences in response to multivitamin supplementation. As evidenced in previous research, improvements due to multivitamin supplementation may be modulated by nutritional status, therefore this was also addressed in Chapter 3. Based on the results of Chapter 3, and the need for further work in the area, Chapter 4 aimed to understand how reported dietary intake affects markers of everyday functioning. This both gave deeper meaning to results obtained in Chapter 3 and explored how lifestyle factors, such as diet, affected these outcome measures.

Finally, Chapter 5 aimed to understand how the COVID-19 pandemic impacted markers of everyday function in older adults. Data was obtained as a consequence of imposed lockdown in which participants had completed baseline assessment pre lockdown and follow up during lockdown. This chapter moved away from nutraceutical research and instead aimed to understand the experienced effects of a pandemic and imposed isolation on everyday functioning.

In summary, Chapter 2 identified those issues that were considered important in everyday functioning for older adults. These issues became the targets for measurable outcomes in assessing the effects of a multivitamin supplementation in Chapter 3 and the additional role of dietary intake was considered in Chapter 4. Finally, in Chapter 5, the COVID-19 pandemic gave a unique opportunity to assess the impact of lockdown in a vulnerable population. Taken together, these chapters contribute to the overall aim of the thesis, to assess and improve everyday functioning in older adults.

# CHAPTER 2: WHAT OLDER FOLKS WANT: A QUALITATIVE ONLINE EXPLORATORY STUDY OF CURRENT AND DESIRED LEVELS OF EVERYDAY FUNCTIONING IN ADULTS AGED 70 AND OVER

Summary

In Chapter 1 the effects of ageing on everyday functioning were outlined in detail. However, no research to date has explored older adults' own views on their perceived levels of everyday functioning and in which areas they would like to see improvements. This qualitative study was designed to explore three main research questions:

1) What aspects of everyday functioning are you unable to do or have difficulty doing?
2) What improvements would make your life easier or more enjoyable?
3) What improvements would you expect or like to see from taking an age-targeted multivitamin product?

These questions were designed to ascertain important aspects of everyday functioning in adults aged 70 and over. Data were analysed using thematic analysis and the findings were used to inform the subsequent intervention outlined in Chapter 3.

## 2.1 Introduction

There are currently over 11.8 million people aged 65 and over in the UK, with this figure rising every year (Gilbert-Johns et al., 2020; Rutherford & Socio, 2012). As a person ages, they experience declines in physical functioning, including a loss of bone density which can increase the risk of osteoporosis, poor muscular strength, restricted flexibility, and reduced vital capacity (Amarya et al., 2015; American College of Sports Medicine, 2012). In turn, decreased levels of physical functioning are associated with problems with muscles and joints (Bowling & Grundy, 1997) which contribute to a decline in everyday functioning.

Everyday functioning, also referred to as activities in daily living, relates to how well an individual can function independently in day to day life (Patterson et al., 2001); and is an indicator of quality of life (Debes et al., 2016). Everyday functioning is strongly correlated with an individual's motor function, coordination, and cognitive function (Stern et al., 1990; Tomaszewski Farias et al., 2009). As well as the physical changes due to ageing, there are also physiological changes, in particular declines in immune system functioning. This gradual deterioration of the immune system, known as immunosenescence (Aw et al., 2007), affects many cells in the body including T cells (cell-mediated immunity and cytotoxic adaptive immunity), B cells (humoral, anti-body immunity), and natural killer cells (Valiathan et al., 2016). This decline in immune response can lead to increased susceptibility to autoimmune diseases, infection, and cardiovascular disease (McElhaney & Effros, 2009; Stern et al., 2003). Such physiological deterioration can also have a significant impact on an individual's everyday function and quality of life, again highlighting the profound effect of ageing on day-to-day life. Therefore, it is increasingly important to understand and attempt to improve everyday functioning in older adults to promote successful independent living for longer (Tomaszewski Farias et al., 2009)

There is a wealth of evidence suggesting that staying physically active can help maintain a good quality of life (Mathieu, 1999). However, many older adults state that involvement in physical activity can be constrained by debilitating health conditions, which can lead to decreased quality of life (Grant, 2001). Debilitating health can also lead to other negative outcomes such as social isolation and loneliness (Van Den Berg et al., 2016). However, this relationship is bidirectional as social isolation and loneliness can affect health via biological processes and increasing likelihood of engaging in health-risk behaviours such as smoking and being inactive (Shankar et al., 2011). Both loneliness and social isolation can, therefore, impair quality of life and well-being, and have a significant impact upon an individual's everyday functioning (Steptoe et al., 2013).

Many aspects of everyday functioning can also be affected by stress. Being exposed to stress leads to a physiological response stemming from the sympathetic-adrenal-medullary (SAM) axis and hypothalamic-pituitary-adrenal (HPA) axis (Huang et al., 2013). These are two parallel arms of the neuroendocrine system, which release the effector hormones adrenaline (SAM) and cortisol (HPA) (Lovell & Wetherell, 2011). Activation of these axes leads to the response of a variety of other physiological mechanisms, e.g., the immune and cardiovascular system, which ensures the maintenance of homeostasis during a potential threat (Mulder, 2011). This is an adaptive response acutely, but chronic over-activation of the SAM and HPA axes can result in maladaptive responses in which the interconnected biological systems overcompensate leading to negative health outcomes (Lupien et al., 2006). This dysregulation can lead to a range of negative physical and psychological consequences for the individual, for example, low mood and depression, detriments to the cardiovascular and immune system and poorer sleep, all of which can impact everyday functioning (Hawkley & Cacioppo, 2004; McEwen, 2004). An established model of chronic stress is that of caregiving, that is, those providing care for significant others that are unable to care for themselves e.g., a partner (Kuster & Merkle, 2004). Caregiving causes significant dysregulation of physiological systems leading to detrimental effects on physical and psychological health, and these effects are exacerbated in older caregivers who are already experiencing declines in functioning (Lovell & Wetherell, 2011).

Although the over-arching effects of ageing and stress on physical and psychological functioning are well-established, less is known about the individual needs and aspirations of older adults in relation to their everyday functioning. That is, how do older adults feel about their levels of everyday functioning and to what extent has ageing and stress impacted upon their ability to perform and engage in activities of necessity and leisure. Considering older adults' personal views would be advantageous in designing and testing the efficacy of interventions, which are designed to improve these functions. Adopting a more person-centred approach, will place the needs and priorities of the sample group at the centre of the research, making results meaningful and valuable to the target population.

As previously discussed in Chapter 1, multivitamin supplementation may have the potential to improve some of these detriments. As older age is associated with greater likelihood of dietary supplement use (Rock, 2007), it is important to establish what exactly users would like to gain from taking supplements. Research has indicated that users consider multivitamins to be helpful to maintain good health, and advertisements suggest they may lead to increased energy levels (Sekhri & Kaur, 2014). But there is currently no known research which specifically investigates what this population would like to improve by consuming a multivitamin. The information derived from a person-centred approach would be extremely advantageous in the designing of clinical trials to measure the efficacy of multivitamin products on these parameters, which could subsequently be used by supplement companies for marketing purposes.

Based on this, the current study aimed to understand current and desired levels of everyday functioning in those aged 70 and over and to establish what improvements they would like to see which would benefit their quality of life. This included those that provide care for another individual in order to assess the potential impact of caregiver stress upon their experiences in day-to-day life. The secondary aim was to understand what improvements individuals would expect or like to see from taking an age-targeted multivitamin product. The study has three research questions:

1) What aspects of everyday functioning are you unable to do or have difficulty doing?
2) What improvements would you make your life easier or more enjoyable?
3) What improvements would you expect or like to see from taking an age-targeted multivitamin product?

A preregistered exploratory online qualitative questionnaire was utilised to gather views of adults aged 70 and over in relation to everyday function (https://osf.io/cwj8v/). This novel methodology was chosen to expand knowledge of the needs of this group in order to further knowledge and better inform subsequent interventions.

## 2.2 Method

### 2.2.1 Design

A qualitative, exploratory online questionnaire was utilised to investigate the experiences of those aged 70 and over, the activities that they find debilitating in everyday life and any improvements they would like to see which could increase their quality of life. Qualitative methods were applied to a quantitative design. The qualitative aspects allowed free response to each question, and the proportion of participants endorsing each theme could then be quantified. Firstly, thematic analysis (Braun & Clarke, 2006) was employed to answer the set research questions. After this, percentage of participants endorising each theme was quantified, to highlight how prominent this theme was in the data.

### 2.2.2 Participants

All participants were recruited online. The survey link was shared on social media including Facebook and Twitter, through internal databases and shared by organisations associated with the target population. The survey was also shared on Prolific, an online crowdsourcing website which is a dedicated research subject pool. Prolific has clear guidelines for use, and minimum fixed payment per unit of time required to complete studies, which is shared with both researchers and participants when they sign up to the platform. Prolific collects subject characteristics upon sign up, so study specific demographics can be chosen by the researcher. To take part, participants had to be aged 70 or over; and in order to maximise the representativeness of those taking part, there were no other exclusion criteria. For demographic information see results (section 2.3)

### 2.2.3 Materials

An online questionnaire was developed and presented using Qualtrics. Demographic information was collected (age, sex as assigned at birth, caregiver status), followed by seven open-ended questions.

The first question asked participants to describe any important activities they are unable to do and what prevents them from doing these activities, followed by any activities they find difficult and why they find these difficult. The next two questions asked respondents to describe any activities they would like to do more of in everyday life that would make life easier and then more enjoyable. The next question asked participants to consider any other factors that affected their day-to-day functioning which were not covered in previous questions. The final two questions regarded multivitamin supplementation and asked participants if they were to take an age-targeted multivitamin supplement what results they would expect to see and what they would like to see (these questions were included as the results of the questionnaire were going to be used to help determine outcome measures for the subsequent multivitamin supplementation study). All open-ended questions encouraged detailed written responses and were designed to allow participants to answer freely with no predispositions or direction given.

### 2.2.4 Procedure

This study was granted ethical approval by the University Ethical Approval system at Northumbria University (granted November 2018). The questionnaire was available in paper form if participants were not comfortable using a computer to write responses. In this case, the questionnaire was printed out and sent via post to the participant to be completed on paper and posted back to the researcher who inputted responses manually. Both online and paper responses followed the same procedure.

Participants were provided with an information sheet containing full details of the study, after reading this they had to click to provide consent to take part and create a code word which could be used to identify data should the participant want to later withdraw. Participants then began the questionnaire, they were instructed to answer questions in as much detail as possible, but they could skip any questions they felt did not apply to them or they were not comfortable answering. Upon completion of the questionnaire, participants were debriefed and given the option to leave their email addresses if they would like to find out the results of the study or would like to receive further information about the subsequent multivitamin supplementation study. If participants took part via the online website Prolific, they were reimbursed £1.00 upon full completion of the questionnaire.

### 2.2.5 Analysis

All data were analysed using the six stages of a thematic analysis (Braun & Clarke, 2006) to identify key themes. The coder thoroughly read the responses (*familiarisation with data*), then coded all responses to summarise the information *(generating initial codes).* Codes were then organised into initial themes identified from the data (*searching for themes*). These themes and coded data were then considered by the researcher, who reviewed whether they were answering the set research questions (*reviewing themes).* They were then revised, defined and titled, subthemes were identified, and quotes for each theme were chosen *(defining and naming themes)*. The final phase *(producing the report)* is reported below. Within the written report, each identified theme will be supported with illustrated quotations from the data, full consideration of these themes will be explored in the discussion section.

Thematic analysis was performed to explore what improvements those aged 70 and over would like to see in everyday functioning to benefit their quality of life. The secondary aim was to decide outcome measures determined by these results for a subsequent intervention study to place the priorities of the sample group at the centre of the research. All data were analysed and coded by the principal researcher using the software programme NVivo 12 (QSR International).

Each question was analysed separately but have been grouped together based on similarity between responses to answer three main questions:

1) What aspects of everyday functioning are you unable to do or have difficulty doing?
2) What improvements would you make your life easier or more enjoyable?
3) What improvements would you expect or like to see from taking an age-targeted multivitamin product?

## 2.3 Results

A total of 288 individuals consented to participate in the questionnaire, however of these 67 did not answer any questions, leaving a final sample of 221 (118 from Prolific) participants who completed all or some of the questions. The average age of the participants was 73.88 years (SD=4.44), and there were 94 males (mean age = 74.08, SD=4.17) and 127 females (mean age = 73.73, SD=4.65). A sub-sample of 25 participants identified as current caregivers and 42 as previously being caregivers. On average participants reported being a caregiver for 8.8 years, SD= 7.23 (current caregiver) and 7.31 years, SD 8.03 (previous caregiver). Hours of care per week were reported as 60.69 (SD=63.54) and 83.86 (SD=67.54) respectively.

**Research Question 1: What aspects of everyday functioning are you unable to do or have difficulty doing?**

For percentage of participants endorsing each theme, see Table 2.1.

**Theme: Walking**

The first theme in regard to difficulties in everyday functioning was the ability and ease of walking:

*Participant A: 'My main 'problem' is that I cannot walk for the many miles I used to be able to walk; 2-3 miles is about my limit.'*

The main reason cited for the restrictions on walking was due to bodily pains, particularly in joints:

*Participant B: 'I currently cannot walk very far without groin, knee and back pain.'*

*Participant C: 'Walking for long distances due to hip pain at times.'*

**Theme: Sexual activity**

Participants highlighted how they now found sexual activity difficult or were unable to engage in sexual activity altogether, despite still wanting to do this:

*Participant D: '(cannot do…) have sex as I had a stent fitted due to an abdominal aorta aneurysm.'*

*Participant E: 'Sex with partner due to medication.'*

Issues with impotence were identified as a potential cause of these problems:

*Participant F: 'sexually I find it difficult to get an erection/maintain an erection.'*

*Participant G:* 'prostate cancer and hormone therapy to delay its advance'.

**Theme: Recreational Activities**

Participants also reported that they had problems with or were unable to fully partake in a wide range of recreational activities.

Subtheme - Hobbies and social activities

Participants discussed a variety of recreational activities which they were no longer able to engage in. This included restrictions with travelling:

*Participant H: 'I used to travel a lot but now because of my own health problems I have had to curtail.'*

Health problems were cited as a restriction for being able to attend the cinema, theatres, concerts, or lectures for enjoyment. One of the most cited reasons was hearing problems and how this can cause embarrassment, or it may seem like an activity was a waste of finances:

*Participant I: 'We don't go to the cinema very much now as I have hearing damage. Wife says it is a waste of money'*

Reading for enjoyment was also hindered and this was often due to issues with vision:

*Participant J: 'It is now becoming increasingly difficult to read as, even with prescription reading glasses, it no longer feels normal'.*

Caregiver responsibilities were highlighted as an additional barrier to engaging in recreational activities:

*Participant K: 'as my wife is unable to board a coach we are both unable to go on excursions whether that be for a short break holiday or a one day break with friends.'*

*Participant L: 'I would like more time to myself, to get away more, walking, travelling and touring, but have a 99 year old mother in law and a 95 year old mother.'*

Subtheme - Exercise

The impact of health conditions on different types of exercise were displayed throughout:

*Participant M: 'Badminton/squash no longer able to play because of osteo-arthritis in both knees'*

*Participant N: 'Have stopped doing a martial art due to some ageing stiffness'*.

Other aspects that were discussed in terms of preventing exercise included a shortness of breath and pain caused by previous injuries:

Participant O: '*I can only manage the warm-up to exercise, by which time I have to stop because of breathlessness'*

*Participant P: 'Exercise classes and long walks due to injuries to both shoulders and knee'.*

Another issue which was identified was the fear of falling which restricted the ability to undertake exercise due to anticipated risk:

*Participant Q: 'I can partake some days, then sometimes get worried about falling down on other days'*

*Participant R: 'I would like to go swimming but would be virtually impossible - might fall.'*

**Theme: Household tasks**

Participants discussed a range of household tasks they were no longer able to complete, with fear of falling being a predominant reason:

*Participant S: 'I do not now feel very safe on ladders so avoid any work that involves them'.*

*Participant T: 'Up until about three years ago I did my own DIY, painting and decorating, easy carpentry. I can't do this now; I am nervous of climbing stepladder'.*

Most of the household tasks could be considered 'heavy' household activities which require a moderate level of strength, or which could exacerbate physical pain:

*Participant U; 'I find hoovers and hoovering very awkward and cumbersome'*

*Participant V: 'making beds, ironing, hoovering, the sheer effort of doing these things make my back ache more than it does'.*

Issues with gardening were also highlighted as part of this theme:

*Participant W: 'Gardening, because I am no longer strong enough to do the heavy work'*

*Participant X: 'Gardening is more difficult as I cannot bend easily or kneel down.'*

**Theme: Activities using mobility and strength**

Participants also discussed a range of difficulties due to restrictions in physical mobility and strength including difficulties kneeling down and standing back up from a sitting position:

*Participant Y: 'I am now unable to kneel or crouch'*

*Participant Z: 'Getting up from a sitting position. Need to hang on to something to get me up.'*

Consequences due to loss of strength were also reported:

*Participant AA: 'Cannot carry heavy shopping bags. Not enough strength'*

*Participant AB: 'Heavy lifting or moving furniture. I do not have strength'.*

Loss of strength was also discussed in terms of grip strength, particularly opening jars and preparing meals:

*Participant AC: 'I have difficulty opening bottles etc due to arthritis in my (dominant) left hand'*

*Participant AE: 'Peeling vegetables, especially those that are hard, like Swedes, carrots, parsnips and even potatoes sometimes'.*

Fear of falling due to restricted mobility was also discussed:

*Participant AF: 'I have balance problems and am very unsteady at times.'*

*Participant AG: 'I also have poor balance, which makes going downstairs without a handrail difficult/dangerous.'*

**Table 2.1.** Percentage of participants endorsing each theme, in relation to research question 1.

| Theme | Percentage of participants endorsing this theme |
|---|---|
| Walking | 40% |
| Sexual activity | 25 % |
| Recreational activities: | |
| *Hobbies and social activities* | 18% |
| *Exercise* | 14% |
| Household tasks | 25% |
| Mobility and strength | 25% |

**Research Question 2: What improvements would make your life easier or more enjoyable?**

It is not surprising that there is considerable overlap in the themes identified as problematic in question 1, and the themes related to making life easier and more enjoyable, in question 2. However, these themes will be discussed with relevance to question 2 specifically.

For percentage of participants endorsing each theme, see Table 2.2.

**Theme: Ability to do more enjoyable activities**

Participants discussed a variety of different activities they would like to engage in that would make their daily life easier and more enjoyable. The most cited was an increase in the amount of social interaction they had. This was particularly discussed in relation to interaction with grandchildren/ great grandchildren:

*Participant A: 'if it wasn't so difficult for me to walk far I could see more of my great grandchildren as I did before I was ill. I used to enjoy taking them to school and then fetching them home in the afternoon'*

*Participant B: 'I would like to be able to be more active with my grandchildren and to generally be able to carry them further and to be more able to take them on walks and go on uneven ground in the countryside and be able to get up and down on the floor with more agility.'*

As well as limited social interaction with family there was a lot of discussion about how increased social interaction with peers would make daily life more enjoyable or easier:

*Participant C: 'I would like to meet more people with the same interests as me. But I find most people my ages are already old in their minds.'*

There was also discussion about being restricted in travelling and how being able to do this would improve quality of life:

*Participant D: 'I should like to go out more on bus or train rides as I enjoy the travelling, not necessarily the destination. At present, such trips have wound down to being practically non-existent because of the physical effort needed around the actual travelling activity itself.'*

*Participant E: 'Go on holidays without having to take medical stuff.'*

**Theme: Improvements Walking**

It was suggested that improvements in walking would make life easier for a number of reasons:

*Participant F 'I would like to be able to walk long-ish distances without the pain that currently limits me. I could then enjoy rambles, the ability to not have to worry about distances I might need to walk at destinations, and of the highest importance, the ability to burn calories whilst walking and so lose that extra weight I shouldn't be carrying'*

Another aspect that was discussed was that walking without getting as tired would make life easier:

*Participant G: 'Impossible I'm sure......but if everyday walking didn't make me so tired it would be easier to achieve more in a day'*

*Participant H: ‘if everyday life didn't make me tired I could join in activities that involve walking or standing a lot. This would make my social, and family life more varied.’*

**Theme: Exercise**

One particular type of exercise which was highlighted as important to improve daily life was Yoga/Pilates and the positive implications this had for the individual:

*Participant I: ‘I'd like to do a second Pilates session every week to keep me mobile but most of all to give me confidence that I'm doing my best to maintain my core strength’*

*Participant J: ‘More Pilates to keep body supple’*

There was also discussion around the beneficial mood effects of exercise:

*Participant K: ‘Swimming, I used to love swimming it made me feel free, as if I had no cares’*

**Theme: Improved health and mobility**

The final theme in response to what improvements would make life easier or more enjoyable was a general improvement in different aspects of physical health and mobility. One of the main aspects discussed would be to have an improved mobility to be able to kneel and bend down:

*Participant L: ‘I would like to be able to get down on my knees easier.’*

*Participant M: ‘Being able to get up and down without "creaking”.’*

There were other aspects of physical movement and mobility that were impaired and consequently led to a fear of falling:

*Participant N: ‘I have tried a Staying steady course, but it seems to have made no difference.’*

*Participant O: ‘I find it more difficult to get in and out of the bath and am afraid of falling if alone in the house.’*

Another aspect which was reiterated from previous themes was that an improvement in grip strength would make life easier:

*Participant P: 'I'd like more independence that is doing things for myself instead of having to ask my husband - such as opening a bottle of water!'*

The final aspect discussed under this theme was that having less bodily pain would improve the ability to complete different daily tasks:

*Participant Q: 'Be pain free - which would make my mobility much better - then I could walk to the shops - then I could kneel down - then I could do housework'*

**Table 2.2.** Percentage of participants endorsing each theme, in relation to research question 2.

| Theme | Percentage of participants endorsing this theme |
|---|---|
| Ability to do more enjoyable activities | 34% |
| Improvements walking | 26% |
| Exercise | 24% |
| Improved health and mobility | 20 % |

**Research Question 3: What improvements would you expect or like to see from taking an age-targeted multivitamin product?**

For percentage of participants endorsing each theme, see Table 2.3.

**Theme: No Improvements**

One strong idea throughout the data in response to this research question was the idea that there would be no improvements from consuming an age-targeted multivitamin product. Participants discussed how they would not expect to see any improvements:

*Participant A: 'Probably none as I'm currently healthy so any improvements would be minimal and probably indiscernible'*

There was also a lot of scepticism around multivitamins as a whole. Participants felt cynical about the claimed abilities of these supplements;

*Participant B: 'Debatable - but I am cynical - I would think it was a con trick - I wouldn't expect to see any physical improvement or memory improvement.'*

*Participant C: 'not too sure any, often suspect claims for multivitamin offerings as hype.'*

It was also apparent that many participants believed their diet was sufficient and provided all necessary nutrients so there would be no additional benefits:

*Participant D: 'not sure that I would see anything as I consider that my diet is very good and I get all the necessary nutrients to maintain a healthy life balance'*

*Participant E: 'None, I eat a good mixed diet of freshly prepared food'*

This highlights how some older adults prefer getting required nutrients from their diet rather than supplements, and do not see the benefits that multivitamins can offer.

**Theme: Energy and Sleep Improvements**

Participants discussed how they would like to experience a general increase in energy levels:

*Participant F: 'I would love to have more energy.'*

*Participant G: 'I'd hope to get some improvement in energy.'*

It was also suggested decreased feelings of tiredness would be desired:

*Participant H: 'More energy and not feeling so tired all of the time'*

*Participant I: 'Reduced tiredness at the end of a day.'*

There was also a want for improved sleep, which could be a potential cause for both the poor energy levels and feelings of tiredness discussed:

*Participant J: 'something to make sleep easier.'*

*Participant K: 'I would like to be able to sleep better.'*

**Theme: Physical Appearance**

The next theme was improvements in their physical appearance. This was discussed in a range of contexts but most prevalent was an improvement in the appearance of skin;

*Participant L: 'Less wrinkles and smoother skin'*

*Participant M: 'anti-visible ageing, better skin condition'*

Within this theme participants also discussed how they would like a multivitamin to be able to assist with weight loss/control:

*Participant N: 'Better weight control'*

*Participant O: 'Weight loss would be nice but perhaps not possible'*

**Theme: Improved Mood**

Participants would like to experience an improvement in their mood and wellbeing, and specifically they would like to feel happier in day-to-day life:

*Participant P: 'I would not take a tablet like that but I would like it to make people happier.'*

*Participant Q: 'Improved mental wellbeing.'*

*Participant R: 'Better general and mental health.'*

Within this theme there was also a discussion around wanting to have a more positive outlook on life:

*Participant S: 'Most importantly I would like to feel more positive about life in general.'*

*Participant T: 'Being able to enjoy life as it used to be.'*

**Theme: Physical Health**

The final theme related to an improvement in a variety of physical health outcomes, the most cited was that participants would like to see improvements in joint movement, flexibility and function:

*Participant U: 'More flexible joints and less joint pain'*

*Participant V: 'I would like to see improvement in my joints with less pain and more mobility.'*

*Participant W: 'maybe they would help my joints. I have a lot of pain in my knees when walking.'*

There was also discussion of more general improvements in physical mobility:

*Participant X: 'A complete return to the mobility I had before I became chronically ill.'*

*Participant Y: 'Be able to sit down and get up again without assistance.'*

Within this theme participants also discussed how they would like to feel less bodily pain after consuming a supplement:

*Participant Z: 'I would like it to make my body feel younger, have less aches and pains.'*

*Participant AA: 'To make a difference in how I feel and make all the aches and pains go away.'*

As well as physical improvements there was also discussion around biological and immune response:

*Participant AB: 'I would also expect that it would help strengthen the body to reject the infection of influenza or the common cold.'*

*Participant AC: 'Improved resistance to infection'*

**Table 2.3.** Percentage of participants endorsing each theme, in relation to research question 3.

| Theme | Percentage of participants endorsing this theme |
|---|---|
| No improvements | 37% |
| Energy and sleep improvements | 35% |
| Physical appearance | 14% |
| Improved mood | 14% |
| Physical health | 55% |

## 2.4 Discussion

### 2.4.1 Research Question 1 and 2

The current study is the first to explore the current levels of everyday functioning in those aged 70 and over and the improvements they would like to see in order to benefit their quality of life. Exploratory online questionnaires, analysed using thematic analysis, found that the main aspects of everyday functioning those aged 70 and over were unable to do or had difficulties doing were walking, sexual activity, recreational activities, household tasks, and general activities involving mobility and strength. The main improvements they would like to see to make life easier or more enjoyable were the ability to do more enjoyable activities, improvements in walking, being able to partake in exercise, and improved health and mobility.

The ability to engage in sexual activity was placed with high importance in this sample. This has commonly been found with older adults who have a current sexual partner attributing importance to sex (Gott & Hinchliff, 2003). It has been previously suggested that the importance of sexual activity decreases when experiencing medical barriers, but results of the current study showed that it remained importance despite facing the common medical issues found in older adults (such as prostate issues, stents and medication affecting impotence) (Tetley et al., 2018). Sexual difficulties in older adults can have a negative impact on psychological wellbeing (Hinchliff et al., 2018) and therefore represents an important area that needs to be addressed. An increased conversation around older adult’s sex life is therefore, needed for those with health problems who may need advice in how to mitigate the impact on their sex life. Health practitioners are best placed to initiate these discussions as they are likely to have the most opportunity, however, previous work shows that they are reluctant to do so (Gott et al., 2004).

As well as impacting sexual activity, health problems were also discussed as a barrier to completing recreational and enjoyable activities. These activities provide opportunity for enjoyment and socialising and being unable to do this led to feelings of frustration and isolation. Engaging in hobbies (both socially and independently) is one of the key issues identified as helping to alleviate loneliness in older adults (Smith, 2012). Furthermore, not engaging in hobbies is also associated with a higher risk of mortality and decline in activities of daily living (Tomioka et al., 2016). Being a caregiver in this population led to additional restrictions in partaking in recreational activities. This was attributed to either the health requirements of the person they provide care for as being too great to permit this, or not having the time alongside their caregiving duties to do other activities. As previously indicated increased feelings of burden in caregivers of those with Alzheimer's disease leads to decreased participation in desired activities (Hwang et al., 2009). This study provides evidence that interventions and further support are required to enhance opportunities and access to meaningful and important recreational activities for both older adults and older adult caregivers who may need more support to do this.

In terms of activities that were desired, being able to do more exercise was one of the most discussed, for both physical reasons and to improve mood. Extensive research has shown the positive effects of exercise on mood states including the reduction of anxiety, stress, and depression through physiological, biochemical, and psychological mechanisms (Mikkelsen et al., 2017). This is particularly important as depression and anxiety are commonly seen in the ageing population, and forms of exercise have been shown to significantly decrease these mood problems (in postmenopausal woman) (Abedi et al., 2015). Engaging in exercise can also elicit benefits elsewhere including cognition and reaction time (Boyle et al., 2020), indicating the importance of exercise on a range of psychological outcomes in older adults.

Physical deterioration is a recurring cause of many of the detriments experienced in everyday functioning. Loss of strength and physical pain restricted strenuous activities that require moderate levels of strength (e.g., vacuuming or changing beds). The other main cause cited for this inability to do household work was fear of falling, which is likely interlinked as declining muscle mass, strength and power are contributing factors to increased fear of falling (Trombetti et al., 2016). It was not clear whether this was due to previous experience of falling or anticipated fear; this may be an issue as those with a fear of falling have a higher risk of falling and reduced activities of daily living (Vellas et al., 1997).

Mobility issues were also highlighted as an underlying cause for many of the everyday activities' participants were unable or had difficulty completing. It has been established that mobility limitations result in higher dependence for daily activities and decreased quality of life (Metz, 2000; Yeom et al., 2008). Difficulties kneeling and standing up from a sitting position were commonly discussed and are an integral part of many common everyday activities such as gardening, shopping, and cleaning (Hernandez et al., 2010). Another key prominent aspect was declining grip strength, which affects daily activities such as opening jars, carrying shopping, and preparing meals. Lower grip strength is correlated with worse functional, psychological, and social health, and an accelerated decline in activities of daily living (Kozakai, 2017; Taekema et al., 2010), and may also be a useful proxy to determine overall physical fitness and wellbeing (Cesari et al., 2012).

Based on the evidence that physical issues are the underlying cause of the difficulties highlighted, it is suggested that targeting decline in muscle strength and mobility could be crucial in enabling older adults to continue completing the everyday activities previously discussed as a detriment in their life. When highlighting the desire to engage in exercise both Yoga and Pilates were cited most, due to the physical benefits associated such as increased mobility and strength, feeling more supple, and an improvement in balance. Exercise interventions, such as Pilates, have been shown to improve balance, lower limb strength, and flexibility (de Souza et al., 2018). Furthermore, exercise interventions in the community can reduce fear of falling (Kendrick et al., 2014) and fall risk (Pata et al., 2014). This may, therefore, be a suitable intervention for older adults which could help improve different aspects of everyday functioning.

### 2.4.2 Research Question 3

The current study is also the first to use a qualitative approach to explore both the expected and desired outcomes associated with taking an age-targeted multivitamin product. Results from thematic analysis found participants expected either no improvements; or improvements to energy/sleep levels; physical appearance, mood, and physical health.

There was a general scepticism of multivitamin products shown in the data. Participants indicated that they believed advertised benefits are overexaggerated compared to actual results. Given intervention studies often present disparate results which are commonly mistranslated in the media (Perez, 2011), it is important that research trials are accurately explained for a lay audience. Accuracy in marketing will ultimately lead to long lasting relations with consumers (Schmidt, 2011), and this may help overcome the scepticism shown.  A preference for getting nutrients directly from diet was also shown, in the context of not seeing any improvements from a multivitamin. It Is suggested nutrient intake should be met primarily through a balanced diet due to additional benefits of diet such as energy, protein, fatty acids and fibre which cannot be addressed via supplementation (Marra & Wellman, 2008). Furthermore, individuals consuming recommended levels of vitamins through their diet are unlikely to achieve any additional health benefits from supplementation (Marra & Wellman, 2008). However, supplementation should be encouraged when individuals do not comply with recommended daily amounts of nutrients or are at risk of vitamin deficiency (Thomas, 2006). Undernutrition occurs more frequently with age and older adults often suffer from vitamin deficiency (particularly Vitamin B12 and D) (Biesalski & Tinz, 2017). Taken together this may suggest there needs to be more emphasis and marketing specifically targeting this population.

Along with the potential for vitamin deficiency, feelings of fatigue are often self-reported by older adults (Zengarini et al., 2015). Accompanied by changing sleep patterns and difficulties initiating or maintaining sleep (Crowley, 2011), it is unsurprising that improvement in this area was desired. There is evidence showing multivitamin supplementation can reduce feelings of fatigue in those with chronic fatigue syndrome (Maric et al., 2014), and increase energy levels (Sarris et al., 2012) and improve self-reported sleep quality in elderly subjects (Wouters-Wesseling et al., 2003). However, contrasting research has shown multivitamin supplementation was associated with poorer sleep, including more awakenings, higher total wake time during the night and higher rates of insomnia (Lichstein et al., 2007). Furthermore, administration of a vitamin B complex supplement has been shown to lead to worse self-reported sleep quality and higher tiredness on waking (Aspy et al., 2018). Thus, highlighting the need for future research to investigate multivitamin supplementation on sleep and energy levels, particularly in older adults.

Age related changes in sleep have been found to be a contributing factor to poorer mental health (Gadie et al., 2017) and it was expressed by participants they would like to see mood altering effects from a multivitamin. Many of the earlier themes related to detriments to health and poorer health can lead to unhappiness (Liu et al., 2016), providing a further potential reason there may be a need for mood improvements in this sample. Early research showed short term multivitamin supplementation had little effect on mood in healthy older adults (Cockle et al., 2000), however it was suggested there may be more promising results if the supplementation period was longer, or the participants had poorer nutritional status at baseline. Further research exploring multivitamin supplementation in older adults has shown improvements in mood 1-2 hour post dose (Macpherson et al., 2015), improved ratings of stress measured several hours after dose (Macpherson et al., 2016) and significant reductions to a depression anxiety and stress scale following 8 weeks supplementation (Harris et al., 2011) These findings suggest multivitamin supplementation may have the ability to elicit mood improvements, but this warrants further research particularly in those with poorer nutritional status.

Alongside improvements in mental health there was a desire for improvements in physical health.  This is logical given the physical detriments highlighted in research questions 1 and 2; in particular, issues with joints, flexibility, and mobility. There is potential in this area as multivitamin supplementation has been shown to improve mobility in postmenopausal women (measured via habitual walking speed) (Strike et al., 2016). Moreover, a recent meta-analysis of randomised controlled trials provided evidence that multivitamin supplementation can significantly improve certain aspects of mobility (chair raise time and handgrip strength), particularly in non-healthy participants (Veronese et al., 2019). It was also suggested that improvements in immune function would be desired/expected after supplementation, with particular emphasis on resistance to common colds, flu, and infection. Early reviews indicated supplementation can enhance immune function in older adults but for some nutrients there is indication that high doses are not beneficial suggesting an inverted U-shaped relationship (Mitchell et al., 2003). Again, it was suggested the nutritional status of the population needs to be taken into consideration before randomisation. However, further reviews have suggested most of the evidence to support this relationship is weak and conflicting (El-Kadiki & Sutton, 2005) and low bias studies indicate no benefit from the use of multivitamin supplementation for preventing infection in older adults (Sternberg & Roberts, 2006).

Finally, participants wanted to see improvements in their physical appearance, including less signs of visible ageing. Nutritional status is important for skin health and appearance and is vital for maintaining normal functioning for processes such as collagen synthesis (Park, 2015). Intake of vitamin C (both dietary and supplementary) has been associated with better skin ageing, improved skin elasticity, hydration, and radiance (Cosgrove et al., 2007; Costa et al., 2015; Segger & Schönlau, 2004). Although no research to date has specifically looked at multivitamin supplementation on skin ageing, supplements containing carotenoids, polyphenols, probiotics and ginseng have shown to have positive effects on appearance (Pezdirc et al., 2015). Therefore, a multivitamin containing these active ingredients may elicit similar effects, but further research is needed to verify these claims. Within this theme there was also discussion around how it would be desirable for a supplement to aid in weight loss or weight control. Observational research has shown that men who regularly consume vitamin and dietary supplements tend to have a lower body weight than those who do not consume these supplements (Major et al., 2008). However, there is no direct evidence that supplementation can enhance weight and fat loss, which was considered by participants even when desiring this outcome.

The current study has a number of strengths. It is the first to use a qualitative methodology to further understand the current and desired levels of everyday functioning in older adults aged 70 and over. The perceived and desired outcomes from consuming a multivitamin supplement were also assessed. This has increased knowledge in the field, and by taking a person-centred approach, has highlighted some of the key challenges faced by this population. The results from this study could be used to inform researchers, clinicians, and policy makers when designing interventions targeting the areas raised as important themes. Where evidence exists on these themes, this information could also be used by supplement companies for targeted advertising. The methodology employed here is suggested as a beneficial starting point for designing subsequent research and ensuring outcome measures are directly relevant to the needs and priorities of the sample population.

The findings should be considered in light of some limitations. Firstly, although the questionnaire was available as a paper copy in some instances, most data collected was predominately online. As older adults vary in their internet ability, with those from less-privileged backgrounds having lower skills and less likelihood of engaging with this type of online activity (Hargittai et al., 2019) it is possible that responses may be biased to those in the population who can engage effectively with the internet and may not represent diverse views in this population. Furthermore, as the study used qualitative exploratory methods, conclusions are specific to this sample and not definitive to the overall population. However, these data still provide valuable information that otherwise has not been collected. Future research is warranted based on the results found and have been suggested throughout.

### 2.4.3 Overall Conclusions

The current study used an exploratory online qualitative questionnaire to understand current and aspired levels of everyday functioning in adults aged 70 and over. Key themes were identified to answer the research questions set. This has expanded knowledge on the individual needs and goals of older adults which have not previously been explored. There are clear underlying issues pertaining to health and mobility, which would be beneficial to address in this population and the results presented have clear implications for a range of individuals, which have been discussed throughout. Taking this type of approach to research is viewed as an advantageous novel approach to subsequent research design.

# CHAPTER 3: THE EFFECT OF A 12 WEEK MULTIVITAMIN SUPPLEMENT ON EVERYDAY FUNCTIONING IN OLDER ADULTS: A DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUPS TRIAL

Summary

In this chapter the results of a 12-week multivitamin supplement trial on everyday functioning in adults aged 70 and over is presented. Within this introduction, the biological mechanism of effect of vitamins and minerals on the outcomes of everyday functioning highlighted in Chapter 2 are discussed. The literature shows promising results from previous multivitamin trials; however, exclusion criteria in previous research has been very restrictive, resulting in participants that aren't representative of the population being studied and there has been little research considering nutritional intake at baseline. The current study has addressed these issues by having minimal exclusion criteria for participation to maximise representation and by including food frequency measures to derive habitual vitamin and mineral intake. Results from the intervention and interactions between treatment and habitual nutritional intake are reported in this chapter.

It was shown that multivitamin supplementation led to increased feelings of friendliness in females. In males there was lower levels of prolonged, and overall stress reactivity, and lower emotional loneliness, following multivitamin. Various interactions were found between reported dietary intake of micronutrients and multivitamin. Leading to questions regarding the effect of nutritional intake on outcome measures at baseline before supplementation, which will be reported in Chapter 4.

## 3.1 Introduction

Dietary supplementation has increased in the United Kingdom over recent decades (Lentjes, 2019). Sales of over-the-counter vitamins and minerals grew by 14.3% in 2020 with sales value being around £495 million (PAGB, Consumer Health Association, 2020). The National Diet and Nutrition Survey estimated 23% of adults aged 19-64 and 39% of adults aged 65 years and over are taking at least one dietary supplement (Department of Health and Social Care, 2012). Improving overall health and wellness, filling nutrient gaps in diet, immune health, healthy ageing, and increasing energy have been listed as motivations for consuming dietary supplements (Dickinson et al., 2014). While the most popular supplements in older adults aged 65 and over are fish liver oils (Denison et al., 2012), multivitamin supplements are favoured in younger adults (Radimer et al., 2004).

The terms multivitamin/multimineral/multi-nutrient supplements are used commonly but there is no standard definition, and the terms can refer to any products with varied compositions and characteristics (for the purpose of this thesis multivitamin will be used) (Yetley, 2007). In the UK, dietary supplements may contain ingredients including vitamins, minerals, amino acids, essential fatty acids, fibre, and plant and herbal extracts (Food Standards Agency, 2021). Therefore, multivitamins may contain a combination of these ingredients. Multivitamins sold commercially in the UK often contain amounts of vitamins and minerals approximating the Nutrient Reference Value (EU guidance on the average daily amount needed of each vitamin/mineral to prevent deficiency) (Mason, 2007).

In the UK the leading vitamin brand is Vitabiotics Ltd, London, with their multivitamins being the biggest seller, for both men and women. Their general multivitamin formula (for women) contains starflower oil, evening primrose oil, citrus bioflavonoids, beta-carotene, vitamins D, E, K, C, B1, B2, B3, B6, B12, folic acid, biotin, pantothenic acid, magnesium, iron, zinc, copper, manganese, selenium and chromium. The male formula also contains the additional ingredients siberian ginseng extract, coenzyme Q10, L-Carnitine, L-Arginine, L-Methionine and silicon, which gives an indication of the varied components included in a popular commercially sold multivitamin product.

This introduction aims to outline various factors and functions related to multivitamin supplementation in older adults. This includes bioavailability, physiological effects, health benefits and effects on various aspects of everyday functioning.

### 3.1.1 Bioavailability

For substances acting within the body, bioavailability is considered the quantity of an administered dose that enters circulation and is not metabolised, complexed or excreted before exerting its biological effect (Heaney, 2001). However, currently there is no standardised scientific definition of bioavailability in regard to dietary supplements (Yetley, 2007). The metabolism of multivitamin supplements differ compared to foods due to various nutrient-nutrient interactions, so the definition used in those fields cannot be applied to these supplements (Comerford, 2013). As the bioavailability of individual vitamins and minerals is well established in literature this will briefly be considered before discussing multivitamin supplements specifically. It must also be noted that the majority of this evidence does not come from older adults. Therefore, the results discussed may not be representative of the bioavailability in older adults.

#### 3.1.1.1 Beta carotene

Vitamin A is needed for many functions in the human body such as proper immune function and growth development (Grune et al., 2010). Humans cannot synthesize vitamin A de novo, so adequate amounts need to be consumed from the diet in the form of carotenoids (found in dark leafy green vegetables and orange and yellow fruits and vegetables) which have provitamin A activity (Haskell, 2012). There are around 60 carotenoids found in human diets, but only alpha-carotene, beta-carotene, gamma-carotene and beta-cryptoxanthin have been identified as having provitamin A activity (Grune et al., 2010). Of these, beta-carotene has the highest vitamin A activity, potentially twice that of the other provitamin A carotenoids (Weber & Grune, 2012). This is due to its chemical structure; beta-carotene is symmetrical, so one molecule can theoretically yield two molecules of vitamin A (Weber & Grune, 2012).

Despite this superior activity, maximum absorption directly from natural sources is still too low to reach recommended intake, due to consumption of fruit and vegetables being low in the population (Haskell, 2012). Low bioavailability is due to resistance of carotene-protein complexes and plant cell walls during digestion to allow adequate release (Rein et al., 2013). Therefore, it has been suggested that beta-carotene should be extracted and isolated for delivery as a supplement to improve bioavailability (Donhowe & Kong, 2014).

#### 3.1.1.2 B-vitamins

The B-vitamin complex used within this thesis comprises of eight water soluble vitamins: thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), vitamin B6, biotin (B7), folic acid (B9), and vitamin B12. They are grouped together due to their water solubility and the ubiquitous and interacting cellular coenzyme roles they play, being precursors in the majority of cellular functions (Huskisson et al., 2007; Kennedy, 2016). Overall functions can be split into two main roles: catabolic metabolism (generation of energy) and anabolic metabolism (construction and transformation of bioactive molecules) (Kennedy, 2016). All the B vitamins (except folate) are involved in at least one of the energy production systems within a cell (Tardy et al., 2020). They play a direct role in the citric acid cycle, the electron transport chain and the formation of adenosine triphosphate (ATP) which is used for energy in a cell (Kennedy, 2016), this supplies the majority of the energy required for survival, repair and growth (Ramsay, 2019).

Water- soluble vitamins are absorbed via diffusion and are not stored in the body (therefore they need to be supplied daily via diet) (Bellows et al., 2012). These vitamins diffuse through the intestinal walls into the bloodstream, the environment of the intestinal lumen make absorption direct (Combs Jr & McClung, 2016; Ofoedu et al., 2021). All of the B vitamins (except riboflavin) are absorbed via passive diffusion, with riboflavin being absorbed via a carrier dependent mechanism to overcome concentration gradient (Said, 2011). Clinical studies have shown significant increases in serum levels of each B vitamin following supplementation, indicating high levels of bioavailability (Lindschinger et al., 2019), but also highlighting sub-optimal B vitamin status in the populations studied (Kennedy, 2016).

#### 3.1.1.3 Vitamin C

Vitamin C (also known as ascorbic acid with terms used interchangeably) is synthesised by all plants and most animals (Smirnoff et al., 2001). Humans cannot synthesise vitamin C as the enzyme required for the last step is not functional, therefore it needs to be consumed via dietary intake (Du et al., 2012), and, like the B vitamins, vitamin C is water-soluble. Due to its chemical nature vitamin C is an electron donor (commonly called an antioxidant) which protects cell components against free radicals formed during metabolism (Kaźmierczak-Barańska et al., 2020; Padayatty & Levine, 2016). It is also a cofactor function to several enzymes required for the synthesis of amino acid derived macromolecules, neurotransmitters and neuropeptide hormones (Englard & Seifter, 1986; Padayatty & Levine, 2016).

Vitamin C is absorbed from the lumen of the intestine and renal tubules, facilitated by enterocytes and renal epithelial cells respectively (Wilson, 2005). From here it is circulated in the blood and enters all of the other cells in the body to exert its effects (Wilson, 2005). It is found in particularly high concentrations in the pituitary and adrenal glands (Carr & Vissers, 2013). A review of studies in humans has shown no differences in bioavailability between synthetic supplemented vitamin C and natural vitamin C from food source, regardless of subject population, study design or intervention used (Carr & Vissers, 2013).

#### 3.1.1.4 Vitamin D

Vitamin D has well established roles in immunity and bone metabolism and is inversely associated with the incidence of several diseases for example, rickets (Borel et al., 2015). There are two main forms of vitamin D. Vitamin $D_2$ (ergocalciferol) is obtained from plants, particularly mushrooms and yeast (Balachandar et al., 2021). Vitamin $D_3$ (cholecalciferol) is acquired from exposure to sunlight (synthesised de novo in the skin when exposed to UV-B radiation), and through dietary intake found in animal food sources, such as flesh of fatty fish, beef liver, dairy products, and egg yolk, with this this form being better absorbed in humans (Balachandar et al., 2021; Borel et al., 2015; Del Valle et al., 2011). Vitamin D is a fat-soluble vitamin and absorption follows the same process as all major lipids (Balachandar et al., 2021; Tso & Fujimoto, 1991) including emulsification, dissolution in miscelles, diffusion through the unstirred water layer, and permeation across the enterocyte's membranes (Maurya & Aggarwal, 2017). Once absorbed from the intestine this is metabolised in the liver (to calcidiol), with predominant effects exerted through the endocrine and autocrine actions of calcitriol via activation of vitamin D receptors in cells (Kennel et al., 2010).

Deficiency of vitamin D is often addressed via supplementation (Thacher & Clarke, 2011). Vitamin D supplements which are microencapsulated have been shown to improve absorption efficiency in rats (Šimoliūnas et al., 2019). This has been repeated in patients with polycystic ovary syndrome, with microencapsulated vitamin D showing better absorption than other forms of vitamin D supplementation (Yanachkova et al., 2021). Thus, highlighting the beneficial effects of supplementation of vitamin D, particularly in microencapsulated form.

#### 3.1.1.5 Vitamin E

The term vitamin E is a generic term covering eight naturally occurring fat-soluble compounds (α-, β-, γ-, δ-tocopherol, and α-, β-, γ-, δ-tocotrienol) (Mène-Saffrané & DellaPenna, 2010; Meydani et al., 2018). Vitamin E mainly acts as an antioxidant, can be a pro-oxidant, and has non antioxidant functions such as being a regulator of gene expression (Schneider, 2005). Of the different compounds, α-tocopherol is the most abundant and biologically active form of vitamin E, the other forms do not contribute to vitamin E requirement because they are not converted to α-tocopherol in humans and are therefore not recognised by the transfer protein in the liver (Meydani et al., 2018; Schneider, 2005). Vitamin E follows the principal pathway of other lipid soluble vitamins, transported by miscelles in the intestine, from the blood it is transported either to extrahepatic tissues or to the liver (Galli et al., 2017).

Evidence suggests there is variance in bioavailability of vitamin E supplements. Research has suggested that natural source vitamin E has approximately twice the bioavailability of synthetic (Acuff et al., 1994; Kiyose et al., 1997). Furthermore, it has been shown that encapsulated vitamin E is poorly absorbed, especially when consumed with a low-fat meal (Leonard et al., 2004). However, the quality of some of this research has been questioned (Landvik, 2004) due to inconsistencies in methods and procedures suggesting it does not provide meaningful comparisons. Therefore, further research is needed to fully understand the bioavailability of vitamin E supplements.

#### 3.1.1.6 Vitamin K

Vitamin K is a fat-soluble vitamin which exists in two forms: $K_1$ the plant form and $K_2$ a series of compounds with unsaturated side chains, synthesised by bacteria and referred to as menaquinones (Greer, 2010). Absorption of vitamin K in the intestines follows the well–established pathway of most dietary lipids (Shearer et al., 2012). Vitamin $K_1$ is primarily taken up by the liver and $K_2$ preferentially accumulating in arteries and other extra hepatic tissues such as bone and cartilage (Caluwé et al., 2020). The biological role is to act as a cofactor of vitamin-K dependent proteins (McCann & Ames, 2009). Vitamin K is needed for normal coagulation as several proteins in this process are vitamin K dependent (Shea & Booth, 2022). More recently it has been implicated in cardiovascular disease, osteoarthritis, dementia, cognitive impairment, issues with mobility and frailty (Simes et al., 2020). It has been shown that vitamin K supplementation leads to greater bioavailability when compared to food sources (Garber et al., 1999; Sokoll et al., 1997) and this effect is more pronounced in those who are already deficient (Theuwissen et al., 2014).

#### 3.1.1.7 Iron

Iron is an essential trace element that cannot be synthesised by humans so must be obtained through the diet and is found in abundance in plants and animals (Avery, 2021). There are two types of dietary iron: non-haem (present in plant food and animal tissues) and haem (from haemoglobin and myoglobin found in animal source foods) (Hurrell & Egli, 2010). The main biological function of iron is oxygen transport, but it also contributes to over 200 enzymatic systems essential for cellular functions, including those related to growth, immunity, muscle activity, bone strength and the nervous system (Blanco-Rojo & Vaquero, 2019; Skikne & Hershko, 2012).

Non-haem iron is degraded during digestion in the gastrointestinal tract due to the action of pepsin and hydrochloric acid. When it is released from food most non-haem iron is present in the ferric form which has low bioavailability (Han, 2011). For haem iron there is a specific haem-carrier protein at the brush border, once internalised this is released by haem oxygenase and then follows the same pathway as non-haem iron (Blanco-Rojo & Vaquero, 2019; Shayeghi et al., 2005). Iron supplementation has been suggested to be the most effective way to maintain adequate iron levels (especially in those with anaemia) as tit produces rapid changes and shows high levels of bioavailability (Fairweather-Tait & Teucher, 2002; Olivties et al., 1999).

#### 3.1.1.8 Multivitamin bioavailability

As stated earlier the bioavailability of multivitamins differ due to nutrient-nutrient interactions (Comerford, 2013). Research has indicated there are clear differences in the apparent bioavailability of vitamins compared to minerals from the same multi-micronutrient supplement (Navarro & Wood, 2003), and this suggests that it is not possible to measure bioavailability of a single nutrient as a marker of general bioavailability of a supplement. It is not practical or necessary to show in vitro demonstration of each individual vitamin and mineral (Srinivasan, 2001); however, increasing evidence has shown multivitamin supplements can improve micronutrient status of some of the ingested vitamins and minerals, especially in at risk populations (Comerford, 2013), showing they can have good levels of bioavailability.

Bioavailability is generally assessed via plasma blood levels from pre to post supplementation. This of course leads to issues with only being able to assess particular vitamins so cannot indicate bioavailability of every ingredient of a multivitamin. Early research indicated that healthy individuals taking multivitamins for 8 weeks showed improvements in plasma status of vitamin B6, B12, C, D and E, but not vitamin A, thiamine or cytokine production (McKay et al., 2000). It has been evidenced in those aged 55-75 that multivitamin supplementation led to a significant increase in mean plasma levels of vitamin E, beta-carotene, folate and vitamin B12 compared to placebo, but no significant difference in riboflavin and vitamin C levels (Maraini et al., 2009). Furthermore, in the group receiving multivitamins, increases in plasma levels of vitamin A, E and C were significantly higher in those with lower nutritional status at baseline compared to those in the highest quartile. Multivitamin supplementation has also been shown to increase levels of serum aluminium, copper, zinc and selenium levels in women undergoing IVF, but showed no effects on calcium and magnesium (Özkaya et al., 2011). In community dwelling older adults, multivitamin supplementation led to increases in serum vitamin D, B12 and folate, but no difference in serum zinc levels (Grieger et al., 2009). Similarly in older adult males (aged between 50 and 74 years), multivitamin supplementation increased blood serum levels of vitamin B12 and folate, whilst reducing homocysteine, compared to a placebo (Harris et al., 2012).

This evidence indicates there is good bioavailability in multivitamin supplementation, which may be similar to that of individual nutrients. However, there are clear issues with this as nutrient bioavailability and individual requirements can confound research results (Marra & Wellman, 2008). Based on this, the factors that may affect bioavailability should be considered.

### 3.1.2 Factors affecting bioavailability

There are various demographic variables associated with the use of dietary supplements including being a woman, older age, higher education level, and regular physical activity (Rock, 2007).

Micronutrient requirements differ by sex, as the criterion for biological requirement includes a component that is related to body size, which on average differs between sexes (Prentice, 2021). Despite this there are no major differences in recommendations for dosages of key dietary supplements based on sex (Wohlgemuth et al., 2021). There is little research specifically on sex differences in absorption of supplements, however it has been suggested that absorption for a variety of substances is generally less efficient in females (Schwartz, 2003). Physiological differences which may alter absorption can be due to differences in sex hormone concentrations (Wohlgemuth et al., 2021), sex differences in metabolic enzyme expression, and activity in the gut wall (Beierle et al., 1999). There is little research investigating sex differences in bioavailability of supplements; however, evidence has shown that women absorb the extract curcumin to a larger extent than men, which may be due to differences in the enzymes involved in biotransformation (Schiborr et al., 2014). Based on this, the effects of multivitamin supplementation may also differ based on sex.

There is also evidence that nutrient status can affect bioavailability. Omega-3 status has been shown to have a relationship with B-vitamin supplementation. Those with higher baseline omega-3 status show better response to B-vitamin supplementation, compared to participants with lower status showing no improvement (Jernerén et al., 2015; Oulhaj et al., 2016; Van Soest et al., 2022). Zinc deficiency can affect utilisation of vitamin A due to its role in the release of vitamin A from the liver and may also impair folate bioavailability (Sandström, 2001). Emerging evidence has shown the gut microbiome can influence the bioavailability of micronutrients, and that deficiencies in certain micronutrients such as zinc and magnesium can affect the efficiency of the gut microbiome (Barone et al., 2022). Deficiencies in one nutrient can impede absorption of another, suggesting supplementation with multivitamins may be a beneficial way to overcome this.

Lifestyle factors can also impact bioavailability of supplements. Disease, medication/drugs, levels of physical activity, race, body size, emotional status of an individual, and age can affect rate of gastrointestinal tract transit and drug metabolism (Allam et al., 2011). In particular, age-related reductions in nutrient absorption are especially important when considering countries with an ageing population (Gibson, 2007). Changes in the secretory and absorptive capacity of the intestine affect bioavailability of certain micronutrients, in particular vitamin B12, vitamin D, and vitamin B6 (Russell, 2000). Renal function also declines with age (Sokoll et al., 1994) which can influence bioavailability of nutrients excreted mainly be the kidney such as selenium, iodine, and chromium (Gibson, 2007). Therefore, the evidence previously discussed may not be applicable to older adults, with the majority of evidence coming from healthy young adults. The ageing process is clearly an important factor in the consideration of the effectiveness of multivitamin supplementation.

### 3.1.3 Multivitamins and health

Is it well established that multivitamin supplementation can improve nutrition status and the sequencing of the human genome has allowed identification of interactions between nutrient intake and activity of specific genes related to health, giving rise to the field of nutrigenomics (Schwartz, 2014). Nutrigenomics is the term used to describe the field that evaluates the impact genetic variants have on dietary response, and the effect nutrients may have on gene expression (Fenech et al., 2011). Given the potential of multivitamins to reduce the risk of chronic disease (Blumberg, 2018), a broad range of observational and randomised clinical control trials have been conducted to examine nutrient gene interactions in the context of multivitamin supplements and chronic disease, across a range of populations.

As outlined in Chapter 1, the ageing process leads to a decline in immune function. Early research showed that administration of multivitamins could boost immunity and reduce occurrence of infections in older adults (Chandra, 1992). This is supported by further research showing that older adults supplemented with multivitamins had fewer total days of respiratory illness and fewer days of antibiotic use (Jain, 2002). However, a meta-analysis has suggested that the evidence for the use of multivitamin supplements to reduce infections in older adults is weak and conflicting (El-Kadiki & Sutton, 2005). Despite this, contemporary research still suggests that multivitamin supplementation, at the recommended dietary allowance level, can improve cellular immune parameters and reduce risk of infections (Gombart et al., 2020).

Given the requirement of multivitamins for the efficacy of a number of biological processes, several studies have explored the links between multivitamin supplementation and diseases characterised by dysregulation in these processes. There are obvious roles for multivitamins and cardiovascular processes. In particular the role of vitamin B6, B12 and folate in metabolising homocysteine, with higher levels of homocysteine being linked to an increased risk of cardiovascular disease (McNulty et al., 2008). Despite this, there is minimal evidence for a beneficial role of supplementation on outcomes in cardiovascular disease (CVD). No links between multivitamin supplementation and CVD or cardiovascular outcomes have been observed in postmenopausal women (Neuhouser et al., 2009) or the general public (Kim et al., 2018). In a large-scale prospective cohort study in male physicians, there was no association between current multivitamin use and the risk of major CVD events or CVD death; however, there was a significant relationship between supplementation and lower risk of cardiac revascularisation (Rautiainen et al., 2016).

Stronger links have been reported between supplementation and cancer outcomes. Early work in the Linxian General Population trial in China investigated the incidence and mortality from all cancer, oesophageal cancer, stomach cancer, and gastric cancer comparing multivitamin supplementation to non-use. There were reductions in incidence of gastric cancer, mortality rate from cancer, and mortality rate from stomach cancer in groups receiving beta-carotene, α tocopherol, and selenium, with or without other nutrients (Blot et al., 1993). In a sub study in this population, supplementation with beta-carotene, α tocopherol, and selenium had so significant effect on dysplasia or early cancer of the oesophagus or stomach (Wang et al., 1994). The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study (Hercberg et al., 2004), found a daily capsule of vitamin C, vitamin E, beta-carotene, selenium, and zinc lowered total cancer incidence and all-cause mortality in men but not in women, potentially due to men having lower baseline status of vitamins. Further research has shown that long term daily multivitamin use leads to a significant reduction in total cancer among men with a baseline history of cancer (Gaziano et al., 2012).

### 3.1.4 Multivitamins and everyday functioning

Given vitamins are essential for normal cell function and physiological processes and are intrinsically involved in every aspect of brain function (Kennedy & Haskell, 2011), supplementation with multivitamins may benefit psychological functioning (Kennedy et al., 2016). The main aspects of psychological functioning that are of interest in this trial are those that were identified as themes in Chapter 2 relating to aspects of everyday functioning that older adults would like to improve.

Poor mood has been associated with deficiency of several micronutrients in older cohorts. There have been associations between lower levels of vitamin B12 and folate with higher levels of depression (Stanger et al., 2009; Tolmunen et al., 2003), vitamin D deficiency with low mood (Wilkins et al., 2006), circulating B vitamin and/or homocysteine levels and depression (Sánchez-Villegas et al., 2009), and lower selenium with higher anxiety and depression (Benton & Cook, 1991). This has led to a body of research examining the effect of multivitamin supplementation on mood. In 20 healthy young adults, supplementation of multivitamin has shown increased self-rated contentment acutely (Scholey et al., 2013) and reductions in anxiety and perceived stress, in 80 participants after 28 days' intervention (Carroll et al., 2000).

Sex differences in subjective response of tiredness and stress have been shown acutely following multivitamin supplementation, with females showing improvements (Dodd et al., 2020). In 50 healthy older adults, multivitamin supplementation for 8 weeks has shown significant reduction in overall scores on measures of depression, anxiety and stress (Harris et al., 2011) and reduced ratings of perceived mental stress (Macpherson et al., 2015). Vitamin status has also been shown to be correlated with mood measures before supplementation (Cockle et al., 2000), suggesting that multivitamins may have more benefit to those with poorer nutritional status.

Observational studies have shown that vitamins including folic acid, vitamin B6, vitamin B12, vitamin C, vitamin E, and vitamin D may have cognitive benefits and delay age-associated cognitive decline (Devore et al., 2010; Haan et al., 2007; Slinin et al., 2010). Dietary deficiency can cause defects in mitochondrial function and cellular energy production, thus impacting cognitive health (Shah, 2013; Swaminathan & Jicha, 2014; Weih et al., 2007). Evidence as to whether multivitamin supplementation can improve cognitive performance has, however, been conflicting. Improvements in cognitive performance accompanied by reduced mental fatigue during sustained mental effort following supplementation of a multivitamin with guarana, have been shown acutely in 129 healthy young adults (Scholey et al., 2008). Further work has shown improvements in stress, vigour, and attenuation of negative effects of extended task completion on mood and fatigue following multivitamin in healthy young adults (Haskell et al., 2010; Kennedy et al., 2010). This was found after 9 weeks in 216 healthy females (Haskell et al., 2010) and after acute administration in 215 healthy young males (Kennedy et al., 2010).

In older adults there have been improvements shown in working memory in 56 women after 16 weeks' supplementation (Macpherson et al., 2012) and episodic memory in 51 men after 8 weeks' supplementation (Harris et al., 2012). The majority of evidence; however, indicates that multivitamin supplementation elicits no improvement in cognitive function in older adults. No effects on cognitive function have been reported after acute supplementation in 76 older women (Macpherson et al.,2015), and chronic supplementation in 116 older adults after 16 weeks (Harris et al.,2015), 910 older adults after 12 months (McNeill et al., 2007) and 5947 older adult men after 12 years' supplementation (Grodstein et al., 2013). It has been suggested this may be due to the population being too well nourished and there may be the scope for greater benefits in older adults with nutritional deficiency (Grodstein et al., 2013; McNeill et al., 2007).

Diet and vitamin intake is also believed to play an important role in the regulation of sleep and sleep quality (St-Onge et al., 2016). Vitamin D deficiency is associated with poorer sleep quality and shorter sleep duration (Gao et al., 2018), higher plasma levels of vitamin C with longer sleep duration (Noorwali et al., 2018), deficiencies in the B vitamins and magnesium with impaired sleep (Peuhkuri et al., 2012), and serum zinc levels with sleep duration (Song et al., 2012). Intervention studies have reported improvement in sleep quality in 54 nurses following 1-month zinc supplementation (Gholipour Baradari et al., 2018), but reports of lower subjective sleep quality and higher tiredness upon waking in 100 participants following 5 days' supplementation with a vitamin B complex (Aspy et al., 2018). Specifically focusing on multivitamin supplementation, evidence has been conflicting, consumption of a liquid nutrient drink for 6 months led to better sleep compared to placebo in 68 older adults (Wouters-Wesseling et al., 2003). But there were no significant reports of improved sleep in 114 participants following 16 weeks' consumption of a multivitamin supplement containing B vitamins (Sarris et al., 2012), and conversely disturbed sleep maintenance associated with multivitamin use in a cross sectional study (Lichstein et al., 2007).

There is also a strong bidirectional relationship between diet and physical activity, especially in older adults. A vast majority of this research focuses on vitamin D, which is unsurprising given its role in bone health and frailty. Lower levels of vitamin D have been associated with lower self-reported physical activity levels (Anand et al., 2011) which could be due to less time spent outside, and higher levels positively associated with handgrip strength in females (Valtueña et al., 2013). Vitamin B12 deficiency has been associated with frailty in older women (Matteini et al., 2008), and lower levels of homocysteine with higher levels of physical activity (Dankner et al., 2007). Furthermore, higher levels of serum vitamin C, vitamin D, and alpha carotene were shown to be positively associated with higher daily steps in middle aged adults (Choi & Ainsworth, 2016). Little research has looked at the effect of multivitamin supplementation on physical activity, especially in older adults. In well-nourished men, 12-week multivitamin supplementation had no effect on any parameter related to physical performance in 22 healthy physically active men (Singh et al., 1992). It could be hypothesised this would have greater efficacy in older adults who have experienced a decline in physical functioning and are more likely to be undernourished; however, it has been shown that 10 weeks' supplementation with a multi-nutrient liquid had no effect on physical performance in 55 frail older adults (Singh et al., 2000). Further research is warranted to consider diet at baseline, as this will establish if multivitamin supplementation can elicit improvements in specific undernourished groups.

Subjective feelings of loneliness and social frailty have also been associated with risk of malnutrition (Eskelinen et al., 2016; Pek et al., 2020), and social interaction was highlighted as one of the key areas of importance to older adults in Chapter 2. One possible explanation for this is that feelings of loneliness can affect appetite through a decline in mood and thus intake of nutrients is reduced (Fratiglioni et al., 2000). Recent work has shown that nutritional intervention (alongside functional group-based exercise) for 12 weeks was effective at reducing social isolation and improving quality of life in 60 older women with sarcopenia (Pinheiro et al., 2020). Given the promising results observed and the importance put on social interactions by older adults, this is an area that warrants further investigation.

The interventions discussed provide some promising evidence, but results are conflicting. A range of positive effects have been found in varying trial designs, with a range of sample sizes, and both acute and chronic supplementation, with a range of durations studied. Positive results have been found from as little as 1-hour post dose to after 6 months' supplementation. All intervention studies which describe how adherence was measured (which were all measured via pill counting upon completion and recording in treatment diaries) have reported good compliance. Only participants which report between 80 and 120% compliance have been used in analysis, which is standardised across all studies who report this. Thus increasing validity of results reported.

### 3.1.5 Rationale and aims

Based on the evidence discussed it is clear that multivitamin supplementation has the potential to improve different areas of everyday functioning in older adults. However, the research is conflicting with much of the evidence showing no improvements following supplementation. Further research in this area is warranted given the detriments reported in various aspects of everyday functioning in older adults which may negatively affect wellbeing and quality of life. It has also been evidenced that there may be sex differences in response to multivitamin supplementation which may be due to differing nutritional needs and absorption of micronutrients. However, little research has considered this, either considering both sexes together, or, only focusing on one sex. There is, therefore, a requirement to look at differing response to treatment based on sex.

It has been suggested the inconclusive results found in literature may be due to sampling issues in clinical trials, in particular the possibility that the participants were too "healthy" and well-nourished at baseline. Nutritional inadequacies in older adults have consistently been shown in the literature, in European older adults 24% of men and 47% of women have inadequate intake of one or more nutrients (De Groot et al., 1999). Research has shown that folic acid, selenium, iodine, vitamin D, and vitamin C are at higher risk of inadequate intake in Europe (Viñas et al., 2011). Furthermore, older adults who have no health complaints, are not taking medication, and have a healthy BMI are likely to be well nourished, so it is unlikely they will benefit from a multivitamin supplement. Research with less stringent inclusion/exclusion criteria is needed in older adult groups who may already be experiencing detriments and are likely to see the most benefit.

Based on the inconclusive evidence and issues identified in previous research, the current study had two aims. The first aim was to investigate the effectiveness of a multivitamin supplement on meaningful outcomes of everyday functioning in ‘everyday’ older adults aged 70 and over. The meaningful outcomes being derived from the qualitative results of Chapter 2. The second aim was to investigate individual differences based on how reported nutritional intake at baseline interacted with the multivitamin supplement on markers of everyday functioning.

## 3.2 Method

### 3.2.1 Design

This study employed a randomised, placebo-controlled, double blind, parallel groups design. Participants were randomly assigned to receive either multivitamin or placebo (see section 3.2.2.1 for full breakdown of treatments). The dependent variables were grouped into three overall categories: wellbeing, mood and memory; physical health and activity; and social interaction and loneliness. Within this, the following dimensions were assessed: wellbeing, stress, general health, daily functioning, mood trait measures, sleep quality, memory, activity levels, fear of falling, social network size, and loneliness. The study was preregistered at Clinical Trials.gov (reference: NCT04112732).

### 3.2.2 Participants

To be eligible to participate in the study, participants had to be aged 70 or over. Participants were recruited through mail shots to local community centres, churches and older adult groups in the North-East region. Online recruitment included study adverts being posted to local community pages and through age targeted sponsored adverts on Facebook. Exclusion criteria were minimal, but participants could not take part if they had an allergy to soya. As stated by Vitabiotics Ltd (London) as a recommendation before consuming this multivitamin, individuals who were currently under medical supervision, had epilepsy, a thyroid disorder, haemochromatosis or suffered from a food allergy had to consult their doctor or pharmacist before taking part. Those already taking a multivitamin, or any individual vitamin contained in the supplement had to have a four-week washout period before taking part, other supplements were considered on a case-by-case basis. Participants were included who were currently consuming CBD oil, turmeric, cod liver oil, rose hip, glucosamine, and evening primrose oil. As there were no exclusion criteria based on medical conditions, see Appendix I for frequency of medical conditions in the sample.

A priori G*Power analysis was calculated based on a medium effect size (F= 0.24) seen with similar nutritional interventions, to achieve a power of 0.8, 128 females and 128 males were needed. 266 participants (142 female, 124 male) aged 70 and over were recruited and enrolled onto the study.

### 3.2.3 Materials

#### 3.2.3.1 Treatments

Participants were allocated to a single treatment according to a predetermined randomisation schedule that was prepared by an independent party offsite. Treatment was consumed as a single capsule, participants were instructed to take one per day with their main meal of the day with water or a cold drink, for 12 weeks. Participants were provided with treatment diaries throughout the trial to note date and time of treatment consumption, this was to encourage adherence to protocol. Placebo and multivitamin were identical in appearance and smell. The multivitamin used was a commercially available product sold by Vitabiotics Ltd, London (Wellwoman 70+ tablets / Wellman 70+ tablets).

Ingredients differed slightly between the male and female multivitamin, the breakdown of each of the treatments is provided in Table 3.1.

**Table 3.1.** Breakdown of each ingredient included in the male and female formula, () represents % of daily Nutrient Reference Value, where this is not included there are no recommended daily values.

| | Multivitamin | |
|---|---|---|
| | Female | Male |
| Lutein Esters | 2 mg | 2 mg |
| Co-enzyme Q10 | 10 mg | 10 mg |
| L-Carnitine | 10 mg | 20mg |
| Alpha Lipoic Acid (ALA) | 20 mg | 20 mg |
| Phosphatidylcholine | 7 mg | 7 mg |
| Silicon | 10 mg | 10 mg |
| Citrus Bioflavonoids | 10 mg | 10 mg |
| Betacarotene | 2 mg | 2 mg |
| Vitamin D (as D3 800 IU) | 20 µg (400%) | 20 µg (400%) |
| Vitamin E | 12 mg (100%) | 12 mg (100%) |
| Vitamin C | 80 mg (100%) | 80 mg (100%) |
| Thiamin (Vitamin B1) | 14 mg (1273%) | 14 mg (1273%) |
| Riboflavin (Vitamin B2) | 4 mg (286%) | 4 mg (286%) |
| Niacin (Vitamin B3) | 30 mg NE (188%) | 30 mg NE (188%) |
| Vitamin B6 | 10 mg (714%) | 10 mg (714%) |
| Folic Acid | 200 µg (100%) | 200 µg (100%) |
| Vitamin B12 | 100 µg (4000%) | 100 µg (4000%) |
| Biotin | 50 µg (100%) | 50 µg (100%) |
| Pantothenic Acid | 6 mg (100%) | 10 mg (167%) |
| Iron | 10 mg (71%) | 6 mg (43%) |
| Zinc | 15 mg (150%) | 15 mg (150%) |
| Copper | 1000 µg (100%) | 1000 µg (100%) |
| Manganese | 0.5 mg (25%) | 0.5 mg (25%) |
| Selenium | 120 µg (218%) | 55 µg (100%) |
| Chromium | 75 µg (188%) | 75 µg (188%) |
| Iodine | 150 µg (100%) | 150 µg (100%) |
| Siberian Ginseng Extract equiv. to | - | 20 mg |
| Pumpkin Seed Extract equiv. to | - | 100 mg |
| L-Glutathione | - | 10 mg |
| Vitamin A (2666 IU) | - | 800 µg RE |

### 3.2.3.2 Questionnaires

Appropriate questionnaires were sought to index the outcomes of everyday functioning in older adults identified as targets for improvement in the results of Study 1 (Chapter 2), and are as follows:

*Wellbeing*

The UK Office of National Statistics (ONS) developed a survey to measure subjective wellbeing in the nation, compromising of four subjective wellbeing questions (Tinkler & Hicks, 2011). These are:

1. Overall, how satisfied are you with your life nowadays?
2. Overall, to what extent do you feel the things you do in your life are worthwhile?
3. Overall, how happy did you feel yesterday?
4. Overall, how anxious did you feel yesterday?

Answers are scored on a ten-point rating scale from “not at all = 0” to “completely = 10”. Question four is reverse scored and scores are summed to give an overall wellbeing score, whereby higher scores represent greater wellbeing. This scale has been recommended to be used in wellbeing surveys (Michaelson et al., 2012). In this study, Cronbachs α = 0.76.

Wellbeing was included as participant indicated in Chapter 2 they would like to see improvements in general mood, following multivitamin supplementation.

*Stress*

The Perceived Stress Scale (PSS) (Cohen et al., 1983) is a 10-item questionnaire which assesses how overwhelming participants perceive their life to be. Measured on a 5- point Likert scale (0 = never to 4 = very often), scores range between 0 and 40, higher scores indicating greater levels of perceived stress within the previous month. Several studies in multiple countries have found the PSS to have good psychometric properties with Cronbach’s α ranging between 0.75 and 0.91 (Andreou et al., 2011; Cohen et al., 1983; Örücü & Demir, 2009). In this study, Cronbachs α = 0.86.

The Perceived Stress Reactivity Scale (PSRS) (Schlotz et al., 2011) measures an individual's typical stress response to different situations. The PSRS consists of 23 items grouped into five subscales (reactivity to social evaluation, reactivity to failure, reactivity to social conflicts, reactivity to work overload, and prolonged reactivity) and one overall score of total stress reactivity. Items present a potentially stressful stimulus and responses are coded on a scale of zero (least reactive) to two (most reactive). Scores are summed to give a score for both the subscales and overall scores. The subscales prolonged reactivity and reactivity to failure, are made up of four items so scores can range from 0 to 8. Reactivity to social evaluation, work overload, and social conflict, consist of five items each and scores can range from 0 to 10. Overall score is totalled from all items, with scores ranging from 0 to 46. For total score and subscales, higher scores indicate higher stress response. Internal consistency of the subscales has been shown to be in the range of 0.70 – 0.80 and the total score 0.91 in a UK sample (Schlotz et al., 2011). In this study, Cronbachs α = 0.92.

Measures of stress were included as they have been shown to be affected by multivitamin supplementation in previous trials.

*State Mood*

Anxiety and depression symptoms were measured using The Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983). This is a 14-item scale (7 questions relating to anxiety and 7 to depression), with responses ranging from 0 to 3 for each statement and overall scores ranging from 0 to 21 per subscale. Scores between 0 and 7 are considered normal, between 8 and 10 are indicative of borderline mood disorder and scores over 11 indicate probable mood disorder (Snaith, 2003). Results from a meta-analysis showed the average Cronbach's alpha for the anxiety subscale was .83 and .82 for depression, showing HADS is a good measure of these symptoms in the general population (Bjelland et al., 2002). In this study, Cronbachs α = 0.89.

The Profile of Mood States (McNair et al., 1971) was also used to measure state mood. This comprises 65 adjectives (e.g., helpful, unhappy), participants are asked to rate how much they have felt this in the last week on a five-point scale from "not at all" to "extremely". Scores are summed to give global scores for seven subscales: tension, depression, anger, fatigue, confusion, vigour, and friendliness. Higher scores on vigour and friendliness reflect a better mood/emotion, lower scores on the other subscales reflect a better mood/emotion. A total mood disturbance score is also calculated by adding the scores from the first five domains and subtracting vigour and friendliness, higher scores represent a greater mood disturbance. The POMS is a well validated questionnaire of mood states in research settings (McNair et al., 1971). In this study, Cronbachs α = 0.93.

Measures of mood were included as they have been shown to be affected by multivitamin supplementation in previous trials and were suggested as a facet participants would like to see improvements in following an age targeted multivitamin supplement in Chapter 2.

*Memory*

The Prospective and Retrospective Memory Questionnaire (PRMQ) (Crawford et al., 2003) was used to measure everyday memory failures. This is a 16 item scale that measures memory failures in two subscales, eight items relating to prospective memory (e.g. do you fail to mention or give something to a visitor that you were asked to pass on) and eight items relating to retrospective memory (e.g. do you fail to do something you were supposed to do a few minutes later even though it's there in front of you, like take a pill or turn off the kettle?). Scale responses range from 1 (Never) to 5 (Very Often) in response to how often the items happen to the participant. Scores can range from 8-40 for each subscale, higher scores indicate more everyday memory failures. Cronbach's alpha for the scales was shown to be 0.84 and 0.80 respectively, showing acceptable internal consistency (Crawford et al., 2003). In this study, Cronbachs $\alpha = 0.90$ for both subscales.

Memory was included as an outcome measure, due to previous multivitamins trials reporting promising results.

*Physical Activity Levels*

The Yale Physical Activity Survey (YPAS) (Dipietro et al., 1993) is a questionnaire developed to assess physical activity in older adults. This comprises two sections: there is a comprehensive physical work, exercise, and recreational activities checklist to assess time spent in these types of activities during a typical week in the past month. Time spent in each activity is multiplied by an intensity code (kcal $min^{-1}$) and then summed across all activities to create an index of weekly energy expenditure (kcal $week^{-1}$). The time spent in all activities is also summed to provide a total time index (h $week^{-1}$). The second section of the questionnaire assesses participants' engagement in five activity dimensions: vigorous activity, leisurely walking, moving on feet, standing, and sitting. Weights are assigned to each category (5 – 1 respectively), the frequency of engagement is multiplied by duration and then this is multiplied by the weighting factor to calculate an index for each dimension. These scores are then summed to produce an overall activity dimension summary index, with higher scores indicating greater physical activity. The YPAS has demonstrated adequate repeatability and is considered a reliable measure of regular physical activity in older adults (Dipietro et al., 1993; Garatachea et al., 2009). In this study, energy expenditure showed Cronbachs α = 0.52, total time index α = 0.57 and overall activity index α = 0.42.

Physical activity was included due to prominent themes in Chapter 2 indicating participants had issues with walking, strength and mobility, and would like to engage in more exercise.

*General Health / Functioning*

The Cohen Hoberman Inventory of Physical Symptoms (CHIPS) (Cohen & Hoberman, 1983) is a measure of perceived burden as a result of physical symptoms. This consists of 33 common symptoms (e.g., 'back pain', 'constipation' and 'heart pounding or racing') and participants must rate from 0 (not bothered by the problem) to 4 (the problem has been an extreme bother) how much that problem has distressed them during the past two weeks. Scores can range between 0 and 132, higher scores indicating greater perceived burden due to physical symptoms and poorer health. CHIPS has been shown to be an internally consistent measurement of physical symptoms in the general population (Allen et al., 2017). In this study, Cronbachs α = 0.90.

The Medical Outcomes Study short form questionnaire (SF-20) (Stewart et al., 1988) measures general health across six domains: physical functioning (6 questions), role functioning (2 questions), social functioning (1 question), mental health (5 questions), health perceptions (5 questions), and pain (1 question). Raw scores are transformed to a 0 % to 100 % scale, with 100 % representing the best possible score on this domain. The exception to this is the pain score where this is reversed so 0 % represents the best possible score. The internal reliability of the questionnaire has been reported to be between 0.81 to 0.87 (Miaskowski et al., 1997; Stewart et al., 1988). In this study, Cronbachs α = 0.84.

These were chosen as outcome variables as issues with physical functioning, poor health and subsequent pain were highlighted consistently in the qualitative results of chapter 2.

*Daily Functioning*

The Instrumental Activities of Daily Living (IADL) (Lawton & Brody, 1969) was used to measure independent living skills as an indicator of daily functioning. This measures eight daily activities: telephoning, shopping, food preparation, housekeeping, laundering, use of transportation, use of medicine, and financial behaviour. Respondents are scored according to their highest level of functioning in that category, either 0 or 1, giving a summary score from 0 (low function, dependent) to 8 (high function, independent). The IADL is widely used in research and has been shown to have high internal consistency ranging from 0.81 to 0.98 (Bottari et al., 2010; Graf, 2009). In this study, Cronbachs α = 0.61.

Concerns about falling were measured using the Falls Efficacy Scale International (FES-I) (Yardley et al., 2005). This is a 16-item questionnaire which states different activities (e.g., 'walking on a slippery surface') and participants are asked to rate how much they would be concerned with falling while doing this activity. Each item is rated from 1-4 for each item with higher scores indicating higher concern. Scores are totalled to give an overall score that ranges from a minimum 16 (no concern about falling) to maximum 64 (severe concern about falling). The internal consistency of the FES-I has been shown to be excellent with a Cronbach's alpha of 0.79 (Delbaere et al., 2010). In this study, Cronbachs α = 0.96.

Included as participants highlighted issues with daily household activities in Chapter 2, both due to physical restrictions and fear of falling, which is covered within these two questionnaires.

The Pittsburgh Sleep Quality Inventory (PSQI) (Buysse et al., 1989) was used to measure sleep quality and patterns. The PSQI assesses seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Participants are asked to provide sleep timings and rate whether they have experienced a range of sleep issues in the past month, which is scored on a 3-point scale from 0 (not during the past month) to 3 (three or more times a week). A global sleep score is created by totalling the seven subfactor scores (ranging from 0-21), with higher scores indicating poorer sleep quality. Meta analysis has shown Cronbach's alpha to range from 0.70 to 0.83 for the PSQI (Mollayeva et al., 2016). In this study, Cronbachs α = 0.75.

Participants in Chapter 2 highlighted they would like to have increased energy and improved sleep quality after consuming a multivitamin, which is why this questionnaire has been included as an outcome measure.

*Loneliness*

De Jong-Gierveld Loneliness Scale (De Jong-Gierveld & Kamphuls, 1985) is an 11-item scale which gives indices of emotional, social and total loneliness. Participants are presented with a list of statements (six relating to emotional loneliness and five social loneliness) and must indicate the extent to which the statement applies to their situation. To score the scale, the neutral and positive answers are scored as "1" and the negative as "0" on the negatively worded questions. On positively worded items the neutral and negative answers are scored as “1” and positive as “0”. Scores can range from 0 to 6 for emotional loneliness and 0 to 5 for social loneliness, a single index of loneliness can also be produced by totalling these two scores where higher scores indicate greater loneliness. The overall scale has been shown to have good validity (Cronbach’s alpha = 0.84), as well as both emotional loneliness (Cronbach’s alpha = 0.88) and social loneliness (Cronbach’s alpha = 0.88) (Pinquart & Sorensen, 2001).

*Social Networks*

The Lubben Social Network Scale (Lubben, 1988) was used to measure social networks and social engagement. This is made up of 12 questions (6 about family ties and 6 friendship ties) relating to different aspects of social networks such active social network, perceived support network and perceived confidant network. All questions are scored on a 0 to 5 scale, with higher scores indicating more social engagement. Total score is a sum of these 12 questions, ranging from 0 to 60, with higher scores representing a larger social network. The reported Cronbach’s alpha of the scale is 0.70 (Lubben, 1988). In this study, Cronbachs $\alpha$ = 0.84.

The Convoy Model of Social Networks (Antonucci & Akiyama, 1987) measured social network size. Respondents are presented with a set of three concentric circles, with the word ‘You’ contained within the middle. Respondents are asked to think about “people to whom you feel so close it is hard to imagine life without them”; these people are entered into the innermost circle. For the middle circle respondents are asked to consider “people to whom you may not feel quite that close but who are still very important to you”. Finally, in the outer circle respondents are asked to place “People whom you haven’t already mentioned but who are close enough and important enough in your life that they are part of your personal network”. The numbers of people within each network are counted and represent support networks in each of the categories and are summed to produce an index of total social network size. Participants were also asked to rate the relationship quality of each person they entered (with 0 being the worst relationship quality and 10 being the best). This was averaged for each circle and overall to give an indication of overall relationship quality. Higher scores indicate greater social networks and better relationship quality for all scales. Extensive research has provided evidence for the validity of the convoy model (Gameiro et al., 2010).

Although loneliness was not directly highlighted within a theme in Chapter 2, participants described how they wished to spend more time doing recreational activities, particularly with family and friends. This, alongside loneliness becoming a growing concern in older adults was the reason this was included as a dependent variable in the current study.

*Dietary Intake*

The study used a Food Frequency Questionnaire (FFQ) developed during the European Prospective Investigation into Cancer Study (EPIC-Norfolk), which has become widely used as a measure of nutritional intake (Bingham et al., 2001). The questionnaire lists 130 food products and participants are asked to indicate the frequency of consumption from nine options from “never or less than once a month” to “6+ times per day” within the previous year. Servings were specified in either units/common portions or in household measures. The frequency is then converted into a portion multiplier, then multiplied with the portion size to attain an average daily food weight for each of the FFQ items. The weights are multiplied by the nutrient composition per gram, then all items are summed to give each participant an average daily nutrient intake. Those with more than 10 missing lines of data are excluded. The EPIC-Norfolk FFQ and associated processing software are widely used in research and have been extensively validated (Bingham et al., 1997; Bingham et al., 2001; Mulligan et al., 2014).

### 3.2.4 Procedure

The original preregistered protocol of this study was developed as a face-to-face laboratory study at Northumbria University. However due to the COVID-19 pandemic the protocol had to be adapted to run as an online intervention. Therefore, there were some tasks completed only by a subset of participants prior to the COVID-19 protocol amendments, which are not being reported here. See Appendix II for description of those aspects of the study completed by participants who took part in the laboratory version prior to COVID-19.

A participant information sheet was sent to interested parties via email. After reading this, potential participants were then booked in for a telephone screening appointment with the principal investigator. During this appointment the study was discussed with the participant, the protocol explained, and any initial questions answered. If participants still wished to take part, they were sent an email link to an online questionnaire to give informed consent, whilst on the phone to the researcher. After this, full demographic information was taken including date of birth, medical conditions, and current medication (to check for eligibility), daily alcohol and caffeine consumption, and participants were asked to state their height and weight. A home address was taken for treatments to be sent to, and each participant was sent two bottles of treatment and a treatment diary via post. Participants were instructed to contact the researcher when they received this, to organise the day they would like to complete testing visit 1.

Prior to the morning of testing visit 1, participants were asked to avoid alcohol for 24 hours and caffeine for 12 hours, and to eat a standardised breakfast of cereal and/or toast. This was to keep procedure standardised to those who completed the study in person, ensure standardisation across visits and participants, and to minimise the impact of other factors. A link to the online questionnaire was sent via email, adherence to protocol was assessed via the questionnaire, and then participants could complete the questionnaires at their own pace. Participants could leave any questionnaire/question they did not feel comfortable answering, but they were prompted if there was missing data. When this was completed, participants were asked to start consuming the tablets they had been sent, one tablet per day with their main meal of the day with water or a cold drink, and to record the time of this daily in the diary provided, along with any adverse events and concomitant medications taken throughout the trial. The FFQ was sent via a separate link and participants were asked to complete this at any point within the 12-week period, as there were no protocol requirements associated with this questionnaire.

After 12 weeks (+/- 5 days) participants completed the same procedure again. Within this online questionnaire they were also asked to record any changes in medication, adverse events, the number of remaining tables, complete the treatment guess questionnaire, and were presented a full debrief sheet when the questionnaires were completed.

### 3.2.5 Treatment of Data

All data was analysed using IBM SPSS Statistics version 26. Data was removed for anyone who did not complete the study in full.

Each participant was provided 100 treatment capsules for the duration of the study. A treatment compliance percentage was calculated to measure adherence to the study protocol. The treatment compliance was calculated by comparing the number of tablets participants reported were left with the actual number of tablets which should have remained (16). Therefore, compliance was calculated as shown in figure 3.1.

$$\text{Treatment Compliance (\%)} = \frac{\text{Number of treatments returned (not consumed)}}{\text{Number of treatments that should have been consumed (Days enrolled in study)}} \times 100$$

**Figure 3.1.** Formula to calculate treatment compliance.

Upon completion of the study participants completed a treatment guess questionnaire (Appendix III). Participants were asked to choose whether they thought they had received the multivitamin or the placebo during the study, to verify the blinding procedure. Responses to the treatment guess were analysed using Chi-Square test, comparing the number of correct and incorrect responses given by each treatment group.

Missing data points were considered per outcome measure. For the Falls Efficacy Scale-International (Yardley et al., 2005), if no more than 4 of the 16 items were missing, the sum score of the items completed was calculated, divided by the number of items completed and multiplied by 16, the new sum score was rounded up to the nearest whole number. For the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) if question 5J was missing the score for that individual item was changed to 0, if any question aside from this was missing then the response was removed. For the De Jong-Gierveld Loneliness scale (De Jong-Gierveld & Van Tilburg, 1990) if there was only one missing data point this was scored as 0, if there were two or more missing values the case was deleted from analysis. For any questionnaires with no explicit instructions on how to handle missing data, the response was removed.

Data was split by sex and Independent Samples t-tests were run between treatment groups to check for any demographic differences. In males there were no significant differences between treatment groups for: Age [$t$ (102) = -.159, $p$ = .874], years spent in education [$t$ (102) =-.733, $p$ = .465], daily alcohol intake [$t$ (102) = .230, $p$ = .818], daily caffeine intake [$t$ (102) = .125, $p$ = .901], or BMI [$t$ (102) = -.058, $p$ = .954]. In females there were no significant differences between treatment groups for: Age [$t$ (122) = -.964, $p$ = .337], years spent in education [$t$ (122) =-1.051, $p$ = .295], daily alcohol intake [$t$ (122) = -.034, $p$ = .973], daily caffeine intake [$t$ (122) = -.384, $p$ = .702], or BMI [$t$ (122) = -.115, $p$ = .909]. Therefore, these variables were not controlled for in subsequent analyses.

Of the 228 per protocol participants, 196 provided dietary intake data, each nutritional outcome was then checked for outliers in the data using boxplots. Individual data points which were indicated as extreme outliers by SPSS (any data point lying outside the following range: 3$^{rd}$ quartile + 3 x interquartile range or 1$^{st}$ quartile – 3 x interquartile range) were removed from the data (see Appendix IV for boxplots showing data points removed). Independent Samples t-tests were run between treatment groups to check for any nutritional differences. In males, the placebo group consumed significantly higher levels of non-starch polysaccharides [$t$ (92) = -2.346, $p$ = .021], saturated fatty acids [$t$ (92) = -2.101, $p$ = .038], and fruit [$t$ (92) = -2.449, $p$ = .016]. In females, the multivitamin group consumed significantly higher levels of saturated fatty acids [$t$ (118) = 2.193, $p$ = .030], and fats and oils [$t$ (118) = 2.305, $p$ = .023]. As these are not ingredients in the multivitamin they were controlled for in analysis.

Descriptive statistics were calculated for all measures and data was analysed separately for males and females using one-way independent groups ANCOVAs. Treatment was the independent factor with two levels: multivitamin and placebo. The dependent measures were the relevant outcomes for each questionnaire at the final visit (after 12 weeks intervention). The relevant outcome for each questionnaire at baseline (before supplementation) was included as a covariate.

Before ANCOVA could be run, homogeneity of regression slopes assumption was checked for each outcome, examining whether there was an interaction between the independent groups factor (Treatment) and the covariate (outcome measure at visit 1). The homogeneity of regression assumption was violated in the following outcomes in males: POMS Fatigue Inertia [$F$ (1, 96) = 7.52, $p$ = .007], Lubben Social Network Scale [$F$ (1, 97) = 4.01, $p$ = .048]. The homogeneity of regression assumption was violated in the following outcomes in females: Falls Efficacy Scale [$F$ (1, 119) = 9.02, $p$ = .003], SF20 Role Functioning [$F$ (1, 120) = 7.52, $p$ = .007], SF20 Social Functioning [$F$ (1, 120) = 8.43, $p$ = .004], SF20 Health Perceptions [$F$ (1, 120) = 10.10, $p$ = .002], SF20 Pain [$F$ (1, 120) = 4.76, $p$ = .031], Instrumental Activities of Daily Living [$F$ (1, 117) = 6.59, $p$ = .013], Convoy Inner Circle Number of Relationships [$F$ (1, 118) = 4.30, $p$ = .040]. However, ANCOVA is still robust when the assumption of equal regression slopes is violated if group sizes are equal (Levy, 1980). As group sizes were equal ANCOVAs were run and reported as planned.

Due to the volume of analysis only significant results are reported in the text, full descriptive statistics, F values and P values can be found in tables. These results are reported in section 3.3.1.

To investigate individual differences in response to treatment, interactions between treatment group and reported mean habitual dietary intake of relevant vitamin/mineral were analysed.

Data was split by sex, descriptive statistics were calculated for all measures and analysed using a two-way independent groups ANCOVA. There were two independent factors, the first was treatment with two levels, multivitamin, and placebo. The second was (respective) vitamin intake with two levels, above mean and below mean. The dependent measure was the relevant outcome for each questionnaire at the final visit (after 12 weeks intervention). The relevant outcome for each questionnaire at baseline (before supplementation) was included as a covariate. Any significant interactions were followed up with simple main effects analysis, data was split by Treatment and one-way ANCOVAs were run between vitamin intakes. As there were two levels, a Bonferroni corrected alpha level was applied of 0.025. Due to the volume of analysis only significant interactions are reported, in section 3.3.2.

## 3.3 Results

Of the 266 participants enrolled, 228 participants completed the study in full as per protocol (124 female, 104 male). Participant disposition is displayed in Figure 3.2 and demographic data in Table 3.2.

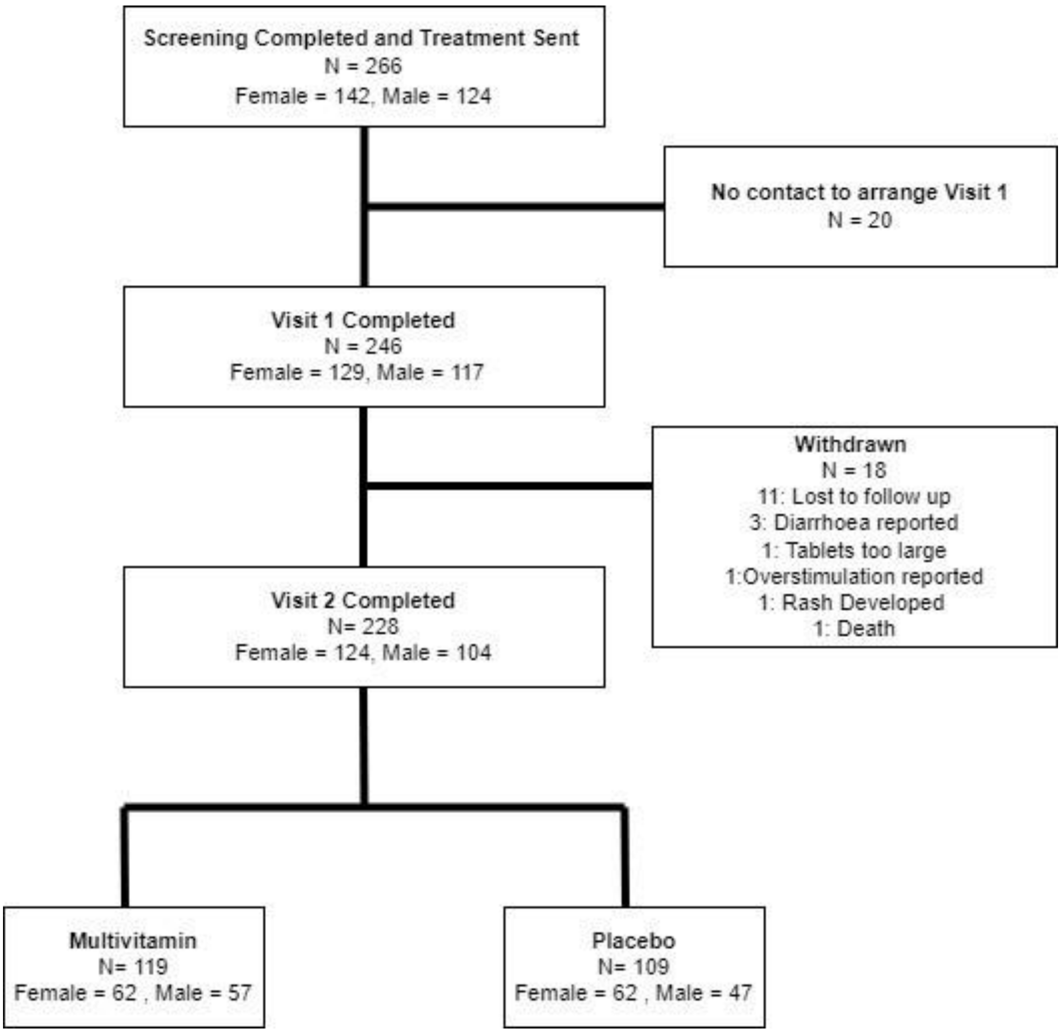


**Figure 3.2.** Participant disposition through the trial. Cumulating in the 228 participants who completed the study per protocol.

**Table 3.2.** Participant demographic information for the 228 subjects who completed the study per protocol (124 females, 104 males). Means, Std. Deviation (SD), minimum and maximum score reported.

| | Female | | | | Male | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Minimum | Maximum | Mean | SD | Minimum | Maximum |
| Age (years) | 73.85 | 4.00 | 70 | 90 | 74.40 | 3.73 | 70 | 87 |
| BMI (kg/m$^2$) | 26.59 | 4.98 | 16.20 | 49.40 | 27.99 | 5.10 | 20.00 | 47.70 |
| Years in Education | 15.15 | 2.99 | 10 | 23 | 15.58 | 2.65 | 10 | 23 |
| Caffeine (mg per day) | 250.28 | 143.95 | 0 | 800 | 238.14 | 140.03 | 0 | 750 |
| Alcohol (units per day) | 0.71 | 0.90 | 0 | 4 | 1.03 | 1.06 | 0 | 6 |

Compliance was observed to be very good on average in both females (100.3% Multivitamin, 100.4% Placebo) and males (99.5% Multivitamin, 99.4% Placebo). One-way ANOVA showed no significant difference for compliance percentage by treatment group for females [$F$ (1, 122) = .007, $p$ = .935] or males [$F$ (1, 102) = .002, $p$ = .968].

There was no significant difference in participants' ability to identify whether they had consumed multivitamin or placebo in both females [$\chi^2$ (1) = .004, $p$ = .951] and males [$\chi^2$ (1) = .003, $p$ = .958].

### 3.3.1 Main effects of treatment

#### 3.3.1.1 Wellbeing, mood and memory

*Profile of Mood States*

In females, there was a significant effect on POMS friendliness [$F$ (1,118) = 4.10, $p$ = .045, $h_p^2$ = .034], with those who received multivitamin reporting higher levels of friendliness compared to placebo.

This trend was followed in males, approaching significance [$F$ (1,97) = 3.60, $p$ = .061, $h_p^2$ = .036], again with those who had multivitamin scoring higher compared to placebo. Displayed in figure 3.3.

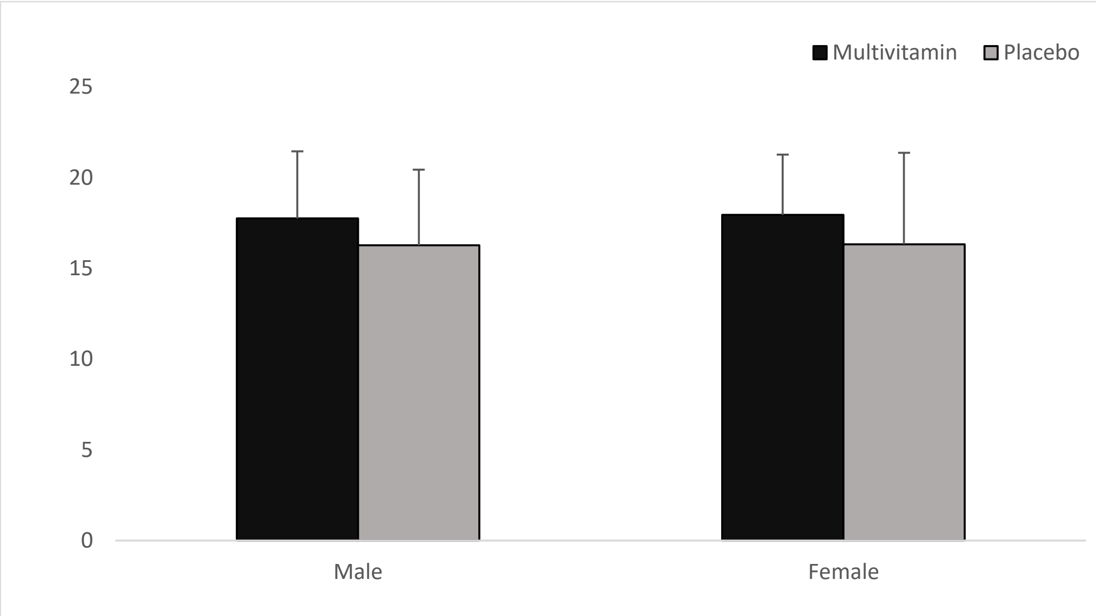


**Figure 3.3.** Unadjusted means for POMS friendliness scores. Error Bars represented standard deviation.

*Perceived Stress Reactivity Scale*

In females, there was a significant effect on POMS friendliness [$F$ (1,118) = 4.10, $p$ = .045, $h_p^2$ = .034], with those who received multivitamin reporting higher levels of friendliness compared to placebo.

This trend was followed in males, approaching significance [$F$ (1,97) = 3.60, $p$ = .061, $h_p^2$ = .036], again with those who had multivitamin scoring higher compared to placebo. Displayed in figure 3.3.

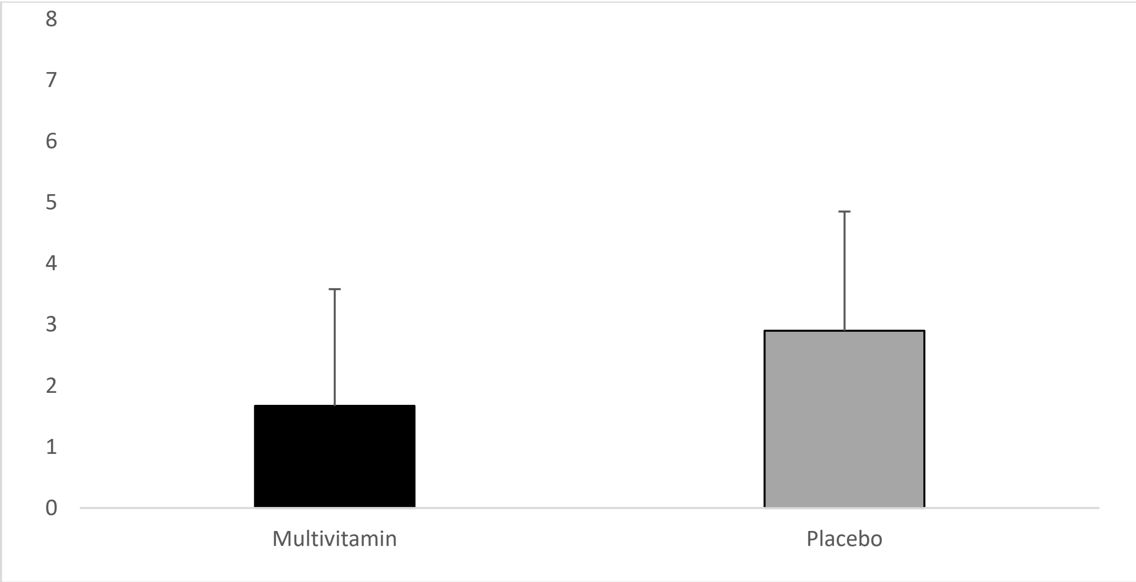


**Figure 3.4.** Unadjusted means for PSRS Prolonged Stress Reactivity in males. Error Bars represented standard deviation.

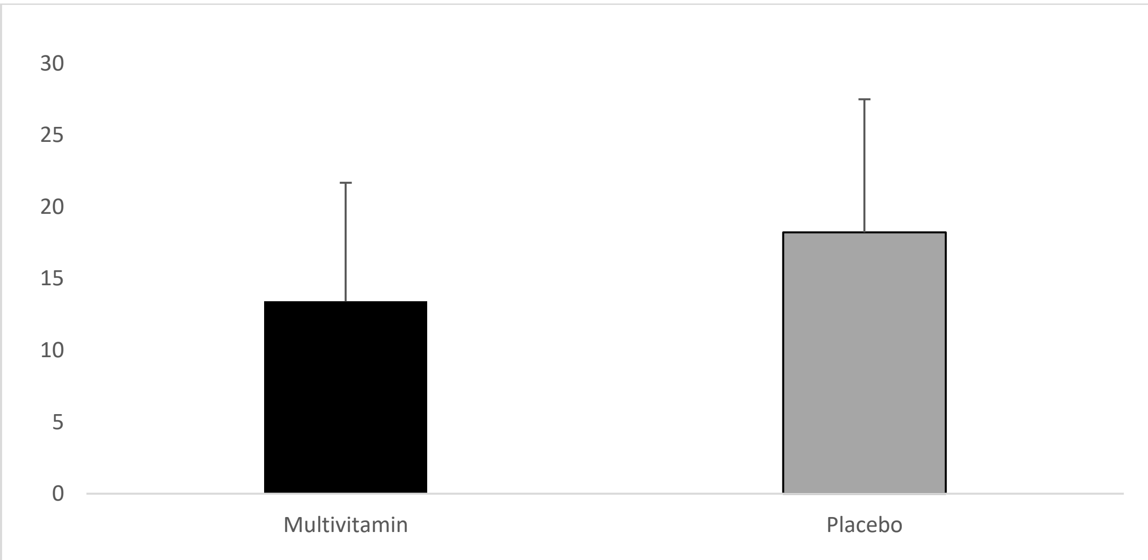


**Figure 3.5.** Unadjusted means for PSRS Overall Reactivity in males. Error Bars represented standard deviation.

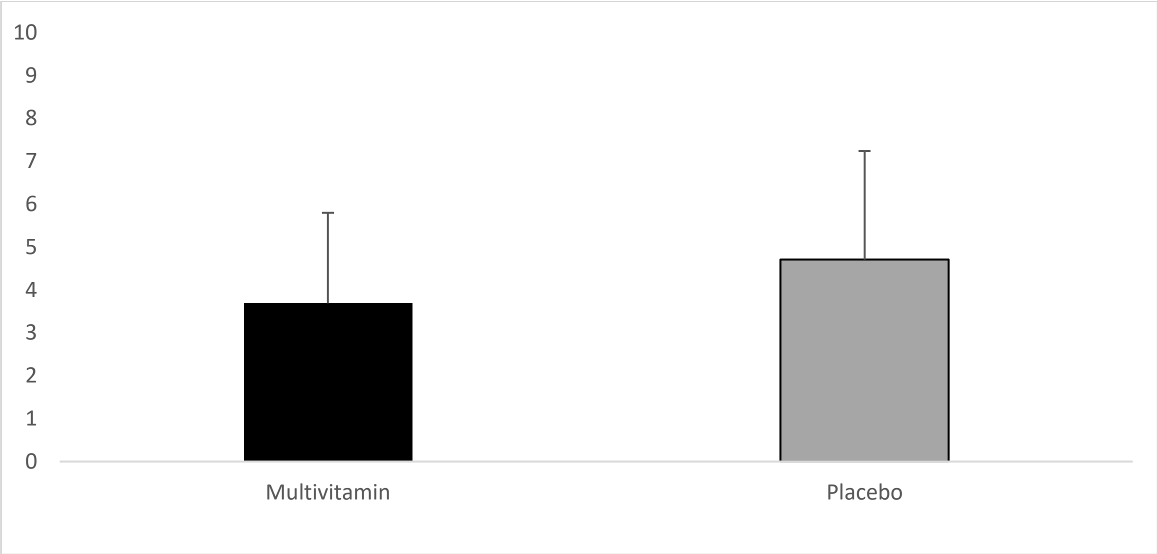


**Figure 3.6.** Unadjusted means for PSRS Social Conflict in males. Error Bars represented standard deviation.

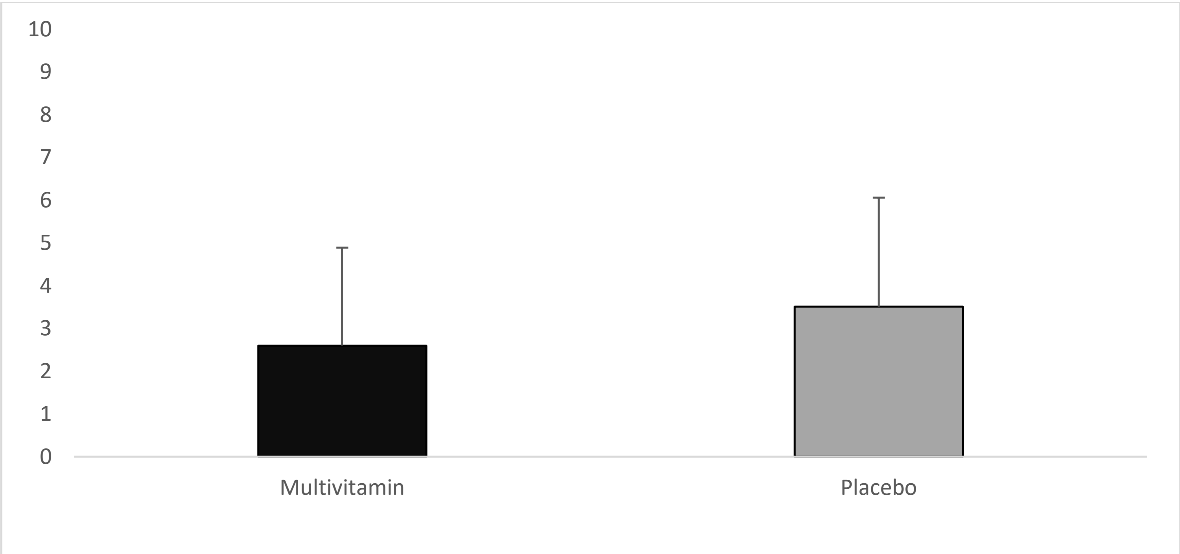


**Figure 3.7.** Unadjusted means for PSRS Social Evaluation in males. Error Bars represented standard deviation.

### 3.3.1.2 Physical health and activity

No main effects of treatment on any physical health and activity outcome measures for males and females. Mean (S.D) scores and statistics for physical health and activity measures are presented in are presented in Table 3.4.

### 3.3.1.3 Social interaction and loneliness

*De Jong Gierveld Loneliness Scale*

In males there was a significant effect of treatment on De Jong-Gierveld emotional loneliness scale [$F$ (1, 101) = 4.23, $p$ =.042, $h_p^2$ = .040], with those having multivitamin reporting significantly lower levels of emotional loneliness compared to placebo. Displayed in figure 3.8. Mean (S.D) scores and statistics for social interaction and loneliness measures are presented in Table 3.5.

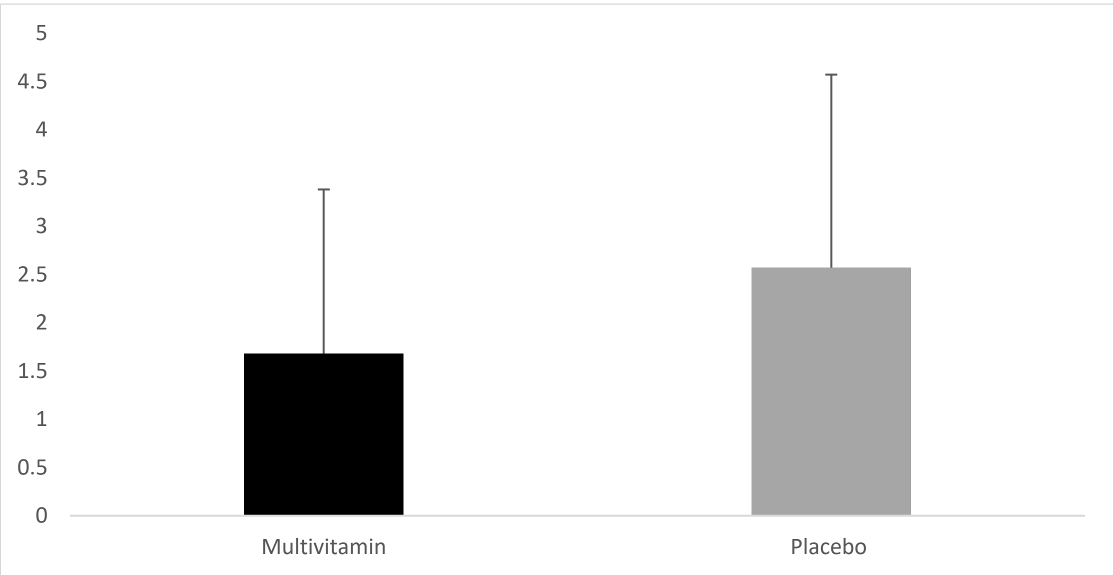


**Figure 3.8.** Unadjusted means for De Jong emotional loneliness score in males. Error Bars represented standard deviation.

**Table 3.3.** Unadjusted Mean (SD), F values and P values for all wellbeing, mood and memory outcomes, split by Sex and Treatment.

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Multivitamin | Placebo | F Value | P Value | Multivitamin | Placebo | F Value | P Value |
| Office National Statistics Wellbeing | 30.53 (5.82) | 30.98 (5.48) | 0.29 | .590 | 29.35 (5.82) | 29.97 (6.63) | 0.65 | .421 |
| Perceived Stress Scale | 10.59 (5.50) | 12.77 (7.54) | 1.69 | .196 | 12.15 (6.31) | 13.48 (6.20) | 1.52 | .220 |
| ***Hospital Anxiety and Depression Scale*** | | | | | | | | |
| Anxiety | 4.14 (3.59) | 4.83 (4.42) | .009 | .927 | 5.02 (3.89) | 4.73 (3.14) | 0.02 | .891 |
| Depression | 3.11 (2.93) | 3.98 (3.49) | 0.66 | .418 | 3.97 (3.34) | 3.69 (3.05) | 0.11 | .738 |
| ***Profile of Mood States*** | | | | | | | | |
| Tension – Anxiety | 4.31 (6.49) | 6.18 (7.90) | 0.82 | .368 | 5.00 (6.86) | 5.52 (6.00) | 0.24 | .626 |
| Depression – Dejection | 4.04 (8.03) | 5.76 (8.84) | 0.35 | .558 | 4.64 (8.29) | 5.43 (8.16) | 0.45 | .506 |
| Anger – Hostility | 2.80 (3.82) | 3.89 (6.72) | 0.16 | .687 | 2.62 (4.89) | 3.45 (5.13) | 1.36 | .247 |
| Vigour – Activity | 21.33 (7.56) | 18.47 (6.84) | 2.40 | .124 | 18.62 (7.40) | 18.93 (8.73) | 0.05 | .822 |
| Fatigue – Inertia | 3.56 (5.65) | 4.98 (6.50) | 0.85 | .359 | 4.00 (6.09) | 5.17 (6.43) | 1.17 | .282 |
| Confusion- Bewilderment | 4.56 (4.98) | 6.56 (5.76) | 1.86 | .176 | 6.52 (5.75) | 6.75 (5.40) | 0.20 | .653 |
| Friendliness | 17.75 (3.70) | 16.27 (3.32) | 3.60 | .061 | 17.95 (4.17) | 16.33 (5.04) | 4.10 | .045 |
| Total Mood Disturbance | -2.05 (29.85) | 8.89 (37.73) | 1.20 | .277 | 4.16 (32.70) | 7.38 (33.90) | 0.41 | .521 |
| **Perceived Stress Reactivity Scale** | | | | | | | | |
| Prolonged Reactivity | 1.67 (1.91) | 2.90 (1.95) | 7.78 | .007 | 2.31 (1.65) | 2.50 (1.72) | 0.29 | .592 |
| Work Overload | 2.29 (2.53) | 3.34 (2.63) | 2.30 | .133 | 2.55 (2.41) | 2.62 (2.55) | 0.01 | .905 |
| Social Conflict | 3.69 (2.11) | 4.71 (2.53) | 3.63 | .060 | 4.53 (2.32) | 4.60 (2.60) | 0.02 | .894 |
| Failure | 3.16 (1.62) | 3.76 (1.59) | 3.04 | .085 | 3.14 (1.65) | 3.34 (1.64) | 0.34 | .562 |
| Social Evaluation | 2.60 (2.29) | 3.51 (2.55) | 3.45 | .067 | 2.96 (2.30) | 2.76 (2.30) | 0.12 | .726 |
| Overall | 13.40 (8.28) | 18.22 (9.28) | 5.72 | .019 | 15.49 (8.53) | 15.82 (8.81) | 0.05 | .832 |
| **Prospective and Retrospective Memory Questionnaire** | | | | | | | | |
| Prospective Memory | 18.91 (7.54) | 20.10 (5.59) | 0.18 | .676 | 20.02 (6.78) | 19.82 (6.66) | 0.00 | .999 |
| Retrospective Memory | 17.54 (7.78) | 17.96 (5.86) | 0.02 | .890 | 18.98 (7.44) | 18.42 (7.09) | 0.11 | .737 |

**Table 3.4**. Unadjusted Mean (SD), F values and P Values for all physical health and activity outcomes, split by Sex and Treatment.

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Multivitamin | Placebo | F Value | P Value | Multivitamin | Placebo | F Value | P Value |
| Cohen Hoberman Inventory of Physical Symptoms | 10.42 (12.08) | 12.81 (12.58) | 0.00 | .996 | 12.92 (14.36) | 15.32 (12.90) | 1.57 | .213 |
| Pittsburgh Sleep Quality Index | 6.55 (2.87) | 6.21 (3.35) | 0.40 | .530 | 7.16 (3.97) | 6.44 (3.58) | 0.91 | .343 |
| Instrumental Activities of Daily Living | 7.60 (0.89) | 7.64 (0.75) | 0.01 | .924 | 7.57 (0.93) | 7.67 (0.77) | 0.32 | .575 |
| Falling Efficacy Scale-International | 21.58 (9.95) | 20.85 (6.22) | 0.42 | .520 | 24.47 (10.15) | 24.57 (9.69) | 0.00 | .949 |
| ***Yale Physical Activity Scale*** | | | | | | | | |
| Total Time | 32.19 (19.47) | 27.54 (15.56) | 1.20 | .276 | 31.34 (21.37) | 32.86 (20.41) | 0.13 | .721 |
| Energy Expenditure | 124.51 (70.76) | 103.60 (62.63) | 2.37 | .127 | 110.02 (76.93) | 116.79 (72.81) | 0.31 | .578 |
| Activity Dimension | 56.05 (30.94) | 51.81 (23.17) | 0.37 | .545 | 47.66 (26.25) | 52.73 (30.58) | 1.37 | .245 |
| ***SF-20*** | | | | | | | | |
| Physical Function | 69.73 (32.03) | 78.71 (19.49) | 2.80 | .097 | 66.13 (29.98) | 64.91 (30.26) | 0.04 | .850 |
| Role Functioning | 82.02 (38.31) | 87.77 (26.00) | 0.59 | .433 | 78.63 (38.64) | 80.24 (36.53) | 0.30 | .588 |
| Social Functioning | 89.82 (25.95) | 95.32 (13.96) | 1.95 | .165 | 88.38 (29.10) | 87.10 (25.38) | 0.00 | .948 |
| Mental Health | 83.19 (15.58) | 79.23 (19.21) | 0.50 | .480 | 78.65 (17.35) | 75.42 (19.32) | 1.08 | .301 |
| Health Perceptions | 71.09 (28.36) | 74.41 (18.04) | 0.42 | .520 | 72.36 (25.14) | 68.00 (27.71) | 0.80 | .374 |
| Pain | 36.14 (26.84) | 39.57 (27.18) | 0.40 | .531 | 39.35 (27.81) | 38.06 (25.79) | 0.07 | .796 |

**Table 3.5**. Unadjusted Mean (SD), F values and P Values for all social interaction and loneliness outcomes, split by Sex and Treatment.

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Multivitamin | Placebo | F Value | P Value | Multivitamin | Placebo | F Value | P Value |
| Lubben Social Network Scale | 31.16 (10.13) | 29.95 (8.86) | 0.86 | .356 | 32.19 (9.18) | 33.74 (8.40) | 0.97 | .327 |
| ***De Jong-Gierveld Loneliness Scale*** | | | | | | | | |
| Social Loneliness | 2.02 (1.81) | 2.49 (1.88) | 0.80 | .373 | 1.87 (1.82) | 1.66 (1.81) | 0.27 | .602 |
| Emotional Loneliness | 1.68 (1.70) | 2.57 (2.00) | 4.23 | .042 | 2.11 (1.85) | 2.07 (1.96) | 0.03 | .873 |
| Total Loneliness | 3.70 (2.49) | 5.06 (3.55) | 3.33 | .071 | 3.98 (3.35) | 3.72 (3.41) | 0.14 | .714 |
| ***Convoy Model Social Relations*** | | | | | | | | |
| Inner Circle Relationships | 4.83 (3.13) | 4.78 (2.80) | 0.00 | .957 | 6.67 (3.87) | 6.05 (4.37) | 0.63 | .430 |
| Inner Relationship Quality | 8.40 (2.30) | 8.53 (1.74) | 0.01 | .924 | 8.83 (1.56) | 8.38 (2.20) | 1.60 | .208 |
| Middle Circle Relationships | 3.43 (2.65) | 3.20 (2.26) | 0.00 | .991 | 4.64 (4.61) | 4.36 (3.42) | 0.26 | .613 |
| Middle Relationship Quality | 6.64 (2.27) | 6.54 (2.63) | 0.01 | .937 | 6.62 (2.42) | 6.49 (2.26) | 0.09 | .763 |
| Outer Circle Relationships | 3.11 (3.42) | 2.43 (2.35) | 1.17 | .283 | 4.07 (4.16) | 3.21 (2.68) | 1.13 | .290 |
| Outer Relationship Quality | 5.42 (3.12) | 5.15 (3.38) | 0.17 | .680 | 5.54 (3.26) | 5.49 (3.08) | 0.01 | .938 |
| Total Relationships | 11.37 (7.34) | 10.41 (5.38) | 0.16 | .687 | 15.38 (10.73) | 13.62 (8.44) | 0.61 | .437 |
| Total Relationship Quality | 7.31 (1.88) | 7.52 (1.56) | 0.25 | .617 | 7.71 (1.59) | 7.51 (1.35) | 0.71 | .400 |

### 3.3.2 Individual Differences in response to treatment

The next stage of analysis aimed to explore individual differences in response to treatment based on vitamin intake at baseline. Vitamins and minerals of interest were those that are contained in treatment: vitamins D, B1, B2, B3. B6, B12, C, E, folic acid/folate, polyunsaturated fatty acids, zinc, selenium, manganese and iodine. In the first instance means for intake of each vitamin were based on population means, taken from the Scientific Advisory Committee on Nutrition (2021) statement on nutrition and older adults living in the community. Participants were therefore categorised as being above or below the mean based on their sex and age group (65-74 or 75+) in the population means. However, when this led to extreme unequal sample size, participants were categorised as being above or below the mean based on the population mean for age alone. If there were still unequal sample sizes following this approach, participants were categorised as being above or below the mean based on their sex and age group (70-74 or 75+) in this sample rather than by population means. The classification approach is identified for each variable as necessary below. Table 3.6 shows the mean used for each vitamin and how this was categorised.

**Table 3.6**: Means used to split participants for each vitamin and coding for how this was categorised

| | Male | | Female | |
|---|---|---|---|---|
| | 70-74 | 75+ | 70-74 | 75+ |
| Vitamin D (µg/day) ++ | 3.50 | 2.80 | 3.50 | 2.80 |
| Vitamin B1 (mg/day) + | 1.70 | 1.54 | 1.38 | 1.26 |
| Vitamin B2 (mg/day) ++ | 1.63 | 1.55 | 1.63 | 1.55 |
| Vitamin B3 (mg/day) +++ | 21.85 | 21.47 | 22.15 | 22.52 |
| Vitamin B6 (mg/day) +++ | 2.13 | 2.19 | 2.19 | 2.15 |
| Vitamin B12 (µg/day) + | 6.30 | 6.80 | 4.80 | 4.50 |
| Vitamin C (mg/day) +++ | 112.64 | 108.30 | 128.06 | 137.62 |
| Vitamin E (mg/day) +++ | 12.64 | 11.29 | 12.25 | 12.86 |
| Folate (µg/day) +++ | 288.10 | 305.94 | 307.72 | 318.07 |
| Polysaturated fatty acids (g/day) +++ | 13.30 | 12.50 | 13.18 | 12.63 |
| Zinc (mg/day) + | 9.00 | 8.60 | 7.50 | 6.60 |
| Selenium (µg/day)+++ | 59.54 | 62.16 | 64.30 | 56.31 |
| Manganese (mg/day) +++ | 3.68 | 3.71 | 3.79 | 3.71 |
| Iodine (µ g/day) + | 183.00 | 191.00 | 157.00 | 134 |

+ Means based on averages for sex and age in population according to the Scientific Advisory Committee on Nutrition

++ Means based on averages for age in population according to the Scientific Advisory Committee on Nutrition

+++ Means based on averages for sex and age in the sample

Vitamin D

*Yale Physical Activity Scale*

In males there was a significant treatment by vitamin D intake interaction in the Activity Dimension subscale [$F$ (1, 73) = 7.81, $p$ = .007, $h_p^2$ = .097]. Pairwise comparisons showed that those with vitamin D intake below the mean at baseline had lower levels of activity following multivitamin (mean = 49.55, SE= 4.78) compared to those above the mean (mean = 71.06, SE = 7.43).

*SF20*

In males there was a significant treatment by vitamin D intake interaction in SF20 social functioning [$F$ (1, 79) = 6.72, $p$ = .011, $h_p^2$ = .078]. Those below the mean intake at baseline showed significantly higher levels of social functioning (mean = 95.69, SE = 3.77) compared to those above the mean (mean =73.24, SE = 5.75) following multivitamin.

In females there was a significant treatment by vitamin D intake interaction in SF20 pain [$F$ (1, 104) = 4.01, $p$ = .048, $h_p^2$ = .037]. Pairwise comparisons showed those below the mean intake at baseline had significantly lower levels of pain (mean = 29.11, SE = 4.26) compared to those above the mean (mean =48.40, SE = 5.64) following multivitamin.

*Instrumental Activities of Daily Living*

In males there was a significant treatment by vitamin D interaction in Instrumental Activities in Daily Living [$F$ (1,75) = 7.40, $p$ = .008, $h_p^2$ = .090]. Pairwise comparisons showed those below the mean intake at baseline had greater independence (mean = 7.83, SE = 0.12) than those who were above the mean (mean=7.39, SE = 0.18) following multivitamin.

*De Jong-Giervald Loneliness Scale*

In males there was a significant treatment by vitamin D intake interaction in the loneliness scale total score [$F$ (1, 79) = 4.15, $p$ = .045, $h_p^2$ = .037]. Pairwise comparisons showed those below the mean intake at baseline had significantly higher levels of social loneliness (mean = 2.54, SE = 0.30) compared to those above the mean (mean = 1.25, SE = 0.46) following multivitamin.

Vitamin B1

There was no treatment by vitamin B1 intake interactions.

Vitamin B2

*Hospital Anxiety and Depression Scale*

In males there was a significant treatment by vitamin B2 intake interaction in the depression subscale [$F$ (1,81) = 5.94, $p$ = .017, $h_p^2$ = .068]. Pairwise comparisons showed those below the vitamin B2 mean intake at baseline had lower levels of depression (mean = 2.47, SE 0.69) than those above the mean (mean = 4.20, SE = 0.59) following multivitamin.

*Convoy Social Network Scale*

In females there was a significant treatment by vitamin B2 interaction in total relationship quality [$F$ (1, 105) = 4.52, $p$ = .036. $h_p^2$ = .041]. Pairwise comparisons showed those below the mean intake at baseline had significantly lower overall relationship quality (mean = 6.85, SE = 0.34) than those above the mean (mean = 7.75, SE = 0.25) following placebo.

Vitamin B3

*Instrumental Activities in Daily Living*

In males there was a significant treatment by vitamin B3 interaction in Instrumental Activities in Daily Living [$F$ (1,77) = 4.48, $p$ = .037, $h_p^2$ = .055]. Pairwise comparisons showed a trend for those below the vitamin B3 mean intake at baseline to have greater independence (mean = 7.77, SE = 0.16) than those who were above the mean (mean=7.31, SE = 0.20) following multivitamin.

Vitamin B6

*Falls Efficacy Scale*

In males there was a significant treatment by vitamin B6 interaction [$F$ (1,81) = 4.16, $p$ = .045, $h_p^2$ = .049] in the Falls Efficacy Scale. Pairwise comparisons showed those below the mean intake at baseline had lower fear of falling (mean = 20.12, SE= 1.74) compared to those above the mean (mean = 25.28, SE = 1.85) following multivitamin.

Vitamin B12

*De Jong-Giervald Loneliness Scale*

In females there was a significant treatment by vitamin B12 intake interaction in total loneliness [$F$ (1,104) = 4.28, $p$ = .041, $h_p^2$ = .040]. Pairwise comparisons showed those below the vitamin B12 mean intake at baseline reported lower levels of loneliness (mean = 2.77, SE = 0.79) compared to those above (mean = 4.70, SE = 0.54) following multivitamin.

Vitamin C

*Prospective and Retrospective Memory Questionnaire*

In males there was a significant treatment by vitamin C interaction in prospective memory score [$F$ (1,81) = 4.99, $p$ =.028, $h_p^2$ = .058]. Pairwise comparisons showed those below the mean intake at baseline reported fewer memory lapses (mean = 18.19, SE = 1.16) compared to those above the mean (mean = 22.80, SE = 1.45) following placebo.

Vitamin E

There was no treatment by vitamin E intake interactions.

Folate

*Profile of Mood States*

In males there was a significant treatment by folate interaction in total mood disturbance [$F$ (1,77) = 4.27, $p$ = .042, $h_p^2$ = .053]. Pairwise comparisons showed those below the mean intake at baseline had less mood disturbance (mean = -10.02, SE = 6.05) than those above the mean (mean = 11.34, SE = 6.79) following multivitamin.

Zinc

*Convoy Social Network Scale*

In males there was a significant treatment by zinc interaction in outer number of relationships [$F$ (1,79) = 8.12.  $p$ = .006, $h_p^2$ = .093]. Pairwise comparisons showed those below the mean had fewer individuals in this social circle (mean = 2.90, SE = 0.57) following multivitamin compared to those above the mean (mean = 4.38, SE = 0.70). This was also found in total social network size [$F$ (1,79) = 4.96, $p$ =.028, $h_p^2$ = .059], those below the mean had significantly fewer individuals in their social network (mean = 9.68, SE = 1.25) compared to those above the mean (mean = 14.09, SE = 1.56) following multivitamin.

Selenium

*SF20*

In females there was a significant treatment by selenium interaction in SF20 Role Functioning [$F$ (1,106) = 4.18, $p$ = .043, $h_p^2$ = .038]. Pairwise comparisons showed a trend for those below the mean to have greater role functioning (mean = 84.66, SE = 6.36) than those above the mean (mean = 68.16, SE = 7.14) following multivitamin.

In females there was a significant treatment by selenium interaction in SF20 Pain [$F$ (1,106) = 7.13, $p$ = .009, $h_p^2$ = .063]. Pairwise comparisons showed those below the mean reported lower levels of pain (mean = 29.08, SE = 4.42) compared to those above the mean (mean = 47.78, SE = 5.00) following multivitamin.

*Convoy Social Network Scale*

In males there was a significant treatment by selenium interaction in relationship quality in the inner circle [$F$ (1, 79) = 4.27, $p$ = .042, $h_p^2$ = .051]. Pairwise comparisons showed those below the mean reported lower average relationship quality (mean = 7.72, SE = 0.39) following multivitamin compared to those above the mean (mean = 9.47, SE= 0.42).

Manganese

There was no treatment by manganese intake interactions.

Iodine

*Hospital Anxiety and Depression Scale*

In females there was a significant treatment by iodine interaction in the anxiety subscale [$F$ (1,106) = 5.49, $p$ = .021, $h_p^2$ = .049]. Pairwise comparisons showed a trend for those below the mean to report lower levels of anxiety (mean = 4.11, SE = 0.62) then those above the mean (mean = 5.69, SE = 0.59) following multivitamin.

*Profile of Mood States*

In females there was a trend toward a treatment by iodine interaction in the Tension-Anxiety Subscale [*F* (1, 103) = 3.84, *p* = .053. $h_p^2$ =.036]. Pairwise comparisons showed a trend for those below the mean to report lower levels of tension and anxiety (mean =2.30, SE = 1.14) compared to those above the mean (mean = 6.10, SE = 1.20) following multivitamin.

*SF20*

In females there was a significant treatment by iodine intake interaction in Role Functioning [*F* (1,106) = 4.63, *p* = .034, $h_p^2$ = .042]. Pairwise comparisons showed those below the mean had lower role functioning (mean = 73.84, SE = 5.84) following placebo compared to those above the mean (mean = 94.73, SE = 8.74).

*De Jong-Giervald Loneliness Scale*

In females there was a significant treatment by iodine intake interaction in the social loneliness subscale [*F* (1,104 = 11.20, *p* = .001, $h_p^2$ = .097]. Those below the mean showed lower levels of social loneliness (mean = 1.32, SE = 0.34) compared to above the mean (mean = 2.49, SE = 0.32) following multivitamin. Within the placebo group, those below the mean showed higher levels of social loneliness (mean = 2.18, SE = 0.29) compared to those above the mean (mean = 1.04, SE = 0.42).

A further treatment by iodine intake interaction in total loneliness scale [*F* (1,104) = 6.60, *p* = .012, $h_p^2$ = .060] was observed in females. Pairwise comparisons showed those below the mean reported lower total loneliness (mean = 3.02, SE = 0.64) compared to those above the mean (mean = 5.07, SE = 0.62) following multivitamin.

*Convoy Social Network Scale*

In females there was a significant treatment by iodine intake interaction in the outer circle relationship quality [*F* (1,105) = 6.78, *p* = .011, $h_p^2$ = .061]. Pairwise comparisons showed those below the mean reported lower relationship quality (mean = 4.46, SE = 0.51) than those above the mean (mean = 7.08, SE = 0.76) following placebo.

## 3.4 Discussion

The main aim of this trial was to explore the effect of 12 weeks supplementation with a multivitamin on outcomes of everyday functioning in ‘everyday’ older adults aged 70 and over. The study was designed to incorporate meaningful outcomes of everyday functioning based on the qualitative results of Chapter 2, to take a more person-centred approach to trial design, and secondly to be less stringent with inclusion/exclusion criteria to allow the effects on an ‘everyday’ older adult sample to be examined. Overall, it was found that supplementation with a multivitamin resulted in a significant improvement in feelings of friendliness in females (with a trend shown in males) and significantly reduced prolonged stress reactivity and overall perceived stress reactivity in males. Furthermore, multivitamin supplementation resulted in significantly reduced emotionally loneliness in males.

Previous multivitamin supplementation trials have shown improvements in subjective feelings of mood including contentment, agreeableness, and elation (Benton et al., 1995; Long & Benton, 2013; Scholey et al., 2013). Similar improvements can be seen in the current study with the improved feelings of friendliness in females. Other research in the area has also shown sex differences in mood in response to supplementation, with only females showing improved agreeableness after 12 months of consuming a multivitamin (Benton et al., 1995). This may be due to the fact females have a higher risk of depression (Albert, 2015), usually display higher deficiencies in a range of micronutrients (Dodd et al., 2020), and are more susceptible to mental distress in response to nutritional insufficiency (Begdache et al., 2020). Therefore, females may be more sensitive to mood improvements following supplementation. This is the first randomised control trial showing improvements in feelings of friendliness in older adult females following multivitamin supplementation; however, Austin et al. (2014) showed in a cross-sectional study, that users of multivitamin supplements reported feeling significantly friendlier than non-users. Despite some similarity in results, sex differences were not explored, and the study was conducted in a very specific sample of military and coast guard personnel so comparisons should be drawn with caution.

The reduction in prolonged stress reactivity and overall perceived stress reactivity shown in males, extends previous literature in the field. It has been suggested that perceived stress is the mood facet reported to show the greatest improvements following chronic multivitamin supplementation (Long & Benton, 2013). For instance, reductions in perceived stress score have been shown in healthy males after 28 days’ supplementation (Carroll et al., 2000) and 33 days’ supplementation (Kennedy et al., 2010). In older adult females, acute consumption of a multivitamin (3 hours post dose) led to significant reduction in stress ratings

(Macpherson et al., 2015) and there were significant reductions for older adult males following four weeks of supplementation (Harris et al., 2011). However, in the current study reductions were shown in perceived stress reactivity, which is a different construct to perceived stress. Overall perceived stress reactivity refers to subjective reaction to different stressful situations, specifically focusing on person-environmental interactions, which makes this construct more sensitive to change (Limm et al., 2010).  Furthermore, prolonged stress reactivity refers to the difficulty relaxing after high workload (Schlotz et al., 2011). No previous multivitamin trials have focused specifically on stress reactivity. Therefore, the results found here add important and novel information to the field, suggesting multivitamin supplementation can improve a range of stress facets, with further work being warranted.

The mood benefits of chronic multivitamin supplementation have largely been attributed to folate, B6, and B12 due to their roles in neurotransmitter synthesis (Huskisson et al., 2007), suggesting a clear mechanism of effect for these results. This may also provide an explanation for the sex differences observed, if male participants were lower in these vitamins at baseline compared to females, there is a higher likelihood for an improvement to be observed. Participants were instructed not to take treatment on the final day of testing, however there was no measure of whether this was adhered to, so it is a possibility, following the results of Macpherson et al. (2015), that the stress reduction may be due to the acute effects of multivitamins. Further work is needed to compare acute versus chronic effects of multivitamin on stress, building on the work by Dodd et al. (2020), to extend this to older adults.

Perhaps the most surprising finding was that multivitamin supplementation reduced emotional loneliness in males. This has previously not been a focus of research studies, but the approach taken within the current research has highlighted this important finding. This area is scarcely researched, most likely due to there being no clear biological mechanism of effect between the two. However emerging research has shown that the origin of loneliness may have a biological stress related aspect (Campagne, 2019), and as clearly evidenced, multivitamin supplementation can affect feelings of stress in older adult populations. Subjective feelings of loneliness have also been associated with risk of malnutrition (Eskelinen et al., 2016; Pek et al., 2020). Therefore, it could be hypothesised that the inverse relationship is being observed, reducing stress via improved nutrition may reduce feelings of loneliness. Again, this only being observed in males may indicate a worse nutritional intake at baseline compared to females. To date, only one published RCT has been conducted looking at the effect of nutritional intervention (alongside functional group-based exercise) on loneliness in older adult women. The nutritional intervention consisted of pre-training fruit juice and post-training banana smoothie, and it was shown that those who were randomised to the nutritional intervention showed reduced loneliness scores. However, there are clear methodological issues with this study, those who were in the nutritional intervention sat together to consume the intervention and eating with others has often been linked to reduced feelings of loneliness (Björnwall et al., 2021). Taken together this is a novel, but promising area of research which warrants further exploration.

Results of the main intervention add valuable information to the topic area and build upon previous work in the field. However, there were many aspects of everyday functioning which showed no improvement following multivitamin supplementation, despite theoretical reasons and previous evidence indicating it should. There are several potential explanations for this. The increase in vitamin levels needed to elicit clear effects may not be achievable through supplementation as multivitamin absorption and bioavailability has been questioned (Yetley, 2007) and age associated changes in absorption have been shown to impact mineral bioavailability in older adults (Han, 2018). There is a need for future research to measure pre and post supplementation serum levels of vitamins and minerals to establish whether multivitamins, particularly in older adults, are having the theorised effect on nutritional status. Furthermore, although acute effects of multivitamins have been observed, it must be considered that 12 weeks of supplementation is not enough time to see any improvements in certain outcomes, particularly self-reported health, and physical activity. In fact, it has been suggested that longer-duration randomised controlled trials looking at multivitamin treatment are needed, spanning longer than 12 months to determine true efficacy (Macpherson et al., 2013; NIH State-of-the Science Panel, 2007).

Finally, although the study had minimal exclusion criteria, the participants included were still relatively healthy. Although there was a wide range, the average BMI and alcohol intake were still below the national averages based on sex and age (Conolly & Davies, 2018; Osborne & Cooper, 2018). For both males and females, the average number of years in education was around 15, with most participants being educated to degree level. It has consistently been shown that individuals with higher education levels have better diet quality (Freitas et al., 2017; Thorpe et al., 2019), this is reflected in the current sample as when categorised based on vitamin and mineral intake, for the majority participants had to be split based on mean intake in the sample rather than on averages in the population (see table 3.6 for reference). Despite having higher than average vitamin and mineral intake, the interaction between intake and treatment has still provided valuable information.

To summarise these interaction results: for measures of mood, memory and wellbeing, various interactions were found between baseline vitamin/mineral intake and administered treatment. Following multivitamins, males below the mean intake for vitamin B2 and folate at baseline showed lower levels of depressive traits and lower total mood disturbance, and females below the mean intake of iodine showed lower levels of anxiety. This suggests that the multivitamin supplement may have beneficial effects on mood, but only for those who have lower vitamin/mineral intake when they begin taking the supplement. In males, those who were below the vitamin C mean and consumed placebo showed fewer memory lapses, which is contrary to previous literature in the field that has shown vitamin C levels to be positively associated with memory and cognitive function (Travica et al., 2017). Given this was an isolated effect observed in the placebo group, it may suggest that it is not the vitamin C intake alone which is impacting on memory, but there may be other unknown factors in this subgroup which has led to fewer memory problems.

Similar relationships between dietary vitamin intake and multivitamin supplementation were observed on measures of physical health, activity, and daily functioning. Following multivitamin supplementation, males below the mean of vitamin D had higher levels of physical activity, those below the mean intake of vitamin D and B3 had greater independent activities of daily living and those below the mean intake of vitamin B6 had lower fear of falling. In females following multivitamin those below the vitamin D and selenium mean intake showed lower levels of pain, those below the mean selenium intake also had better role functioning. However, in females, following placebo, those below the mean iodine intake had lower role functioning, suggesting this may be solely due to iodine intake. Iodine is used for the synthesis of thyroid hormone (Shan et al., 2005), therefore lower levels of iodine can result in disordered thyroid functioning (Laurberg et al., 2010). Emerging research has suggested a link between thyroid hormone levels, frailty and independent activities of daily living (Liu et al., 2021), suggesting a potential explanation for lower iodine intake and lower role functioning. This may also explain why this effect was only shown in females in this cohort, as many female participants reported thyroid problems during enrolment into the study.

The most consistent, yet surprising interactions existed between treatment and vitamin/mineral intake on measures of social interaction and loneliness. Following multivitamin, in males, those below the vitamin D mean intake showed higher social functioning but higher levels of loneliness. In males, those below the mean intake of selenium and zinc at baseline reported lower relationship quality and fewer individuals in their social circle following multivitamins. Conversely, in females following multivitamins, those below the mean vitamin B12 and iodine intake had lower levels of loneliness. Whereas females who consumed placebo and were below the iodine mean intake showed higher levels of loneliness. This indicates that in females who have a low intake of iodine, consuming a multivitamin may have beneficial effects on feelings of loneliness. The links between vitamin intake and response to treatment on measures of loneliness are not well understood with no clear mechanism of effect. However, it is clear that there are sex differences in response to multivitamins based on dietary micronutrient intake, with negative effects on those below mean intake in males and positive effects on those below the mean intake in females.

These results show there are clear differences in response to multivitamin supplementation based on nutritional intake which has not been explored in much of the previous research in the area. As there were no effects of treatment alone on these outcomes, this provides evidence that multivitamins have a greater effect in those who have a poorer diet and lower vitamin and mineral intake. There seems to be clear sex differences in these interactions with more consistent results being found in males which was also shown in the results of multivitamin alone, which may be due to characteristics of the male sample. Demographic information showed males reported drinking more alcohol than women, ate less fruit and less veg but more potatoes, and had a higher BMI, indicating worse lifestyle factors which can lead to a better response to treatment. Mineral intake seems to be more important in females with more interactions being shown here. However, it cannot be concluded that these differences are due to the supplement alone, therefore, to fully understand these results, further analyses are needed to determine whether these effects existed at baseline before supplementation or whether they are a direct result of treatment.

As indicated earlier in this section, the nutritional intake of this sample was still relatively good in comparison to the general population in this age range, yet clear differences were observed. It can be hypothesised that these results would be more pronounced in individuals who are below the mean intake in the population or clinically deficient in the vitamins and minerals. Given there were minimal exclusion criteria in the current trial, it was still limited by self-selection bias, with participants who volunteer for supplementation already likely to have optimal nutrient status (Morris & Tangney, 2011). This was further evidenced by Young et al. (2020), whereby participants were screened prior to enrolment in the study aiming for 50%

participants with an optimal diet and 50% with a sub-optimal diet. To randomise 140 participants with this ratio, 501 volunteers had to be screened and of the 461 volunteers who provided dietary screening information 74.4% met the criteria for an optimal diet, showing a clear bias of individuals who volunteer for supplement trials. To fully understand the interaction between multivitamin supplementation and nutrient intake future research needs to consider using *a priori* screening for diet quality to ensure accurate interpretation of nutrient effects.

Despite this potential limitation with the current study, there are also methodological strengths. Typically research studies, especially clinical trials, have been designed by researchers with no input from members of the public (Mullins et al., 2014), creating a researcher-centred study (Tritter, 2009). But more recently there has been a push for more inclusive research design, to allow research questions and outcomes that are important to the study population, increasing the relevance and value of trial-based evidence (Tong et al., 2022). The current study utilised this approach, incorporating qualitative research to determine meaningful outcome measures and taking a person-centred approach to supplementation trial design. This approach has not been applied in this area previously, and its application is recommended for future work in the area.

To conclude, 12 weeks of multivitamin supplementation in older adults aged 70 and over was shown to improve feelings of friendliness in females, and to reduce perceived stress reactivity and emotional loneliness in males. These results replicate and build upon effects shown in previous research. Unlike many previous trials this was conducted on ‘everyday’ older adults with little to no exclusion criteria for taking part, providing a more accurate indication of how these supplements may affect individuals in everyday life, rather than in non-representative healthy samples. The study also built on the recommendations of previous work and measured nutritional intake to look at the interaction between nutrition status and multivitamin supplementation. Differences were found between those above and below the mean intake of vitamins and minerals based on multivitamin supplementation. However, baseline analysis is needed to further explore the impact of habitual vitamin and mineral intake on outcome measures, independent of treatment to determine whether these differences already existed.

## CHAPTER 4: DIETARY INTAKE AND EVERDAY FUNCTIONING IN OLDER ADULTS AGED 70 AND OVER.

Summary

This chapter will explore the effects of dietary intake on markers of everyday functioning in older adults. Based on the results of Chapter 3 clear interactions were shown between nutritional intake and multivitamin supplementation. To fully understand this, any differences at baseline before supplementation must be explored. There is a large body of literature investigating micronutrient intake on psychological functioning, which will be discussed in this chapter. Most of this literature has shown positive associations between vitamin and mineral intake and outcome measures relating to everyday functioning. Surprisingly results of this study showed that those below the mean intake of a variety of vitamins and minerals performed more favourably on everyday function outcomes, than those above the mean. Potential issues with methods of dietary data collection are explored here based on these results.

## 4.1 Introduction

Ageing is a risk factor for noncommunicable chronic diseases, such as diabetes, cancer, and heart disease and an increased risk of frailty, cognitive decline, and disability (Bales & Ritchie, 2002; Clegg & Williams, 2018). All of which have high associated costs of diagnosis, treatment, and care (Shlisky et al., 2017), and present an issue for policy makers due to greater demands on social, insurance, health, and welfare systems (Doyle et al., 2009; Dyer, 2006; Polder et al., 2002). However, progress in medical knowledge and technology, along with the changing relationship between morbidity and life expectancy and the effect of education may alleviate some of this strain (Spijker & MacInnes, 2013).

One of the main factors which can maintain the effectiveness of body systems is nutrition (Kuh & Shlomo, 2004). Nutritional health is essential to overall health, independence, quality of life, mental function, and wellbeing and can help to prevent or delay the onset of certain diseases (Davies, 2011; Stanner, 2009). Therefore, nutrition can play an important role in healthy and independent ageing, which will become more important as the proportion of older adults rises (Phillips, 2003). Older adults often have reduced energy needs due to reduced total energy expenditure, so it is particularly important that nutrient density of diet is high, to meet recommended dietary guidelines (Ferro-Luzzi et al., 2000; Roubenoff et al., 2000).

It has been estimated there are more than 3 million individuals at risk of malnutrition in the UK with the majority of these people living in the community (Elia & Russell, 2009). In 2021 the Scientific Advisory Committee on Nutrition published a statement on nutrition and older adults living in the community, in this they set the dietary reference value for energy, macronutrients and micronutrients for older adults in the UK. The requirements are set for males and females separately in 10-year age bands including 65-74 and 75 and over. However, for micronutrients the dietary reference values are generally the same for all adult age groups, with the exception of vitamin B1, B3, B6 and iron (van Dijk et al., 2021). The results of the National Diet and Nutrition Survey were also published with this report and showed evidence of low micronutrient intake below recommended nutrient intake values, particularly in women and those aged 75 and over (Roberts et al., 2018). Lowest intake was reported for vitamin A, B2, B12, D, iron, folate, magnesium, selenium, and zinc (Bates et al., 2014; Roberts et al., 2018). There are multifactorial causes of micronutrient deficiencies in older adults such as decreased food intake, reduced energy expenditure due to sedentary lifestyle and loss of metabolically active body cell mass (Biesalski et al., 2003). Given the importance of micronutrients on human physiological and psychological functioning (see Chapter 3, section 3.1.1) deficiencies can lead to a range of negative outcomes in older adults.

Nutritional factors are critically important for the maintenance of immune function, with nearly every aspect of the immune system being compromised by inadequate nutrition (Brownie, 2006). A wealth of evidence has shown vitamins including vitamin A, B6, B12, C, D, E and folate; trace elements including zinc, iron, selenium, magnesium and copper play important and complementary roles in supporting the immune system and inadequate intake leads to a decrease in resistance to infections and an increase in disease burden (Calder et al., 2020). In particular, micronutrient deficits of vitamin E, zinc, selenium, and vitamin B6 have been shown to exacerbate dysregulation of the immune system in older adults (Omran & Morley, 2000). Vitamin E is considered one of the most effective nutrients in enhancing immune function (Pae et al., 2012) due to its multiple diverse immunological effects, having roles as an antioxidant, inhibitor of protein kinase C activity, and interacting with enzymes and transport proteins (Lee & Han, 2018). Deficiency in vitamin E can lead to an overall decline in immune function such as impaired T-cell response, decreased lymphocyte proliferation, and reduced delayed hypersensitivity response (Wells & Dumbrell, 2006). Numerous animal and human studies have shown vitamin E deficiency impairs both humoral and cell-mediated immune functions (Han & Meydani, 2006). In human’s vitamin E deficiency is rare, therefore only a limited number of studies have shown how deficiency supports the essential role in immune function (Lewis et al., 2019).

Zinc deficiency affects many different components of the immune system, occurring on many levels and involving the expression of several hundred genes (Cousins et al., 2003; Haase et al., 2007), being required for the biological activity of different enzymes, proteins, cellular proliferation, and genomic stability (Mocchegiani et al., 2013). Zinc is essential in both cell-mediated and humoral immunity, and in older adult patients zinc supplementation improved resistance to infection (Prasad et al., 1993; Sandstead, 1994). Selenium is another essential mineral for efficient and effective operation of the immune system (Arthur et al., 2003). It can influence the functioning of all components of the immune system and its ability to respond to infections and cancers (Spallholz et al., 1990), deficiency has also been associated with increased incidence and severity of viral infections such as influenza and HIV (Gill & Walker, 2008).

Vitamin B6 has been implicated in the regulation of immune response associated with a wide range of diseases including inflammation and certain cancers (Lotto et al., 2011; Rimando & Suh, 2008; Wu & Lu, 2012). Vitamin B6 plays a role in the production of T lymphocytes and interleukins (Meydani et al., 1991; Qian et al., 2017) and recent research has shown those with COVID-19 with severe inflammation had lower levels of vitamin B6 (Kumrungsee et al., 2020). In large scale studies, the lowest level of this vitamin was detected in patients with chronic inflammation and conversely those who had high levels had low levels of inflammation (Sakakeeny et al., 2012).

Undernutrition can also increase the risk of cardiac problems (Omran & Morley, 2000). Evidence from various studies have shown a link between elevated homocysteine levels and an increased risk of cardiovascular diseases (CVD) (McNulty et al., 2008). This is considered a continuum, the higher concentration of homocysteine, the higher the risk of CVD (Jacobsen, 1998). As folic acid, vitamin B12 and B6 are required for metabolism of homocysteine, low blood levels of these vitamins could lead to increased blood homocysteine levels (Chrysant & Chrysant, 2018), deficiencies of these vitamins are the most common cause of mild to moderate elevated homocysteine levels (Refsum et al., 2004). Vitamin B1 deficiency has also been indicated as a risk factor for heart failure, due to its role in ATP production, limiting this may contribute to myocardial dysfunction (Azizi-Namini et al., 2012). Early research showed an inverse relationship between vitamin E and CVD (Rimm et al., 1993; Stampfer et al., 1993) and evidence from cell cultures indicate vitamin E may prevent the development of the disease (Meydani, 2004). Clinical data has shown vitamin C plays a pivotal role in a number of processes linked to the development of CVD (Morelli et al., 2020) and vitamin D metabolites play a role in pathways integrated in cardiovascular function and disease, with deficiency being linked to several cardiovascular risk factors (Lavie et al., 2011; Wang et al., 2012). Minerals such as selenium and zinc are also involved in pathways that can modulate inflammation and are thought to play a role in reducing CVD risk (Sunkara & Raizner, 2019).

There are clear effects of nutritional deficiencies on specific aspects of health in older adults, and nutritional status may also play a role in physical performance, functional status, and frailty (Mugica-Errazquin et al., 2021). As frailty is categorised on five criteria: low muscle strength, unintentional weight loss, feelings of exhaustion, poor physical performance, and reduced physical activity (Bonnefoy et al., 2015), deficits in any of these domains would also indicate frailty. In terms of physical performance, vitamin D has been the focus of the majority of research as it modulates skeletal and cardiac muscle function (Houston et al., 2007) and plays an integral role in regulation of calcium transport and protein synthesis within the muscle cell (Mosekilde, 2005; Pfeifer et al., 2002). Lower serum vitamin D has been associated with muscle weakness, poor physical performance, balance problems, and falls (Houston et al., 2007). Vitamin D status is positively associated with different physical performance tasks including the walking test, chair stands, and tandem stands (Sohl et al., 2013). Sex differences have also been shown with lower serum levels being associated with worse coordination and weaker strength in women, and slower walking time and lower upper limb strength in men (Toffanello et al., 2012).

Aside from vitamin D intake, nutritional status as a whole has been shown to affect functional outcomes such as the timed ‘up and go’ task and is a predictor of falls (Chien & Guo, 2014; Vivanti et al., 2011). In institutional settings, frail residents were more likely to be malnourished and have lower health related quality of life (Salminen et al., 2020). Lower serum concentrations of vitamins B6 and B12 have been to show to predict issues with activities of daily living and risk of impairment in mobility (Bartali et al., 2006; Struijk et al., 2018). Poor intake of vitamins A, C, and E have been associated with decline in physical functioning and greater risk of frailty (Bartali et al., 2008; Bartali et al., 2006; Das et al., 2020). Adequate zinc intake may help preserve physical function and reduce the progression to frailty (Vega-Cabello et al., 2022).

As well as attributing to physical function, both fat soluble and water-soluble vitamins contribute to brain function via a range of biochemical mechanisms (Kennedy & Haskell, 2011). Vitamin D plays many roles related to brain function including neurotransmission functions (Kennedy & Haskell, 2011), vitamin E may play an indirect role in inhabitation and activation of essential enzymatic processes (Brigelius-Flohé, 2019) and the B-vitamins play key roles at all levels of brain function as co enzymes and precursors of co-factors in enzymatic processes (Kennedy & Haskell, 2011). Therefore, deficiencies in one or more of these vitamins may lead to reduced brain function, thus impacting cognition.

To give a brief overview of the literature: many studies have shown an association between low vitamin D levels and cognitive impairment at a cross sectional level (Feart et al., 2017; Jorde et al., 2015). However, five systematic reviews examining vitamin D levels and cognitive function were assessed (Krause & Roupas, 2015), and despite showing an association between the two, causality was not established, and a possible reverse causality was suggested. Systematic review evidence has shown lower vitamin C levels in adults who are cognitively impaired, a direct correlation between vitamin K levels and cognitive performance (Alisi et al., 2019), and elevated levels of vitamin E being associated with reduced risk of cognitive impairment in older adults (Mangialasche et al., 2013). There is extensive epidemiological evidence that sub optimal folate status, B-vitamins and elevated concentrations of homocysteine contribute to cognitive dysfunction (Agnew-Blais et al., 2015; Clarke et al., 1998; Doets et al., 2014; Ford et al., 2013; O'Connor et al., 2022) and to a greater rate of cognitive decline during ageing (An et al., 2019; Blasko et al., 2012; Zylberstein et al., 2011). Evidence also exists for a relationship between trace mineral intake and cognitive function with research showing a deficiency of selenium may contribute to cognitive decline (Cardoso et al., 2014), lower levels of zinc are associated with worse cognitive function (Ortega et al., 1997), and high magnesium intake may improve cognitive function in older adults (Peeri et al., 2021).

It is well established that sleep problems can negatively impact dietary intake through physiological and metabolic pathways (Fernandez et al., 2018; Pistollato et al., 2016), recently more research has focused on the reverse relationship between nutrient levels and associated sleep problems (Grandner et al., 2014). Various reviews have examined the relationship between micronutrient intake/levels and different aspects of sleep. In adults shorter sleep duration was significantly associated with consuming below the recommended intake of copper, folate, iron, magnesium, riboflavin, zinc, and vitamins A, C, E and K (Ikonte et al., 2019), lower vitamin C has also been associated with non-restorative sleep (Grandner et al., 2014). Vitamin D has received particular attention due to having receptors in several areas of the brain involved in sleep regulation and having roles in the production of melatonin, which is the hormone involved in human circadian rhythms and sleep (Romano et al., 2020). Research has consistently shown vitamin D deficiency is associated with poor sleep quality including delayed sleep, duration of sleep, and sleep efficiency (Çakır et al., 2015; Massa et al., 2015; Song & Wu, 2018). In terms of minerals, lower selenium intake has been associated with difficulty falling asleep, greater potassium with less daytime sleepiness, and a positive relationship of zinc and magnesium intake with sleep duration (Grandner et al., 2014; Ji et al., 2017).

Micronutrient intake may also influence mood (Benton & Donohoe, 1999), with various explanatory models as to why this can occur including impact on errors of metabolism, alteration of gene expression and mood disorders being long-latency deficiency diseases (Kaplan et al., 2007). The B vitamins are essential for balancing mood (Mikkelsen & Apostolopoulos, 2018) as they have roles in neurochemical synthesis and their role in homocysteine synthesis is of particular importance (Kennedy, 2016). Evidence has shown a direct positive effect of vitamin B12 on positive affect and a twofold risk of having severe depression in those with B12 deficiency (Edney et al., 2015; Penninx et al., 2000), however, more recent research has not replicated these earlier associations (Elstgeest et al., 2017). Significant positive correlations have also been shown between vitamin B2, B3, B5, B6 and B12 and measures of overall mental health (Davison & Kaplan, 2012). Vitamin C has been shown to me a moderator of mood, hypothesised to be due to its role in the synthesis of the monoamine neurotransmitters dopamine, noradrenaline, and serotonin, which are linked to depressive symptoms (Delgado, 2000; Englard & Seifter, 1986). Observational studies have suggested a relationship between vitamin C status/intake and mood in various populations including older adults (Gariballa, 2014; Oishi & Kawakami, 2009; Pullar et al., 2018). Low levels of vitamin D have been associated with poor mood and clinical depression (Berk et al., 2007) as it has been proposed vitamin D plays an important role in serotonin regulation, which is a regulator of mood (Patrick & Ames, 2014). Research in older adults has shown vitamin D deficiency is significantly associated with the presence of a mood disorder (Wilkins et al., 2006). Trace element deficiencies in relation to mood has also amassed research interest with zinc, magnesium and selenium all being linked to mood, with lower levels predicting worse mood (Benton, 2002; Stanisławska et al., 2014; Tahmasebi et al., 2017; Tarleton & Littenberg, 2015).

As outlined, nutritional intake can affect various aspects of everyday functioning, and this is especially important in older adults in which micronutrient intake may be sub-optimal. These deficits due to inadequate micronutrient intake may also impact other aspects of daily functioning, creating an indirect link between intake and outcome. For instance, it has been evidenced that the origin of loneliness has a biological stress related aspect (Campagne, 2019), therefore nutritional deficiencies worsening stress response may affect loneliness, creating a consequential mechanism of effect. Additionally poor self-reported health, poor functional status, poor mental health, and cognitive deficits have all been identified as being significantly associated with loneliness (Cohen-Mansfield et al., 2016), and as outlined above these are all factors impacted by nutritional intake, showing additional ways nutritional deficiency may have indirect effects on loneliness in older adults.

Based on the evidence reviewed here, it is clear there are serious and debilitating consequences of inadequate micronutrient intake in older adults. However, results are conflicting with some research showing no or weak evidence, while other areas have been under researched or not researched at all. The results of Chapter 3 (section 3.3.3) clearly show there are individual differences in response to multivitamin supplementation based on reported micronutrient intake. Therefore, it is important to understand differences between high and low micronutrient intake before supplementation, to fully understand the responses to supplementation reported in Chapter 3. This is also important as a contribution to the literature investigating how nutritional intake can affect everyday functioning. The current study aims to establish any differences between high and low vitamin and mineral intake in adults aged 70 and over on the outcomes of everyday functioning investigated in Chapter 3.

## 4.2 Method

### 4.2.1 Design

The current study employed a quasi-experimental independent groups design. The independent variable was based on reported vitamin intake on the Food Frequency Questionnaire (see section 3.2.3.2). There were two levels of the independent factor: above or below the mean vitamin intake. Outcome variables were grouped into three overall categories: wellbeing, mood and memory; physical health and activity; and social interaction and loneliness, with the dependent variable being the relevant outcome on each questionnaire at baseline.

### 4.2.2 Participants

All participants were enrolled in the main intervention study (see Chapter 3, section 3.2.2. for full details), therefore the same inclusion/criteria applied to this study. Those included in this study were those who completed the baseline assessment and the Food Frequency Questionnaire (FFQ) (see section 3.2.3.2). Of the participants enrolled in the study, 198 completed the FFQ and were therefore included in this study (111 female, 87 male). Demographic data is shown in Table 4.1.

### 4.2.3 Materials

Questionnaires utilised were the same as those in Chapter 3, see section 3.2.3.2 for full descriptions of all questionnaires used.

### 4.2.4. Procedure

All participants in this study were enrolled in the wider intervention outlined in chapter 3. Participants were sent an information sheet which outlined the study in full, after reading this they were booked in for a telephone screening appointment with the researcher. During this call participant’s completed informed consent and all demographic information was taken. On the day of testing participants were asked to avoid alcohol for 24 hours and caffeine for 12 hours and eat a standardised breakfast of cereal and/or toast and to complete the questionnaire in the morning at least an hour after consuming this. Participants were sent the link to the outcome questionnaires via email, and they completed these at their own pace. They were additionally sent a link to the FFQ which could be completed at any point and there were no restrictions for participants before completing this. Participants were presented with 130 food items and asked how often they consumed this on average in the past year. Food items could be left blank but any participants with 10 or more missing items were removed from analysis. Upon completion of both questionnaires' participants were fully debriefed.

### 4.2.5 Treatment of Data

For the Food Frequency Questionnaire (FFQ), data was checked for outliers using boxplots in IBM SPSS Statistics version 26. Individual data points which were indicated as extreme outliers by SPSS (any data point lying outside the following range: 3$^{rd}$ quartile + 3 x interquartile range or 1$^{st}$ quartile – 3 x interquartile range) were removed from the data (see Appendix IV for boxplots showing data points removed)

Data was split by sex and one-way ANOVAs were run between the independent grouping variable for each vitamin/mineral to check for any significant differences in demographics. For vitamin D intake, in males, there was a significant difference in age [$F$ (1,82) = 5.55, $p$ = .021] and in females a significant difference in alcohol intake [$F$ (1,107) = 7.87, $p$ = .006]. Vitamin B2 intake, in females, there was a significant difference in age [$F$ (1,109) = 4.17, $p$ = .044]. In females there was a significant difference in alcohol consumption based on folate [$F$ (1,107) = 4.74, $p$ = .032] vitamin E [$F$ (1,108) = 3.97, $p$ = .049] and polyunsaturated fat intake [$F$ (1,109) = 6.03, $p$ = .016]. In manganese intake, in females, there was a significant difference in BMI [$F$ (1,109) = 4.91, $p$ = .029]. Based on this it was decided to control for age, alcohol intake and BMI in all analysis to keep this standardised.

Descriptive statistics were calculated for all measures and data was analysed using independent groups ANCOVAs. Vitamin/mineral intake was the independent factor with two levels, above or below the mean vitamin intake. In the first instance means for each vitamin were based on population means, taken from the Scientific Advisory Committee on Nutrition (2021) statement on nutrition and older adults living in the community. Participants were therefore categorised as being above or below the mean based on their sex and age group

(65-74 or 75+) in the population means. However, when this led to extreme unequal sample size (less than 30 participants in one group, which represents ~ 25% of the sample), participants were categorised as being above or below the mean based on the population mean for age alone. If there were still unequal sample sizes following this approach, participants were categorised as being above or below the mean based on their sex and age group (70-74 or 75+) in this sample rather than by population means. The classification approach is identified for each variable as necessary, with the Recommended Nutrient Intake for adults aged 65 and over presented for reference.

The dependent measures were the relevant outcomes for each questionnaire at baseline. Control variables were age, alcohol intake and BMI. Due to volume of analysis only significant results will be presented. Table 4.1 shows the mean used for each vitamin, how this was categorised and the corresponding reference nutrient intake (RNI). The RNI is the amount of a nutrient that is enough to ensure that the needs of nearly all of the group (in this case older adults) are being met.

**Table 4.1**: Means used to split participants for each vitamin, coding for how this was categorised and reference nutrient intake (RNI) based on sex

| | **Male** | | | **Female** | | |
|---|---|---|---|---|---|---|
| | 70-74 | 75+ | RNI | 70-74 | 75+ | RNI |
| Vitamin D (µg/day) [++] | 3.50 | 2.80 | 10.00 | 3.50 | 2.80 | 10.00 |
| Vitamin B1 (mg/day) [+] | 1.70 | 1.54 | 0.90 | 1.38 | 1.26 | 0.80 |
| Vitamin B2 (mg/day) [++] | 1.63 | 1.55 | 1.00 | 1.63 | 1.55 | 1.10 |
| Vitamin B3 (mg/day) [+++] | 21.85 | 21.47 | 16.00 | 22.15 | 22.52 | 12.00 |
| Vitamin B6 (mg/day) [+++] | 2.13 | 2.19 | 1.40 | 2.19 | 2.15 | 1.20 |
| Vitamin B12 (µg/day) [+] | 6.30 | 6.80 | 1.50 | 4.80 | 4.50 | 1.50 |
| Vitamin C (mg/day) [+++] | 112.64 | 108.30 | 40.00 | 128.06 | 137.62 | 40.00 |
| Vitamin E (mg/day) [+++] | 12.64 | 11.29 | 4.00 | 12.25 | 12.86 | 3.00 |
| Folate (µg/day) [+++] | 288.10 | 305.94 | 200.00 | 307.72 | 318.07 | 200.00 |
| Polysaturated fatty acids (g/day) [+++] | 13.30 | 12.50 | 17.00 | 13.18 | 12.63 | 13.00 |
| Zinc (mg/day) [+] | 9.00 | 8.60 | 9.50 | 7.50 | 6.60 | 7.00 |
| Selenium (µg/day) [+++] | 59.54 | 62.16 | 75.00 | 64.30 | 56.31 | 60.00 |
| Manganese (mg/day) [+++] | 3.68 | 3.71 | 3.00 | 3.79 | 3.71 | 3.00 |
| Iodine (µ g/day) + | 183.00 | 191.00 | 140.00 | 157.00 | 134 | 140.00 |

[+] Means based on averages for sex and age in population according to the Scientific Advisory Committee on Nutrition

[++] Means based on averages for age in population according to the Scientific Advisory Committee on Nutrition

[+++] Means based on averages for sex and age in the sample

## 4.3 Results

Of the participants enrolled in the study, 198 completed the FFQ and were therefore included in this study (111 female, 87 male). Demographic data is shown in Table 4.2.

**Table 4.2**. Participant demographic information for the 198 subjects who completed the study per protocol (124 females, 104 males). Means, Std. Deviation (SD), minimum and maximum score reported.

| | Female | | Male | | Overall | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| Age (years) | 73.69 | 4.08 | 74.36 | 3.79 | 73.98 | 3.96 |
| BMI (kg/m$^2$) | 26.65 | 5.15 | 27.70 | 4.75 | 27.12 | 4.99 |
| Years in Education | 15.17 | 3.03 | 15.68 | 2.62 | 15.39 | 2.86 |
| Caffeine (mg per day) | 254.90 | 144.67 | 248.88 | 142.68 | 252.26 | 143.47 |
| Alcohol (units per day) | 0.67 | 0.89 | 1.03 | 0.95 | 0.83 | 0.93 |

### 4.3.1 Analysis based on reported vitamin and mineral intake

#### 4.3.1.1 B Vitamins

All descriptive statistics for significant results relating to B vitamins (mean, SD and sample size) can be found in tables 4.3 (male data) and 4.4 (female data).

*Vitamin B1*

There was an effect of vitamin B1 intake on the CHIPS in both males [$F$ (1,81) = 8.26, $p$ = .005, $h_p^2$ = .092] and females [$F$ (1,105) = 5.14, $p$ = .025, $h_p^2$ = .047]. In both groups those who were below the vitamin B1 mean showed fewer physical symptoms compared to those above the mean. An effect of vitamin B1 intake on POMS fatigue and inertia subscale in males was observed [$F$ (1,79) = 4.70, $p$ = .033, $h_p^2$ = .056], with significantly lower levels in those below the mean intake.

There was an effect of vitamin B1 intake in males on the PSRS work overload subscale [*F* (1,66) = 6.67, *p* = .012, $h_p^2$ = .092], social conflict subscale [*F* (1,66) = 6.88, *p* = .011, $h_p^2$ = .094] and PSRS total score [*F* (1,66) = 4.46, *p* = .038, $h_p^2$ = .063]. In all, those below the vitamin B1 mean had significantly lower stress reactivity.

An effect of vitamin B1 intake on SF20 role functioning was observed in males [*F* (1,81) = 5.06, *p* = .027, $h_p^2$ = .059], and in females there was a significant effect on the SF20 pain subscale [*F* (1,105) = 4.17, *p* = .044, $h_p^2$ = .038]. For both, those below the vitamin B1 intake mean scored significantly better.

On the Convoy Social Network Scale there was a significant effect of vitamin B1 intake on relationship quality on the outer circle in males [*F* (1,78) = 10.67, *p* = .002, $h_p^2$ = .121], with significantly higher relationship quality below the mean intake.

*Vitamin B2*

There was an effect of vitamin B2 intake in females on both prospective memory [F (1,106) = 8.10, p = .005, $h_p^2$ = .071] and retrospective memory [F (1,106) = 3.96, p = .049, $h_p^2$ = .036]. For both those below the mean reported significantly less memory failures.

An effect of vitamin B2 intake on the POMS confusion and bewilderment subscale was observed in females [F (1,105) = 5.03, p = .027, $h_p^2$ =.046], with those below the mean intake showing significantly lower levels than those above the mean.

There was an effect of vitamin B2 on social loneliness on the De Jong-Gierveld loneliness scale for both males [F (1,81) = 4.21, p = .041, $h_p^2$ = .049] and females [F (1,105) = 7.06, p = .009, $h_p^2$ =.063]. In males those below the mean intake showed significantly higher levels of loneliness, however in females those below the mean showed significantly lower levels of loneliness. There was also a significant effect of vitamin B2 on the Lubben social network scale in males [F (1,79) = 11.45, p <. 001, $h_p^2$ = .127]. Those below the mean intake had a smaller social network than those above the mean. For the convoy social network scale, there was an effect of vitamin B2 on the number of individuals in the middle circle in females [F (1,106) = 6.19, p = .014, $h_p^2$ = .055]. Those below the mean has significantly fewer people in this aspect of their social network than those above the mean intake.

*Vitamin B3*

In males, there was an effect of vitamin B3 intake on wellbeing measured on the ONS4 [F (1,81) = 4.01, p = .049, $h_p^2$ = .047], the PSS [F (1,80) = 5.33, p = .024, $h_p^2$ = .062], the PSRS work overload subscale [F (1,66) = 6.22, p = .015, $h_p^2$ = .086] and PSRS social conflict subscale [F (1,66) = 5.42, p = .023, $h_p^2$ = .076]. For all, those below the mean vitamin B3 intake scored significantly better.

A significant effect of vitamin B3 intake on physical health measured by the CHIPS was observed in females [F (1,104) = 6.54, p = .012, $h_p^2$ = .059] and on the SF20 Health Perceptions subscale [F (1,104) = 8.07, p = .005, $h_p^2$ = .072]. Those below the vitamin B3 mean intake had significantly fewer physical symptoms and better health perceptions.

*Vitamin B6*

In males there was a significant effect of vitamin B6 on the relationship quality of both the middle circle of their social network [F (1,79) = 4.72, p = .033, $h_p^2$ = .056] and the outer circle [F (1,79) = 5.28, p = .024, $h_p^2$ = .063]. In both, relationship quality was higher in those who were below the mean for vitamin B6 intake.

There was a significant effect of vitamin B6 in females on the number of individuals in the most inner circle of their social network [F (1,104) = 4.92, p = .029, $h_p^2$ = .045] and the middle circle of their social network [F (1,104) = 4.36, p = .039, $h_p^2$ = .040], for both those below the vitamin B6 mean had fewer people in their social network.

*Vitamin B12*

There were no effects of vitamin B12 on any outcome measure.

Folate

There were no effects of folate on any outcome measure.

**Table 4.3**. Sample size, unadjusted mean, standard deviation (SD) and *p* values for each significant outcome measure relating to B vitamin analysis in males.

| | Below Vitamin Mean | | | Above Vitamin Mean | | | |
|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | *p* |
| **Vitamin B1** | | | | | | | |
| CHIPS | 61 | 10.00 | 9.29 | 25 | 17.04 | 15.09 | .005 |
| POMS Fatigue Inertia | 60 | 2.82 | 4.43 | 24 | 5.38 | 6.70 | .033 |
| PSRS Work Overload | 50 | 2.04 | 2.15 | 21 | 3.62 | 2.38 | .012 |
| PSRS Social Conflict | 50 | 3.26 | 2.00 | 21 | 4.57 | 1.78 | .011 |
| PSRS Total | 50 | 13.02 | 7.72 | 21 | 17.14 | 7.24 | .038 |
| SF20 Role Functioning | 61 | 89.34 | 24.35 | 25 | 74.00 | 43.59 | .027 |
| Convoy Social Network -Outer Circle Relationship Quality | 58 | 5.79 | 3.13 | 25 | 3.57 | 2.97 | .002 |
| **Vitamin B2** | | | | | | | |
| De Jong-Gierveld Social Loneliness | 34 | 2.94 | 1.79 | 52 | 2.12 | 1.85 | .041 |
| Lubben Social Network Scale | 32 | 24.88 | 9.29 | 52 | 31.40 | 8.23 | <.001 |
| **Vitamin B3** | | | | | | | |
| Wellbeing (ONS4) | 48 | 31.75 | 5.51 | 38 | 29.50 | 5.89 | .049 |
| Perceived Stress Scale | 47 | 9.26 | 6.34 | 38 | 12.34 | 6.39 | .024 |
| PSRS Work Overload | 38 | 1.87 | 2.02 | 33 | 3.24 | 2.45 | .015 |
| PSRS Social Conflict | 38 | 3.13 | 2.03 | 33 | 4.24 | 1.85 | .023 |
| **Vitamin B6** | | | | | | | |
| Convoy Social Network -Middle Circle Relationship Quality | 44 | 7.26 | 2.32 | 40 | 5.98 | 3.00 | .033 |
| Convoy Social Network -Outer Circle Relationship Quality | 43 | 5.90 | 2.91 | 40 | 4.28 | 3.38 | .024 |
| **Vitamin B12** | - | - | - | - | - | - | - |
| **Folate (B9)** | - | - | - | - | - | - | - |

**Table 4.4**. Sample size, unadjusted mean, standard deviation (SD) and *p* values for each significant outcome measure relating to B vitamin analysis in females.

| | Below Vitamin Mean | | | Above Vitamin Mean | | | |
|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | *p* |
| **Vitamin B1** | | | | | | | |
| CHIPS | 48 | 12.31 | 11.33 | 62 | 19.15 | 16.99 | .025 |
| SF20 Pain | 48 | 32.92 | 25.60 | 62 | 44.84 | 27.51 | .044 |
| **Vitamin B2** | | | | | | | |
| PRMQ Prospective memory | 32 | 16.72 | 5.77 | 79 | 29.38 | 5.89 | .005 |
| PRMQ Retrospective memory | 32 | 15.47 | 5.54 | 79 | 17.66 | 5.70 | .049 |
| POMS Confusion Bewilderment | 32 | 5.09 | 4.43 | 78 | 7.94 | 6.15 | .027 |
| De Jong-Gierveld Social Loneliness | 32 | 1.00 | 1.30 | 78 | 2.14 | 1.95 | .009 |
| Convoy Social Network -Middle Circle No. Individuals | 32 | 2.63 | 2.12 | 79 | 4.82 | 3.48 | .014 |
| **Vitamin B3** | | | | | | | |
| CHIPS | 56 | 12.71 | 10.72 | 53 | 19.89 | 18.17 | .012 |
| SF20 Health Perceptions | 56 | 73.23 | 24.86 | 53 | 60.42 | 26.22 | .005 |
| **Vitamin B6** | | | | | | | |
| Convoy Social Network -Inner Circle No. Individuals | 60 | 5.45 | 3.24 | 49 | 6.86 | 4.20 | .029 |
| Convoy Social Network -Middle Circle No. Individuals | 60 | 3.98 | 3.01 | 49 | 5.06 | 3.39 | .039 |
| **Vitamin B12** | - | - | - | - | - | - | |
| **Folate (B9)** | - | - | - | - | - | - | |

### 4.3.1.2 Vitamin C, D and E

All descriptive statistics for significant results relating to vitamin C, D and E (mean, SD and sample size) can be found in tables 4.5 (male data) and 4.6 (female data).

*Vitamin C*

There was an effect of vitamin C intake in females on POMS anger hostility subscale [$F$ (1,102) = 6.28, $p$ = .014, $h_p^2$ = .058], vigour activity subscale [$F$ (1,102) = 8.27, $p$ = .005, $h_p^2$ = .075], friendliness [$F$ (1,102) = 11.40, $p$ = .001, $h_p^2$ = .101] and total mood disturbance [$F$ (1,102) = 4.04, $p$ = .047, $h_p^2$ = .038]. In all, those above the vitamin C mean intake scored significantly better.

*Vitamin D*

There was an effect of vitamin D intake in females on the number of people in the outer circle of an individual's social network [$F$ (1,104) = 4.20, $p$ = .043, $h_p^2$ = .039], with those above the mean having significantly more individuals in this aspect of their social network. There was also an effect on the overall relationship quality of all individuals in females' social network [$F$ (1,104) = 4.69, $p$ = .033, $h_p^2$ = .043], those below the mean had significantly higher overall relationship quality.

*Vitamin E*

In females there was a significant effect of vitamin E intake on the yale physical activity scale, total time [$F$ (1,105) = 4.42, $p$ = .038, $h_p^2$ = .040] and energy expenditure subscale [$F$ (1,105) = 4.39, $p$ = .039, $h_p^2$ = .040], with those below the mean intake having significantly higher levels of physical activity and energy expenditure.

In males a significant effect of vitamin E intake on the relationship quality in the inner circle of the convoy social network model was observed [$F$ (1,79) = 7.95, $p$ = .006, $h_p^2$ = .091], with significantly higher relationship quality in those below the mean intake.

**Table 4.5.** Sample size, unadjusted mean, standard deviation (SD) and *p* value for each significant outcome measure relating to vitamin C, D and E analysis in males.

| | Below Vitamin Mean | | | Above Vitamin Mean | | | |
|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | *p* |
| **Vitamin C** | - | - | - | - | - | - | |
| **Vitamin D** | - | - | - | - | - | - | |
| **Vitamin E** | | | | | | | |
| Convoy Social Network- Inner Relationship Quality | 48 | 9.20 | 0.91 | 36 | 7.97 | 2.65 | .006 |

**Table 4.6.** Sample size, unadjusted mean, standard deviation (SD) and *p* value for each significant outcome measure relating to vitamin C, D and E analysis in females.

| | Below Vitamin Mean | | | Above Vitamin Mean | | | |
|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | *p* |
| **Vitamin C** | | | | | | | |
| POMS Anger Hostility | 62 | 3.95 | 5.84 | 45 | 1.64 | 2.85 | .014 |
| POMS Vigour Activity | 62 | 15.82 | 6.76 | 45 | 19.73 | 7.63 | .005 |
| POMS Friendliness | 62 | 15.52 | 4.18 | 45 | 18.24 | 4.01 | .001 |
| POMS Total Mood Disturbance | 62 | 14.23 | 32.78 | 45 | 2.09 | 32.85 | .047 |
| **Vitamin D** | | | | | | | |
| Convoy Social Network -Outer Circle No. Individuals | 76 | 3.58 | 3.36 | 36 | 4.67 | 3.32 | .043 |
| Convoy Social Network -Overall Relationship Quality | 73 | 7.88 | 1.17 | 36 | 7.24 | 1.70 | .033 |
| **Vitamin E** | | | | | | | |
| YPAS Total Time | 65 | 31.65 | 16.78 | 45 | 26.12 | 12.36 | .038 |
| YPAS Energy Expenditure | 64 | 109.88 | 58.02 | 45 | 91.63 | 46.36 | .039 |

#### 4.3.1.3. Minerals and Polyunsaturated Fatty Acids (PUFAs)

All descriptive statistics for significant results relating to minerals and PUFAs (mean, SD and sample size) can be found in tables 4.7 (male data) and 4.8 (female data).

*Zinc*

There was an effect of zinc intake on the Lubben social network scale in males [*F* (1,79) = 5.32, $p$ = .024, $h_p^2$ = .063], with those below the mean having a significantly smaller social network.

*Selenium*

In males there was an effect of selenium intake on the perceived stress scale [*F* (1,80) = 6.59, $p$ = .012, $h_p^2$ = .076], with lower levels of stress in those below the mean intake. Males below the selenium intake mean also scored significantly lower on the perceived stress reactivity work overload subscale [*F* (1,66) = 5.61, $p$ = .021, $h_p^2$ =.078]

There was an effect in males on POMS anger and hostility subscale [*F* (1,79) = 4.81, $p$ = .031, $h_p^2$ = .057] and POMS total mood disturbance [*F* (1,79) = 4.20, $p$ = .044, $h_p^2$ = .050], with significantly lower levels in those below the selenium intake mean. Trends were observed for both the POMS tension anxiety subscale [*F* (1,79) = 3.69, $p$ = .058, $h_p^2$ = .045] and the vigour activity subscale [*F* (1,79) = 3.76, $p$ = .056, $h_p^2$ = .045] in males, with those below the selenium intake mean scoring more positively.

There was an effect of selenium intake on the HADS depression subscale in females which was approaching significance [*F* (1,106) = 3.86, $p$ = .052, $h_p^2$ = .035], with lower levels in those below the mean intake. An effect was also observed in females on the CHIPS [*F* (1,106) = 6.89, $p$ = .010, $h_p^2$ = .061], with fewer physical symptoms in those below the selenium intake mean. An effect was also observed on the Convoy Social network scale middle circle number of relationships [*F* (1,106) = 7.81, $p$ = .006, $h_p^2$ = .069], those below the mean had significantly fewer relationships in this aspect of their social network. A trend of selenium intake on the overall average relationship quality across all aspects of the convoy social network was shown in females [*F* (1,106) = 3.85, $p$ = .053, $h_p^2$ = .035], with higher relationship quality in those below the selenium mean intake.

*Manganese*

In males there was an effect of manganese intake on the Convoy inner circle relationship quality [$F$ (1,80) = 7.86, $p$ = .006, $h_p^2$ = .089] and overall relationship quality [$F$ (1,80) = 6.21, $p$ = .015, $h_p^2$ = .072], in both those below the mean intake had significantly higher relationship quality.

*Iodine*

In males an effect of iodine intake on prospective memory was approaching significance [$F$ (1,81) = 3.91, $p$ = .051, $h_p^2$ = .046], with those below the mean intake reporting fewer memory failures.

In females there was an effect of iodine intake on the CHIPS [$F$ (1,106) = 5.72, $p$ = .019, $h_p^2$ = .051], with those below the mean intake reporting fewer physical health problems. There was also an effect on the SF20 pain subscale [$F$ (1,106) = 4.46, $p$ = .037, $h_p^2$ = .040], with lower levels of pain in those below the mean intake.

*PUFAs*

In males there was an effect of PUFA intake on the PSRS social conflict subscale [$F$ (1,67) = 4.53, $p$ = .036, $h_p^2$ = .064], with lower levels in those below the mean intake.

An effect of PUFA intake on wellbeing in females was approaching significance [$F$ (1,106) = 3.86, $p$ = .052, $h_p^2$ = .035], with better wellbeing in those below the mean intake. There were also lower levels of depression on the HADS depression subscale [$F$ (1,106) = 4.73, $p$ = .032, $h_p^2$ = .043] and POMS depression dejection subscale [$F$ (1,105) = 7.98, $p$ = .006, $h_p^2$ = .071] in females below the mean PUFA intake. There was an effect of PUFA intake on the POMS fatigue inertia subscale [$F$ (1,105) = 5.69, $p$ = .019, $h_p^2$ = .051], confusion bewilderment subscale [$F$ (1,105) = 9.96, $p$ = .002, $h_p^2$ = .087] and total mood disturbance [$F$ (1,105) = 7.14, $p$ = .009, $h_p^2$ = .064], with lower levels in those below the mean intake. An effect was observed of PUFA intake on the CHIPS in females [$F$ (1,106) = 8.79, $p$ = .004, $h_p^2$ = .077], with fewer physical symptoms in those below the mean intake. There were also significantly better health perceptions on the SF20 subscale in those below the intake mean [$F$ (1,106) = 4.76, $p$ = .031, $h_p^2$ = .043].

**Table 4.7**. Sample size, unadjusted mean, standard deviation (SD) and *p* value for each significant outcome measure relating to minerals in males.

| | Below Mineral Mean | | | Above Mineral Mean | | | |
|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | *p* |
| **Zinc** | | | | | | | |
| Lubben Social Network Scale | 48 | 26.90 | 9.29 | 36 | 31.61 | 8.39 | .024 |
| **Selenium** | | | | | | | |
| Perceived Stress Scale | 46 | 9.07 | 5.89 | 39 | 12.49 | 6.78 | .012 |
| PSRS Work Overload | 37 | 1.86 | 2.00 | 34 | 3.21 | 2.46 | .021 |
| POMS Anger Hostility | 46 | 2.00 | 2.92 | 38 | 4.03 | 5.64 | .031 |
| POMS Tension Anxiety | 46 | 4.02 | 4.46 | 38 | 6.18 | 6.51 | .058 |
| POMS Total Mood Disturbance | 46 | -3.98 | 24.17 | 38 | 8.03 | 32.08 | .044 |
| POMS Vigour Activity | 46 | 22.30 | 7.18 | 38 | 19.42 | 6.31 | .056 |
| POMS Total Mood Disturbance | 46 | -3.98 | 24.17 | 38 | 8.03 | 32.08 | .044 |
| **Manganese** | | | | | | | |
| Convoy Social Networks Inner Circle Relationship Quality | 46 | 9.25 | 0.89 | 39 | 8.03 | 2.56 | .006 |
| Convoy Social Networks Overall Relationship Quality | 46 | 8.09 | 1.32 | 39 | 7.22 | 1.73 | .015 |
| **Iodine** | | | | | | | |
| PRMQ Prospective Memory | 67 | 18.46 | 5.56 | 19 | 21.47 | 6.73 | .051 |
| **PUFAs** | | | | | | | |
| PSRS Social Conflict | 40 | 3.23 | 1.99 | 32 | 4.25 | 1.93 | .036 |

**Table 4.8.** Sample size, unadjusted mean, standard deviation (SD) and *p* value for each significant outcome measure relating to minerals in females.

| | Below Mineral Mean | | | Above Mineral Mean | | | |
|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | *p* |
| **Zinc** | - | - | - | - | - | - | |
| **Selenium** | | | | | | | |
| HAD Depression | 63 | 4.05 | 2.78 | 48 | 5.33 | 4.01 | .052 |
| CHIPS | 63 | 12.97 | 10.30 | 48 | 20.52 | 18.93 | .010 |
| Convoy Social Network Middle Circle No. of Relationships | 63 | 3.84 | 2.82 | 48 | 5.31 | 3.47 | .006 |
| Convoy Overall Relationship Quality | 63 | 7.85 | 1.12 | 48 | 7.33 | 1.72 | .053 |
| **Manganese** | - | - | - | - | - | - | |
| **Iodine** | | | | | | | |
| CHIPS | 64 | 13.52 | 11.27 | 47 | 19.94 | 18.56 | .019 |
| SF20 Pain | 64 | 35.94 | 24.00 | 47 | 45.53 | 29.69 | .037 |
| **PUFAs** | | | | | | | |
| Wellbeing | 66 | 29.17 | 5.87 | 45 | 26.87 | 6.87 | .052 |
| HADS Depression | 66 | 4.03 | 3.06 | 45 | 5.44 | 3.75 | .032 |
| POMS Depression Dejection | 65 | 3.49 | 5.67 | 45 | 8.02 | 10.82 | .006 |
| POMS Fatigue Inertia | 65 | 3.57 | 4.90 | 45 | 6.69 | 7.06 | .019 |
| POMS TMD | 65 | 1.60 | 25.93 | 45 | 19.47 | 37.93 | .009 |
| CHIPS | 66 | 12.95 | 11.28 | 45 | 21.04 | 18.43 | .004 |
| SF20 Health Perceptions | 66 | 72.61 | 25.19 | 45 | 60.38 | 25.98 | .031 |

## 4.4. Discussion

The aim of the current study was to investigate how nutritional intake of vitamins and minerals impacts various outcomes related to everyday functioning in older adults. This was achieved by categorising participants into either above or below the mean intake of each vitamin/mineral based on either population averages or sample averages. As few studies have considered baseline differences, this adds to the growing body of literature on this topic and allows for a greater understanding of the responses to treatment presented in Chapter 3. Results showed habitual intake of various vitamins and minerals had effects on different markers of everyday functioning, and that these differed between males and females. Surprisingly, for many variables, favourable outcomes were shown in those who were below the mean intake.

There was a range of group difference based on mean habitual intake of B-vitamins, which for the majority differed by sex. However, in both males and females, lower intake of vitamin B1 led to fewer physical symptoms reported, indicative of better overall health and reduced feelings of pain in females. Males who reported vitamin B1 and B3 intake below the mean reported lower levels of fatigue, lower stress levels on a range of outcome measures, better role functioning, and higher overall wellbeing. Females who reported below the mean intake of vitamin B2 reported less memory failures and less confusion/bewilderment. These results are surprising given that the B-vitamins play critical roles in the immune system and brain function, and are essential for balancing mood (Calder et al., 2020; Kennedy & Haskell, 2011; Mikkelsen & Apostolopoulos, 2018), where higher intakes are associated with better functioning.

There was also a range of effects of B-vitamin intake on measures of social interaction and social networks, however, this was often in the opposite direction based on sex. Results showed lower social loneliness and higher relationship quality in males who reported below the mean intake of vitamin B1, B2 and B6. However, in female’s, those above the vitamin B2 and B6 mean intake had lower social loneliness and a greater number of individuals in their social network, respectively. Furthermore, in female’s, vitamin D intake posited effects on social relationships with those who had higher intake having more relationships in certain aspects of their social network, but worse relationship quality than those below the mean intake. The effect shown in females is consistent with previous research which has shown loneliness and a lack of meaningful social contacts is related to dietary inadequacies (Walker

& Beauchene, 1991). This also suggests response to vitamin intake on measures of social interaction have clear sex differences which must be considered in future work in the area.

The intake of vitamin C showed prominent effects in females alone. It was shown that females who were above the mean intake of vitamin C had higher levels of vigour and friendliness and lower levels of anger and mood disturbance. Higher vitamin C intake being associated with higher levels of vigour is likely due to poor vitamin C status often manifesting as fatigue and as a result a reduced desire to be physically active (Ben-Zvi & Tidman, 2012; Johnston et al., 2014). Therefore, the opposite relationship is likely to be true, with higher intake of vitamin C leading to increased feelings of vigour, as shown here. The positive association with mood outcomes is also in line with previous research which has consistently shown a relationship between vitamin C intake and mood in older adults (Gariballa, 2014; Oishi & Kawakami, 2009). The current research extends this by showing effects in mood facets aside from depression, which previous literature has largely focused on, indicating vitamin C intake can have effects on a variety of mood outcomes.

The intake of vitamin E also elicited effects in females, results showed that those who consumed below the mean intake had higher levels of physical activity and higher energy expenditure. Previous research has shown the opposite relationship, with older adults who have higher physical activity levels exhibiting greater blood levels of vitamin E (Alghadir et al., 2021). However, it has been shown that there is not a good association between plasma levels of vitamin E and dietary intake (Owen et al., 2005). Therefore, it must be considered the beneficial effects of higher serum vitamin E on physical activity are not reflected here as intake does not equal absorption. It could be suggested that those who have reported lower intake may have better absorption, thus higher serum levels. Further work is needed to assess both dietary intake and serum levels of vitamins and the effect on everyday functioning to see if any differences are found.

There were also clear effects based on mineral intake in the sample. Being below the mean intake of selenium elicited beneficial effects in both males and females. In males this led to lower levels of stress, anger, and total mood disturbance, and in females, lower levels of depression and lower physical health symptoms. Mood effects of selenium have been shown previously (Benton, 2002), but showing the opposite to results shown here, with lower levels predicting worse mood. Females below the selenium mean intake reporting fewer physical symptoms also contrasts with what was expected given selenium's role in supporting the immune system (Calder et al., 2020; Omran & Morley, 2000). Similar results were shown in females based on iodine intake, with those below the mean intake reporting fewer physical symptoms and lower levels of pain. Again, this was in the opposite direction to expectation, due to iodine's role in production of thyroid hormones, deficiency being a risk factor for hypothyroidism with this subsequently being associated with frailty, muscle wasting, and osteoporosis (Boelaert, 2013; Jayaprasad & Francis, 2005; Kehoe et al., 2019). This suggests that lower levels would result in increased negative physical symptoms. Lower iodine intake was also associated with better memory in males, there is little research in terms of iodine intake alone and its effect on cognition and memory. Buchanan et al. (2015) found no evidence that higher iodine intake, measured via both urinary and dietary measures, was associated with better memory performance in healthy older adults. Therefore, it is hard to draw clear conclusions based on the conflicting nature of results in comparison to previous literature.

Similarly, being below the mean intake of polyunsaturated fatty acids was associated with positive effects in participants. In males there was lower stress reactivity in response to social conflict, in females there were positive mood effects such as increased wellbeing, lower depression scores and reduced mood disturbance, lower fatigue, less physical symptoms, and better health perceptions. Previous research has shown that higher intake of certain polyunsaturated fatty acids (omega-6) have been associated with greater depressive symptoms and poorer self-reported mental health in older adults (Conklin, Harris, et al., 2007; Conklin, Manuck, et al., 2007; Milte et al., 2011). Again, the positive health outcomes associated with lower intake may be due to omega-6, as consuming too much has been shown to change normal physiological function to pathophysiological levels which can cause harm in a dose responsive manner (Yamashima et al., 2020). This may, therefore, be a contributing factor for these effects, and further work is needed to explore differential mood effects of omega-3 and omega-6.

Mineral intake also had effects on measures of social interaction and loneliness. Lower intake of manganese, in males, and selenium, in females, was associated with a smaller social network. There is little wider research in this specific area, very early research indicated older adults with more extensive social networks also had more adequate diets (McIntosh et al., 1989), which the current research supports in terms of mineral intake. However, the opposite relationship was found regarding B-vitamin intake, suggesting this relationship is not linear across all vitamins and minerals and some may play a more pivotal role than others. Interestingly, in males, having lower intake of manganese led to fewer social connections but relationship quality was rated as higher in this group. This may seem logical as research has shown that denser social networks tend to have better relationship quality (Pinquart & Sorensen, 2001; Stokes, 1985).

Although potential mechanisms of effect have been suggested throughout it must be acknowledged that many of the results were not expected with better scores in those below the mean intake for the majority of vitamins and minerals.  Only vitamin B1, B12, zinc and iodine could be categorised in this sample based on the Scientific Advisory Committee on Nutrition (2021) statement which reports mean intake in the overall population. The sample means for all other vitamins and minerals were higher than that reported in the population based on age and sex, and cut off values used to categorise participants were above the RNI. Therefore, results showing beneficial outcomes of being below the mean intake do not accurately represent low intake of the specific vitamin and mineral. Being below the mean intake in this sample can still represent having higher intake than the mean in the population. Therefore, it may be there are optimum intakes for each and more does not always equal better outcomes. Beneficial outcomes relating to intake of vitamins/minerals may follow an inverted U-shaped curve. Future work is needed in individuals with a range of intake, including clinically low intake, in order to determine optimum intake levels.

As previously mentioned, reported intake does not always correlate with serum levels. This can be due to absorption issues and issues with reporting dietary intake, particularly when using food frequency questionnaires. Although it has been shown there are consistent strong associations between biomarkers and dietary intake assessed by the FFQ (Bingham et al., 2008), various other publications have indicated the FFQ is prone to error, including over estimation of certain food groups and vitamins. Seven-day food diaries provide a more accurate representation of dietary intake and output estimates from this are closer to urinary biomarkers than that of the FFQ (Bain et al., 2015; Day et al., 1999; McKeown et al., 2001; Riboli et al., 2002). Therefore, reported intake must be interpreted with caution.

Furthermore, there was no consideration of diet beyond the vitamins and minerals which were included in the multivitamin. The FFQ provides data on a range of other nutrients and food groups which may elicit effects on the outcomes of interest. For example, protein intake has clear effects on strength, physical function, and functional disability in older adults (Bauer et al., 2013; McGrath et al., 2020; Yuan et al., 2021). Magnesium intake is positively associated with better mood (Tarleton & Littenberg, 2015) and has been shown to improve sleep quality and quantity (Ji et al., 2017). Higher nut consumption has been linked to lower risk of sarcopenia and better cognitive function in older adults, especially when considered as part of the overall diet, suggesting a synergistic effect with other food groups (Tan et al., 2021). Based on this, taking a whole diet approach may be more advantageous than individual micronutrients when considering the effects on everyday functioning.

To conclude the current study aimed to establish differences between high and low micronutrient intake on outcomes relating to everyday functioning in older adults. This was achieved by grouping participants based on their reported nutrient intake as assessed by a food frequency questionnaire. Results have shown clear differences on a range of everyday functioning outcomes based on both vitamin and mineral intake. Surprisingly, many of these results showed preferable outcomes when participants consumed below the mean intake, which contrasts with previous literature in the field. The grouping of variables and accuracy of reporting of dietary intake are potential explanations for this. Future work is needed in this area to both compare reported dietary intake to objective blood biomarkers and to see how this impacts outcome measures.

# CHAPTER 5: THE EFFECTS OF COVID-19 LOCKDOWN ON HEALTH AN PSYCHOSOCIAL FUNCTIONING IN OLDER ADULTS AGED 70 AND OVER


**Summary**

As outlined in Chapter 3 the original study planned for this PhD was due to run as a face-to-face intervention. As the UK went into an imposed lockdown in March 2020 as a response to the COVID-19 pandemic, the research study was adapted to run as an online study (results of which are reported in Chapter 3).

This led to a group of participants who completed their baseline assessment before lockdown and follow up during lockdown. Therefore, this gave the unique opportunity to explore how the COVID-19 lockdown affected the psychosocial functioning of the older adults enrolled in the study. Importantly pre-lockdown data was available, which allowed the direct effects of a worldwide pandemic to be studied prospectively in a population who are likely to have been significantly impacted by imposed restrictions.



The results of this study are reported in this chapter and were published in Gerontology and Geriatric Medicine in September 2021, DOI: 10.1177/23337214211039974

## 5.1 Introduction

The World Health Organization (WHO) declared COVID-19 a global pandemic in March 2020; there have been in excess of 92 million confirmed cases worldwide (World Health Organization, 2020a) and in the UK in excess of 3.2 million cases and more than 90,000 deaths (Gov.UK, 2020). International responses were implemented to contain the spread of the virus, with various states of imposed lockdown applied in most European countries (Brodeur et al., 2021).

There are many psychosocial consequences of pandemics, with research showing that individuals' mental health has been severely affected by COVID-19 and the associated lockdown (Brodeur et al., 2021). In a sample of 775 adults in the United States, 55 % reported that COVID-19 had negative effects on their mental wellbeing (World Health Organization, 2020b). Research has also shown higher rates of mental distress during lockdown (Sibley et al., 2020) and it has been hypothesised that frustration, boredom, low mood, and potentially depression are likely consequences (Venkatesh & Edirappuli, 2020). Some groups are particularly vulnerable including those who contract the disease, those at a heightened risk of contraction and people with pre-existing medical, psychiatric or substance use problems (Pfefferbaum & North, 2020). The older adult population are at a heightened risk for contracting COVID-19 and often have pre-existing medical conditions which places them at increased risk of these additional consequences.

Older adults have been directly impacted by many of the implemented policies to mitigate the pandemic, including self-isolation procedures. As the older population often rely on community centres, social groups and places of worship for social interaction (Armitage & Nellums, 2020) the shielding policies may have disproportionally affected them. This suggests that they may therefore require more effective psychosocial support during this time (Kuwahara et al., 2020), with the WHO highlighting older adults may have a higher chance of becoming anxious, angry, stressed, agitated and withdrawn during the outbreak or while in quarantine (World Health Organization, 2020b).

There has been a wealth of research assessing wellbeing; however, as the pandemic and resulting lockdown were unanticipated, few studies have data relating to before the lockdown. Pre-lockdown data would provide a baseline comparison and would more effectively allow for the assessment of how the current pandemic and resulting restrictions have affected mental health and wellbeing (Brodeur et al., 2021). The current study can address this issue. As part of a longitudinal study assessing wellbeing and everyday functioning in older adults, data were collected in a population of over 70s prior to the UK lockdown in March 2020. For participants in this study, one scheduled follow-up session coincided with the lockdown period. Comparison of the baseline and follow-up therefore allowed for the direct effects of COVID-19 lockdown on psychosocial wellbeing to be studied in a population who are at increased risk of being negatively impacted by these restrictions.

## 5.2. Methods

### 5.2.1 Design

The current study utilised a quantitative repeated measures design. The repeated factor was time which had two levels; baseline (pre-lockdown) and follow-up (during lockdown), which were separated by 12 weeks. Pre-lockdown data was collected Jan - March 2020 and lockdown data March – June 2020. Additionally, participants were invited to complete a third time point (post-lockdown collected in May 2021) in order to follow-up on any lasting impact. The dependent variables assessed the following dimensions: wellbeing, stress, general health, daily functioning, mood trait measures, sleep quality, memory, activity levels, fear of falling, social network size and loneliness. Participants were originally enrolled into a randomised, placebo-controlled, double-blind, independent groups study, assessing the effects of a multivitamin supplement on everyday functioning in older adults (Clinical Trials ID NCT04112732).

### 5.2.2 Participants

The sample consisted of 35 participants who completed a baseline assessment pre-lockdown and a follow-up during lockdown, average age 76.06 (SD = 4.60), with ages ranging between 70 and 90. This consisted of 12 males (mean age =75.58, SD = 4.06) and 23 females (mean age = 76.30, SD = 4.93). Within these 35 participants, 20 were assigned to the multivitamin group (9 male, 11 female) and 15 to placebo (3 male, 12 females). The average BMI in the sample was 26.71 kg/m$^2$, participants on average reported consuming 1.22 units of alcohol and 305.2mg of caffeine per day. All participants were from a white ethnicity and had on average 15.1 years education (SD=3.44). No participants had any food allergies, epilepsy, hemochromatosis or were under medical supervision and all were non-smokers. Four participants had a thyroid disorder and consulted their doctor/pharmacist before taking part. No participants were currently taking multivitamin supplements; consumption of other supplements (e.g., turmeric, cod liver oil, glucosamine and rose hip) were considered on a case by case basis. Participants were reimbursed either £50 or £65 for their time (depending on what aspects of the original intervention study they signed up to).

Twenty-three participants completed post-lockdown, average age 75.65 (SD = 3.84). This consisted of 9 males (mean age =75.44, SD = 3.94) and 14 females (mean age = 75.79, SD = 3.93).

### 5.2.3 Materials

Full descriptions of questionnaire materials including scoring can be found in Chapter 3.

*Wellbeing*

UK Office of National Statistics (ONS) four subjective wellbeing questions (ONS4) (Tinkler, 2015). An additional question was included which was; Overall, how well did you feel yesterday?

*Stress*

The Perceived Stress Scale (PSS) (Cohen et al., 1983) which measures the extent to which participants perceive their lives to be overwhelming, uncontrollable and unpredictable.

*General Health*

The Cohen Hoberman Inventory of Physical Symptoms (CHIPS) (Cohen & Hoberman, 1983) which consists of 33 common symptoms (e.g. ‘back pain’ and ‘constipation’).

The SF-20 measured general health across 6 domains: physical functioning, role functioning, social functioning. mental health, health perceptions and pain (Stewart et al., 1988).

*Daily Functioning*

The Instrumental Activities of Daily Living (IADL) (Lawton & Brody, 1969) was used to measure how an individual is functioning at the present time. This measures eight daily activities; telephoning, shopping, food preparation, housekeeping, laundering, use of transportation, use of medicine, and financial behaviour.

*Mood trait and state measures*

The Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) was used to measure depression and anxiety. Which can indicate borderline and probable mood disorders (Snaith, 2003).

The Profile of Mood States (McNair et al., 1971) comprises of 65 adjectives (e.g., helpful, unhappy) which gives six global scores: tension, depression, anger, fatigue, confusion and vigour and one total mood disturbance score.

*Sleep Quality*

The Pittsburgh Sleep Quality Inventory (PSQI) (Buysse et al., 1989) was used to measure sleep quality and patterns. This asseses seven domains (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction) and one global sleep score.

*Memory*

The Prospective and Retrospective Memory Questionnaire (PRMQ) (Crawford et al., 2003) measured everyday memory. This measures memory failures in two subscales, prospective memory failures and retrospective failures.

*Activity Levels*

The Yale Physical Activity Survey (Dipietro et al., 1993) was used to assess physical activity levels. This gives indications of weekly energy expenditure, total time index and overall activity dimension summary index

*Fear of Falling*

Concerns about falling were measured using the Falls Efficacy Scale International (Yardley et al., 2005). This includes 16 items and participants were asked to rate how much they would be concerned with falling while doing this activity.

*Social Network Size*

The Convoy Method (Antonucci & Akiyama, 1987) measured social network size, which measures number of individuals in different social networks, quality of these relationships and total social network size.

The Lubben Social Network Scale (Lubben, 1988) was also used to measure social networks and social engagement. Questions relate to different aspects of social networks such active social network, perceived support network and perceived confidant network.

*Loneliness*

Loneliness was measured using the 11 item De Jong Gierveld Loneliness Scale (De Jong-Gierveld & Kamphuls, 1985). Measuring emotional loneliness and social loneliness. A single index of loneliness can also be produced by totalling these two scores where higher scores indicate greater loneliness

### 5.2.4 Procedure

Participants completed the initial testing visit during a face-to-face session in the laboratory. Participants had been asked to avoid caffeinated products for 12 hours and alcohol for 24 hours. They were instructed to eat a breakfast of cereal and/or toast at least 1 hour before the visit began. On arrival, participants gave written informed consent, provided lifestyle and demographic data and completed paper questionnaires.  This took around 1 hour in total. Additional tasks of mobility, strength, cognitive demand and stress reactivity were then completed, and participants were given treatment (either multivitamin or placebo) to take for the following 12 weeks. These tasks and activities are not reported here as they were not completed in the follow-up session (full details can be found at Clinical Trials ID NCT04112732).

All participants completed visit one before lockdown restrictions were put in place due to COVID-19. As all face-to-face research was prohibited, baseline questionnaires were amended for online completion at follow-up during lockdown.

Participants completed their follow-up visit from home, 12 weeks (+/- 5 days) after their baseline assessment. For consistency, participants were asked to adhere to the same instructions outlined for the baseline visit. The online questionnaire link was sent via email and participants worked through the questionnaires at their own pace. After completing the questionnaires, participants were debriefed and directed to a portal for participant payment.

In May 2021 participants were contacted and asked to complete the same questionnaires again adhering to the same instructions as outlined above. Additionally, participants were asked nine open ended qualitative questions regarding what they found helpful to coping and reducing any negative effects of lockdown. These questions were relating to socialising, community support, digital support and lifestyle.

### 5.2.5 Treatment of Data

All data was analysed using IBM SPSS statistics version 26. Descriptive statistics were calculated for all measures. Outcome measures were analysed using repeated measures ANOVA; time was the within subjects factor which consisted of two levels, pre-lockdown and during lockdown. Separate repeated measures ANOVA were then conducted on pre-lockdown and post-lockdown outcome measures. The dependent measure was the relevant outcome for each questionnaire. All descriptive statistics, F and P values for all outcome measures are displayed in Table 1, 2 and 3, only significant analyses and effect sizes are reported in text.

Qualitative data was analysed per question, responses were read by the lead researcher and recurring ideas were coded and grouped together to form overarching ideas, which were then combined due to overlap in responses. This analysis was supplementary to the main results to suggest protective factors against isolation and will be highlighted in the discussion but not reported in the results section.

## 5.3 Results

### 5.3.1 Wellbeing, Mood & Memory

Participants reported significantly lower levels of wellbeing [$F$ (1,32) = 4.95, $p$ = .033, d = 0.34], greater levels of perceived stress [$F$ (1, 31) = 5.57, $p$ = .025, d = 0.29], and depressive symptoms [$F$ (1, 32) = 7.18, $p$ = .012, d = 0.3), and higher scores for the mood states of depression-dejection [$F$ (1,29) = 11.76, $p$ = .002, d = 0.3]; confusion-bewilderment [$F$ (1,29) = 8.49, $p$ = .007, d = 0.3] and total mood disturbance [$F$ (1, 29) = 7.94, $p$ = .009. d = 0.31) during lockdown compared with pre-lockdown and there was a trend towards greater levels of tension/anxiety [$F$ (1,29) = 3.84, $p$ =.06, d = 0.33]. Participants reported significantly more memory failures during lockdown for both prospective [$F$ (1, 31) = 34.15, $p <.001$, d = 1.36] and retrospective [$F$ (1, 31) = 28.31, $p <.001$, d = 1.37] memory compared to pre-lockdown. All outcomes shown in Table 5.1.

**Table 5.1**: Mean (SD), sample size (N) for all wellbeing, mood and memory outcome measures pre-lockdown and during lockdown.

| | N | Pre-Lockdown | During Lockdown | F Value | P Value |
|---|---|---|---|---|---|
| Perceived Stress Scale | 32 | 11.09 (6.08) | 13.13 (8.03) | 5.57 | .025 |
| Office National Statistics Wellbeing | 33 | 40.00 (7.75) | 37.39 (7.78) | 4.95 | .033 |
| ***Hospital Anxiety and Depression Scale*** | | | | | |
| Anxiety | 33 | 4.55 (3.46) | 5.00 (4.05) | 1.00 | .325 |
| Depression | 33 | 2.64 (2.66) | 3.58 (3.57) | 7.18 | .012 |
| ***Profile of Mood States*** | | | | | |
| Tension – Anxiety | 30 | 3.97 (5.07) | 6.17 (7.85) | 3.84 | .060 |
| Depression – Dejection | 30 | 2.53 (7.90) | 5.10 (8.97) | 11.76 | .002 |
| Anger – Hostility | 30 | 1.90 (6.81) | 3.5 (5.32) | 2.06 | .162 |
| Vigour – Activity | 30 | 22.70 (6.81) | 21.20 (8.07) | 1.44 | .240 |
| Fatigue – Inertia | 30 | 1.97 (3.93) | 2.90 (5.52) | 2.20 | .148 |
| Confusion- Bewilderment | 30 | 4.73 (5.47) | 6.47 (6.28) | 8.49 | .007 |
| Friendliness | 30 | 18.37 (3.74) | 17.63 (4.84) | 0.81 | .376 |
| Total Mood Disturbance | 30 | -7.60 (30.38) | 2.93 (36.37) | 7.94 | .009 |
| ***Prospective and Retrospective Memory Questionnaire*** | | | | | |
| Prospective Memory | 32 | 21.22 (6.85) | 29.78 (5.67) | 34.15 | <.001 |
| Retrospective Memory | 32 | 20.53 (7.68) | 30.19 (6.37) | 28.31 | <.001 |

### 5.3.2 Physical Health and Activity

There was a significant reduction in CHIPS scores, indicating improved physical health during lockdown [*F* (1, 31) = 6.67, *p* = .015, d = 0.3]. There was a significant increase in time spent engaging in physical activity during lockdown compared to pre-lockdown [*F* (1, 30) = 5.63, *p* =.024, d = 0.57]. All outcomes shown in table 5.2.

**Table 5.2**: Mean (SD), sample size (N) for all physical health and activity measures pre-lockdown and during lockdown.

| | N | Pre-Lockdown | During Lockdown | F Value | P Value |
|---|---|---|---|---|---|
| Cohen Hoberman Inventory of Physical Symptoms | 32 | 14.25 (12.65) | 10.38 (12.99) | 6.67 | .015 |
| Pittsburgh Sleep Quality Index | 32 | 8.09 (3.52) | 7.50 (3.57) | 1.45 | .238 |
| Instrumental Activities of Daily Living | 32 | 7.47 (1.14) | 7.47 (1.16) | .00 | 1 |
| Falling Efficacy Scale- International | 32 | 21.28 (8.18) | 20.84 (8.18) | .21 | .644 |
| ***Yale Physical Activity Scale*** | | | | | |
| Total Time | 31 | 31.58 (21.47) | 44.70 (24.33) | 5.63 | .024 |
| Energy Expenditure | 31 | 115.58 (101.31) | 149.43(79.63) | 2.74 | .108 |
| Activity Dimension | 31 | 58.13 (29.12) | 55.74 (26.55) | 0.15 | .699 |
| ***SF-20*** | | | | | |
| Physical Function | 32 | 74.22 (28.91) | 69.76 (28.64) | 1.34 | .254 |
| Role Functioning | 32 | 80.23 (36.42) | 83.72 (37.35) | 0.69 | .412 |
| Social Functioning | 32 | 90.70 (15.34) | 86.98 (29.88) | 0.86 | .358 |
| Mental Health | 32 | 85.02 (15.81) | 81.95 (16.78) | 2.49 | .122 |
| Health Perceptions | 32 | 75.30 (20.38) | 78.02 (22.36) | 1.16 | .288 |
| Pain | 32 | 36.74 (27.23) | 33.85 (29.77) | 0.72 | .403 |

### 5.3.3 Social Interaction and Loneliness

Social interaction as measured by the Lubben social networks scale significantly increased from pre-lockdown to during lockdown [*F* (1,31) = 4.46, *p* = .043. d = 0.21]. In terms of social network dynamics, participants reported greater levels of relationship quality with those in their outer circle during lockdown compared to pre-lockdown [*F* (1, 31) = 8.61, *p* = .006, d = 0.59]. All outcomes shown in Table 5.3.

**Table 5.3**: Mean (SD), sample size (N) for all social interaction and loneliness measures pre-lockdown and during lockdown.

| | N | Pre-Lockdown | During Lockdown | F Value | P Value |
|---|---|---|---|---|---|
| Lubben Social Network Scale | 32 | 33.91 (10.42) | 36.00 (9.96) | 4.46 | .043 |
| ***Convoy Model Social Relations*** | | | | | |
| Inner Circle Relationships | 32 | 7.26 (5.07) | 6.84 (4.06) | 0.24 | .630 |
| Inner Relationship Quality | 32 | 8.43 (2.39) | 8.48 (1.82) | 0.07 | .796 |
| Middle Circle Relationships | 32 | 5.69 (3.52) | 4.38 (2.78) | 1.32 | .260 |
| Middle Relationship Quality | 32 | 6.45 (2.97) | 6.75 (2.31) | 0.50 | .483 |
| Outer Circle Relationships | 32 | 4.71 (5.97) | 3.84 (2.27) | 0.27 | .611 |
| Outer Relationship Quality | 32 | 4.50 (3.39) | 6.26 (2.47) | 8.61 | .006 |
| Total Relationships | 32 | 17.66 (10.38) | 15.06 (7.24) | 0.72 | .402 |
| Total Relationship Quality | 32 | 7.43 (2.18) | 7.38 (1.64) | 0.00 | .990 |
| ***DeJong Loneliness Scale*** | | | | | |
| Social Loneliness | 32 | 1.66 (1.96) | 1.66 (1.45) | .00 | 1 |
| Emotional Loneliness | 32 | 1.53 (2.12) | 1.47 (1.95) | .04 | .845 |
| Total Loneliness | 32 | 3.19 (3.77) | 3.13 (2.74) | .02 | .902 |

### 5.3.4 Follow up

Additional ANOVAs were conducted on the subsample between baseline and post lockdown to assess whether any changes remained after lockdown ended.

Of the outcomes significantly affected; wellbeing [$F$ (1, 22) = 10.81, $p$ =.003], HADs depression [$F$ (1,22) = -7.64, $p$ =.011] and POMS total mood disturbance [$F$ (1,22) = 4.72, $p$ =.041] continued to be negatively affected post lockdown in this sub-sample.

POMS depression [$F$ (1, 22) = 2.25, $p$ =.148], POMS confusion [$F$ (1, 22) = .90, $p$ =.354], retrospective memory [$F$ (1,22) = 2.99, $p$ =.098] and prospective memory [$F$ (1,22) = 2.98, $p$ =.098] were no longer impacted post lockdown.

No significant effects were observed on PSS, physical activity, CHIPS, social networks or loneliness in this sub-sample.

### 5.3.5 Post hoc analysis (Placebo only)

Further ANOVAs were run on the subsample of participants who had received placebo (as participants were enrolled in a randomised clinical trial). These were run from baseline, to follow up (during lockdown) and post lockdown.

Higher scores for the mood states depression-dejection [$F$ (1,10) = 7.15, $p$ = .023] and anger-hostility [$F$ (1,10) = 11.03, $p$ = .008] during lockdown compared with pre-lockdown was found in the placebo subsample. Neither depression – dejection [$F$ (1,8) = 0.65, $p$ = .445] or anger – hostility [$F$ (1,8) = 0.92, $p$ = .336] were affected post lockdown.

Participants in the placebo group reported significantly more memory failures during lockdown for both prospective [$F$ (1, 12) = 15.10, $p$ =.002] and retrospective [$F$ (1, 12) = 11.20, $p$ =.006] memory compared to pre-lockdown. Neither prospective [$F$ (1, 8) = 4.98, $p$ =.056] or retrospective [$F$ (1, 8) = 5.31, $p$ =.050] were significantly impacted after lockdown, although both were approaching significance.

There was a significant reduction in CHIPS scores in those who received placebo, indicating improved physical health during lockdown [$F$ (1, 12) = 7.17, $p$ = .020], but was no longer impacted post lockdown [$F$ (1, 8) = 0.36, $p$ = .568].

In terms of social network dynamics, participants in the placebo subgroup reported greater levels of relationship quality with those in their outer circle during lockdown compared to pre-lockdown [$F$ (1, 12) = 6.83, $p$ = .023].

## 5.4 Discussion

The current study assessed the effects of the nationwide COVID-19 lockdown on a range of measures of wellbeing in over 70s in the UK. Importantly pre-lockdown data were available, which allowed the direct effects to be studied prospectively in a population who are likely to have been significantly impacted by the restrictions imposed. Results showed that there were largely negative implications for wellbeing, mood, perceived stress and memory, although some improvements were shown in general health, physical activity and social interaction.

Firstly, lockdown led to significantly decreased feelings of wellbeing, increased feelings of depression and confusion, greater total mood disturbance, and a trend towards greater feelings of tension and anxiety. This is consistent with previous research in New Zealand showing that lockdown can lead to higher levels of mental distress, low mood and depression when compared to a matched sample (Sibley et al., 2020; Venkatesh & Edirappuli, 2020). The current results strengthen this conclusion by replicating findings in participants measured pre-and during lockdown rather than through comparisons with a matched sample. Some of these negative mood effects were withheld when focusing on those in placebo group alone, indicating there was little protective factors when consuming a multivitamin during this time.

The observed deterioration in mood could be due to the significant increases in perceived levels of stress. Research from previous crises, such as the severe acute respiratory syndrome pandemic and Ebola virus, have shown that such situations increase stress levels and have negative mental health implications (Cénat et al., 2020; Mak et al., 2009). Given the scale and severity of the current situation it is not surprising that stress levels significantly increased, and this highlights the importance of identifying ways to minimise potential negative consequences. The increased levels of stress may also provide an explanation for the detrimental effects on memory, as greater recent life stress has been associated with more self-reported memory problems (Shields et al., 2017). This is the first study to highlight that there may be detrimental cognitive consequences of lockdown in older adults. This is particularly important as stressful events in older adults can trigger a cognitive decline, with many reporting a stressful event before the onset of dementia (Tsolaki et al., 2010). These memory problems were withheld in the placebo group, despite no significant increase in reported stress levels. There was also a trend for increased memory problems in the placebo subgroup post lockdown, however as this data was collected almost a year after baseline, this long term affect could be attributed to the ageing process.

It is noteworthy that pre-lockdown scores for stress, anxiety and depression fall below the norms for these measures (Cohen et al., 1983; Crawford et al., 2001) indicating a relatively healthy sample; however, scores exceed norm values during lockdown. If such deteriorations are observed in relatively healthy participants, the impact in populations who may already show abnormal / clinical symptoms is of greater concern.

In contrast, there was a significant improvement in self-reported physical health during lockdown, both in the sample as a whole and the placebo subgroup, suggesting this was not due to the multivitamin. There are a number of possible explanations for this. It is plausible that those in this age group, who are likely to be vulnerable, may be making a more concerted effort to improve their health status. Alternatively, as most facilities were closed during the lockdown period it is possible participants were alleviated from many of their normal day to day duties and therefore had more time to rest, meaning physical symptoms such as muscular pain were reduced. It could also be suggested the benchmark for perceiving physical health has increased due to relief of not experiencing COVID symptoms or not wanting to present any signs of illness.

There was a significant increase in the total time engaging in physical work, exercise, and recreational activities during lockdown. This may seem counterintuitive given that most, if not all, recreational activities would have been suspended during this time. However, data analysing google trends showed an increase in interest in exercise immediately after lockdown in the UK (Ding et al., 2020). Potential explanations included compensation for reduced incidental activities, increased expendable time, more awareness of one’s own health and lockdown rules explicitly allowing for exercise as an essential activity. Due to the nature of the measure of physical activity used in this study, this could also reflect an increase in physical activity in the home during this time, as the range of activities listed includes housework and gardening activities. Lockdown coincided with the sunniest spring on record in the UK (Taylor, 2020), which could give the opportunity for more outdoor physical activity. Given that most of the individuals in this sample would have been instructed to stay at home during this time, it seems a plausible explanation that they may have increased the amount of activity completed at home.

Two aspects of social interaction were also improved during lockdown, indicating that lockdown may have had beneficial social implications in this population. Firstly, the Lubben Social Network scale indicated that participants had increased social engagement.

Secondly, there was a significantly improved rating of relationship quality in the outer circle of The Convoy Method of social relationships, in both the sample as a whole and the placebo subgroup. This circle is for people who may be at the peripheral of an individual's social network but are close enough and important enough to be part of their personal network. These results seem contradictory to much of the published literature in this area which would predict elevated levels of loneliness and social isolation in this population due to social distancing measures (Hwang et al., 2020). However, the current crisis has led to an increase in community spirit, with online interaction increasing 82% within the first month of lockdown, mainly concerning support for the most vulnerable, particularly the older adults (Weston, 2020). This could explain improvements in relationship quality with those in extended aspects of social networks; contact with these individuals appear to have increased due to the re-emphasis on community spirit. It is interesting that much published work anticipated that it would be social isolation which led to worsened mental and physical health (Armitage & Nellums, 2020; Webb, 2020). However, this is not evident in the current study, which observed improvements in reports of social interaction and no changes in levels of loneliness.

There is an urgency to study the mental health impact of COVID-19 in real time so that the adverse impact can be anticipated and minimized (Vahia et al., 2020). These findings address this need and help to understand the impact of the pandemic on mental health and wellbeing which will prepare for future pandemics, as well as ongoing national and local lockdowns and identify where support is needed. Our follow-up data indicated that wellbeing and aspects of mood (depression and mood disturbance) were still negatively affected post-lockdown suggesting enduring effects of the pandemic and associated lockdown.

It is important to identify potential protective factors to the detrimental consequences observed and to explore any preventative behaviours the older population can adopt to protect themselves against a chronic stressor such as a pandemic or to help with isolation in general. Participants discussed how keeping in contact with friends and family via zoom/facetime helped throughout but for some individuals there was a need for support/guidance on the practical and technical aspects of how to do this. This highlights the need for technological assistance in older adults which may help combat feelings of loneliness and isolation. Additionally, participants stated how being part of wider groups helped feelings of isolation such as online worship and zoom exercise classes, this may be a helpful alternative for older adults who cannot travel / attend in person activities going forward. In terms of lifestyle factors participants indicated that regular exercise, in particular going out for walks, was beneficial throughout lockdown. These findings suggest this should be encouraged in older adults especially those who live alone. Although these questions were discussed in respect to the pandemic, they have useful implications for tackling isolation and loneliness in older adults in general.

Overall, the findings from the current study provide evidence of both negative and positive consequences of lockdown. The impact of the COVID-19 pandemic lockdown in a sample aged 70 and over in the UK is therefore mixed. Unlike other studies that have attempted to assess the impact of lockdown this is the first study to research this population in the UK with initial measurement collected before lockdown. Negative impacts were observed despite improvements to physical health and increases in physical activity and social interaction. Given the sample were all ‘healthy’ at baseline in comparison to established norms there may be greater impairment in populations who are unable to increase their activity, are more socially isolated or already show clinical mood symptoms pre-lockdown.

# CHAPTER 6: GENERAL DISCUSSION

## 6.1 Summary of Objectives

The aim of this programme of research was to assess and improve everyday functioning in older adults. Given the very limited work in this area firstly, it had to be ascertained what aspects of everyday functioning older adults felt that they had deficits in, and where they would like to improve. This was addressed in Chapter 2.

Following this, the effect of multivitamin supplementation on everyday functioning was investigated. Previous research had provided promising results in older adults, primarily in the domain of cognitive function (Harris et al., 2011; Harris et al., 2015; Macpherson et al., 2013; Pipingas et al., 2015), however this was very restrictive in the outcome measures studied and there were methodological limitations that were addressed in this programme. First, previous trials had largely focused on 'healthy' older adult populations, which can provide valuable insight, but do not accurately reflect the general population of older adults in the United Kingdom. Therefore, Chapter 3 presents a 12-week parallel groups, double blind intervention with little to no exclusion criteria. Through using minimal criteria, the sample population should therefore be more representative of the general population. Second, previous work paid little attention to the roles of diet and nutritional intake at baseline and how they may interact with supplementation. This limitation was also addressed in Chapter 3, where results led to further questions as to how nutritional intake alone impacted everyday functioning.

Based on this, the aim of Chapter 4 was to establish differences between high and low intake of vitamins and minerals on markers of everyday functioning in older adults. This led to a greater understanding of the interactions between intake and supplementation reported in Chapter 3 and added to the knowledge gap in previous research.

Finally, Chapter 5 aimed to understand how measures of everyday functioning were impacted by the COVID-19 pandemic. This was tracked over three time periods to establish initial changes and any long-lasting effects in response to government-imposed lockdowns, which would disproportionally affect older adults. Although this was not an initial aim of the programme, this study provided additional valuable information regarding everyday functioning in older adults.

To summarise, the facilitating and inhibiting factors that impact upon everyday functioning in older adults were explored in Chapter 2. Chapters 3 and 4 then investigated ways in which everyday functioning could be improved through experimental methods in the form of multivitamin supplementation and observationally through dietary intake. Finally, the onset of the COVID-19 pandemic during the course of this PhD programme allowed for a unique opportunity to assess the impact of lockdown on aspects of everyday function in a vulnerable sample.

## 6.2 Overall Results

Chapter 2 of this thesis aimed to assess current levels of everyday functioning in those aged 70 and over. Using a qualitative methodology, this study highlighted areas of difficulty in everyday functioning for older adults, specifically: with walking, sexual activity, recreational activities, household tasks, and any activities involving mobility and strength. This was often attributed to underlying health issues, which led to difficulties engaging in these activities. To improve quality of life participants reported that they would like to be able to engage in personally enjoyable activities, improve their walking, be able to partake in exercise, and have overall improved health and mobility.

The results of Chapter 2 added valuable knowledge to the area, regarding which areas of everyday functioning older adults place importance upon. Given that deficits in these areas can have harmful consequences, these finding provide an important basis for future research. Issues with engaging in sexual activities can negatively impact psychological wellbeing (Hinchliff et al., 2018), engaging in hobbies can help alleviate loneliness and maintain activities of daily living (Smith, 2012; Tomioka et al., 2016), and exercise can decrease mood problems and improve aspects of cognition (Abedi et al., 2015; Boyle et al., 2020). Problems with mobility are an integral part of many common everyday activities (Hernandez et al., 2010) and have been suggested to be a proxy for overall fitness and wellbeing (Cesari et al., 2012), as well as functional, psychological and social health (Kozakai, 2017; Taekema et al., 2010) These are also some of the main factors of everyday functioning to be impacted by physical disability (Burbridge et al., 2020).

The wider aims for Chapter 2 were to use the results to design the subsequent intervention study which would aim to improve aspects of everyday functioning using a multivitamin supplement. Therefore, the expected and desired outcomes of taking an age targeted multivitamin product were also explored. Importantly, there was a scepticism around multivitamins and supplements in general; however, themes relating to improvements in energy/sleep, physical appearance, mood, and physical health were found. Literature shows that administration of multivitamins can lead to improved energy levels, sleep quality, mood, and aspects of physical health (Macpherson et al., 2015; Sarris et al., 2012; Veronese et al., 2019; Wouters-Wesseling et al., 2003), and therefore there is evidence that some of these desired improvements can be attained. These themes were therefore used to develop the outcome measures of the subsequent study. As described in Chapter 2, participants also stated they would like to see improvements in physical appearance, in particular reduced signs of visible ageing. This is an important finding for researchers and vitamin companies, with some promising research in the field (Pezdirc et al., 2015), however as this is not related to everyday functioning this was not an outcome considered in future studies in this thesis.

Chapter 3 therefore focused on improving everyday functioning by implementing a 12-week multivitamin supplementation trial. Outcomes were based on the qualitative results of Chapter 2 and other markers of everyday functioning that have been studied in previous supplementation trials. This built upon previous research in the field and addressed associated limitations, such as stringent inclusion/exclusion criteria and not measuring nutritional intake at baseline. Given there is limited research looking at sex differences in multivitamin supplementation, despite differing nutritional needs and differences in everyday functioning, as well as the formula for males and females differing slightly, all data in the study were split by sex. Overall, it was found that supplementation with a multivitamin resulted in a significant improvement in feelings of friendliness in females and significantly reduced prolonged stress reactivity, overall perceived stress reactivity and emotional loneliness in males.

The improvement in friendliness shown in females has not been shown in any previous multivitamin RCTs. In one cross-sectional study it was shown that users of multivitamin supplements reported significantly higher feels of friendliness than non-users (Austin et al., 2014). There is, therefore, some support for this finding, which requires further exploration in future research. Although not specifically looking at friendliness, early research did show that after 12 months of multivitamin supplementation females showed improved feelings of agreeableness, but this was not found in males (Benton et al., 1995). It was hypothesised that this could be due differences in nutritional intake between sexes at baseline, as mood benefits of multivitamin supplementation are often attributed to vitamin B6, B12 and folate (Huskisson et al., 2007). There was a trend for the same effect in males in the current study, so it may be that analysis was underpowered, further research is required before conclusions can be drawn.

Following multivitamin supplementation there was also a reduction in prolonged stress reactivity and overall stress reactivity in males. Stress reactivity refers to individual differences in response to stressors and prolonged reactivity refers to difficulties relaxing after a high workload (Schlotz et al., 2011). Therefore, lower stress reactivity is indicative of better functioning, as higher stress reactivity is linked to increased risk for ill health and the association between stress and disease (Schlotz et al., 2011). This is the first study to demonstrate effects on stress reactivity but is in line with previous literature that has shown reductions in perceived stress after multivitamin supplementation in healthy males of varying ages (Carroll et al., 2000; Harris et al., 2011; Kennedy et al., 2010).

These trials all had shorter supplementation periods than the current study, all supplementing for approximately 4 weeks. It has even been suggested that acute effects on stress reduction may be possible following multivitamin consumption, as has been shown after a single dose in older adult women (Macpherson et al., 2015). Similarly, stress ratings were reduced during cognitively demanding tasks following multivitamin supplementation in healthy young women, both acutely and following 28 days of supplementation (Dodd et al., 2020). This has been attributed to women reporting higher levels of stress at baseline, which increases their susceptibility to mood modulation. These results provide further evidence of stress reduction effects of multivitamin supplementation, which has consistently been shown throughout the literature and is thought to be the mood facet which shows the greatest improvement across all trials (Long & Benton, 2013). This could be suggested as an effective way to reduce stress in older adults, although further work is needed to establish duration needed to supplement before feeling effects and how long lasting these effects are.

Previous work has suggested that studies should explore differential sex effects of multivitamin supplementation (Dodd et al, 2020). Importantly this is the first study which shows differential sex effects in an older adult population. The observed differences in response may be due to confounding lifestyle factors between males and females in this sample.  Males reported drinking more alcohol, consuming less fruit and vegetables, consuming more potatoes, and had higher BMI, compared to females. These are all indicative of an unhealthier lifestyle, and previous work has consistently suggested that participants who are well nourished and have a healthy BMI are unlikely to benefit from supplementation. The results found here further substantiate this idea with males reporting more improvements following multivitamin supplement compared to females.

Arguably, the most surprising finding of Chapter 3 was that multivitamin supplementation reduced emotional loneliness in males. Although this may be attributed to a Type 1 error, differences were found at baseline based on nutritional intake, as well as multivitamin and nutritional intake interactions, on a range of loneliness outcomes, thus strengthening the observed link. The most plausible explanation for this comes from emerging evidence that the origin of loneliness may have a biological stress related aspect (Campagne, 2019). Furthermore, specifically focusing on emotional loneliness, it has been found that perceived stress mediates the relationship between emotional loneliness and poor sleep quality (McHugh & Lawlor, 2013). It was concluded by McHugh and Lawlor (2013) that emotional loneliness is a stressful experience, and it may be more beneficial to target and reduce stress as a therapeutic intervention. Given that in the current study reduced stress and emotional loneliness was only found in males following multivitamin supplementation, it could be that these outcomes are related, with stress potentially mediating this effect.

Overall, these results indicate that multivitamin supplementation can improve some aspects of everyday functioning in older adults. Furthermore, as the importance of these outcomes were highlighted in Chapter 2, these findings have real world relevance for the target population. However, one of the main themes found in Chapter 2 indicated that participants were sceptical of multivitamins and supplementation in general, stating that advertised benefits were overexaggerated and they were unlikely to feel any differences following supplementation. Intervention studies have often been mistranslated in the media (Perez, 2011) which could explain these feelings of scepticism. Even with the results showing benefits, companies must overcome this scepticism if they want to effectively market their products to this target population specifically. It is therefore important that findings regarding supplementation, including the current results, are accurately explained for lay audiences, without overstating results, as ultimately this will lead to better relations with consumers (Schmidt, 2011).

Chapter 3 also showed interactions between reported habitual dietary intake and multivitamin supplementation. To further understand these interactions, Chapter 4 assessed how nutritional intake independently impacted outcomes associated with everyday functioning. This would help to understand the interactions shown with treatment (discussed in section 6.3) and also highlight which areas of nutritional intake impact everyday functioning. Understanding this further can provide recommendations regarding those areas of nutrition that older adults need to focus on to improve their day-to-day function. A wide range of results were found, often in an unexpected direction, and some favourable outcomes in those below the mean intake. In line with the results for multivitamin supplementation shown in Chapter 3, there were also clear sex differences, highlighting the need for further research into both nutrition and supplementation to take this into account.

Those with lower dietary intake of vitamin B1 reported fewer physical health symptoms in both sexes, and lower pain in females. Lower intake of B1 and B3 in males led to lower levels of fatigue and stress, and higher role functioning and wellbeing, which was surprising given the critical role the B-vitamins play in the immune system and for balancing mood (Calder et al., 2020; Kennedy & Haskell, 2011; Mikkelsen & Apostolopoulos, 2018). Furthermore, in males with lower intake of vitamin B2 and B6, there was reduced social loneliness and better relationship quality. As discussed earlier this was not an expected result and theoretically in the opposite direction to expected, however this was consistently shown throughout the data in males. In females this relationship was often in the opposite direction where intake below the mean for vitamin B2 and B6 led to reduced number of social relationships. Intake of vitamin D also impacted social connections in females, with those who had higher intake having increased number of social relationships but worse relationship quality. It could be suggested those with higher dietary vitamin D intake may have better functional mobility and thus are more physically able to go out and socialise, which would lead to greater number of social relationships, but this does not necessarily lead to better relationship quality.

In females the intake of vitamin C elicited effects which were in the direction hypothesised based on previous literature. Higher intake of vitamin C resulted in a range of beneficial mood effects such as improved friendliness, lower levels of anger, and lower mood disturbance. Vitamin C has consistently been shown to be associated with mood in older adults (Gariballa, 2014; Oishi & Kawakami, 2009). Given the role vitamin C plays in the synthesis of neurotransmitters dopamine, noradrenaline, and serotonin, all of which have been linked to depression (Pullar et al., 2018), there is clear support for this link. Previous work has often focused exclusively on the link between vitamin C intake and depressive symptoms, due to the deductive nature of previous work in the area, the current results extend upon this by showing vitamin C intake can influence a range of mood outcomes. It was also shown that females with higher vitamin C intake also displayed higher levels of vigour. Vitamin C is also a cofactor for enzymes involved in the synthesis of carnitine, which is required for the generation of metabolic energy and has been implicated in feelings of fatigue and lethargy (Du et al., 2012). Providing further evidence for the link between vitamin C and subjective energy levels in older adults.

Although vitamin C elicited effects in the expected direction, in females, the effect of vitamin E intake was in the opposite direction to that expected. Those who were below the mean intake had higher levels of both physical activity and energy expenditure, whereas previous research has found the opposite (Alghadir et al., 2021). It could be suggested that dietary intake of vitamins and minerals, does not equate to absorption and circulating levels. Extensive evidence shows age can affect the absorption of essentially all vitamins and minerals (Galan et al., 2005; Lee & Han, 2018; Owen et al., 2005), furthermore absorption can be affected by a range of different factors including age and medication use (Aslam et al., 2017). Therefore, there may be another factor having a systematic effect across measures. As those who consumed less vitamins/minerals consistently reported better everyday functioning on a range of outcomes, it is more likely that the results are due to dietary intake; however, this should be interpreted with caution.

Lower selenium intake in males led to lower levels of stress, anger, and mood disturbance and in females, less reported physical health symptoms. Similarly, in females, lower iodine intake was associated with fewer physical health symptoms and lower levels of pain. It could be hypothesised this is due to the role of iodine in hypothyroidism (Boelaert, 2013; Jayaprasad & Francis, 2005; Kehoe et al., 2019), given that a large proportion of the sample reported thyroid issues, there are clear confounding factors at play which could potentially explain these results. Lower iodine in males was associated with better reported memory, which is again an unexpected result. Much of the research on iodine focuses on deficiency during foetal development, as deficiency in utero can lead to irreversible cognitive impairment (Redman et al., 2016). However, in older adults as iodine deficiency will often lead to hypothyroidism, when this is treated with thyroid hormone replacement this can improve previous cognitive deficits (Miller et al., 2006).

Finally, it was shown that being below the mean intake of polyunsaturated fatty acids (PUFAs) elicited positive effects, particularly in females. This included positive mood effects such as increased wellbeing, lower depression levels and mood disturbance, lower fatigue, less physical symptoms, and better health perceptions. Generally, PUFAs are considered to have beneficial health effects, however omega-3 and omega-6 (the two main families of PUFAs relevant to human health) have opposing effects on metabolic functions in the body (Saini & Keum, 2018). Omega-3s have been shown to have antidepressant effects and a to be a protective factor against cancer, diabetes, osteoporosis, and bone fractures (Bazinet & Layé, 2014; Saini & Keum, 2018). Whereas higher omega-6 intake has been associated with inflammatory, cardiovascular, and Alzheimer's disease (Patterson et al., 2012). Furthermore, higher omega-6 has been shown to change normal physiological function to pathophysiological (Yamashima et al., 2020) and that a diet higher in omega-6 is linked to an increase in depressive symptoms (Yonezawa et al., 2020). Based on the dietary information produced from the FFQ used in this study, there is no distinguishing between omega-3 and omega-6 intake. Further investigation would be required to determine if being lower in one specific PUFA is beneficial in older adult females.

For the results which show better functioning in those below the mean intake, it could be suggested there is an optimal level of intake for peak functioning, which follows an inverted-U shape. The sample in the study reported a good diet. The grouping for the majority of vitamins and minerals had to be based on means in the sample, rather than national averages reported by Scientific Advisory Committee on Nutrition (2021), as intake was considerably higher. It may be that there is an upper optimum level for intake, and those in the higher intake group have gone beyond this. Those in the lower intake group may be in the optimal level of the inverted-U shape, rather than representing objective low intake.

Furthermore, despite the minimal exclusion restrictions, the sample were still healthy, consuming high levels of fruit and vegetables, and vitamin/mineral intake above national averages. The average BMI and alcohol intake were below national averages based on sex and age (Connolly et al., 2017; Osborne & Cooper, 2018), and most participants were educated to degree level. Previous clinical trials have also shown that participants tend to be from a higher socioeconomic status (Unger et al., 2013), and this can influence dietary habits (Sahyoun et al., 2004). Therefore, it could be suggested that any improvements shown after multivitamin supplementation, and differences based on dietary intake, are likely to be more pronounced in populations who have an unhealthier lifestyle and diet. Targeted interventions are needed to investigate this.

The final study in this thesis assessed how the COVID-19 lockdown affected everyday functioning in older adults. Results showed that there were largely negative implications for wellbeing, mood, perceived stress, and memory, although some improvements were shown in general health, physical activity, and social interaction. Given the increased levels of stress, it is not surprising there was a deterioration in mood as other pandemics have been shown to lead to negative mental health implications (Cénat et al., 2020; Mak et al., 2009). Higher stress was also a potential explanation for the detrimental effects shown on memory, greater stress is associated with greater self-reported memory problems (Shields et al., 2017). Although the results here were in response to a specific situation, it does highlight how stress can affect everyday functioning. Before the pandemic there were around 9.1 million unpaid carers in the UK, with around 23% of these being aged 65 or over, there were reportedly 4.5 million new carers since the beginning of the pandemic, 14% of these being over 65 (Carers UK, 2020). The results shown here are likely to be further exacerbated in this group, highlighting the importance of identifying ways to minimise the negative consequences of increased stress. This was originally intended to be explored within this programme of work, however due to low numbers of carers recruited, unsurprising due to restrictions put in place during the pandemic, this was not achievable. Based on the results of the previous studies in this thesis, it could be beneficial for future work to examine the nutritional intake in this group, given there has been beneficial effects of both nutritional intake and multivitamin supplementation on these outcomes.

Although there were negative consequences of the COVID-19 lockdown, there were improvements reported in self-reported physical health, total time engaging in physical work, exercise, and recreational activities during lockdown. There were several theoretical reasons suggested for this including making a more concerted effort to improve their health status, alleviation from many of their normal day to day duties leading to more time to rest or to do activities at home they enjoy, increased expendable time, and lockdown rules explicitly allowing for exercise as an essential activity. Since the publication of the findings presented in Chapter 5, further research has been conducted in the area which supports these explanations. Qualitative work has shown older adults in the UK enjoyed feeling less social pressure, having more time for their hobbies and having an opportunity to focus more on their health by going for regular walks and taking up new forms of physical activity (McKinlay et al., 2021).

Finally, within this chapter it was shown that lockdown had beneficial social implications in this population, including increased social engagement and improved relationship quality in those at the peripheral of an individual's social network. These results seem contradictory to much of the published literature in this area which would predict elevated levels of loneliness and social isolation in this population due to social distancing measures (Hwang et al., 2020). The results have since been supported by subsequent qualitative work in the areas which has shown older adults felt higher levels of social support during lockdown and reported higher feelings of connectedness with social contacts (McKinlay et al., 2021). The hypothesised explanation for this; an increase in community spirt concerning support for the most vulnerable, particularly older adults, has not been explicitly researched. However, observational work has shown the ways in which connections to older adults were maintained throughout the pandemic, including organisations offering befriending services over zoom and telephone calls, and informal groups in the community providing support to those self-isolating (Burke, 2020).

To summarise the results of this thesis, everyday functioning has been assessed via qualitative methods which laid the foundation for all of the subsequent work presented. Both Chapters 4 and 5 have provided unique methods to measure everyday functioning and the potential influence of nutritional intake and the COVID-19 pandemic, respectively. This has given a deeper understanding of factors that can impact everyday functioning in older adults which has developed knowledge in this field. Given the ageing population and its consequences for health and care services and the impact on public expenditure (Howdon & Rice, 2018), it is therefore, imperative that further work is conducted in this area.

Chapter 3 has shown that multivitamin supplementation is a potential method to improve everyday functioning in older adults; however, it does not provide a one size fits all solution. There is still further work required to fully understand subgroups of older adults who would benefit the most from supplementation . The use of multivitamin supplements as a way to improve functioning in older adults has been shown to produce an overall cost advantage to healthcare (Elia et al., 2016), however this can lead to health inequalities in this group. Income and socioeconomic status are associated with dietary supplements, with those that have lower income being less likely to use them (Cowan et al., 2018). Therefore, there needs to be a focus on education of diet and nutritional intake in older adults, as well as consideration of the affordability of multivitamin supplements.

## 6.3 Dietary Intake

Responses to treatment were explored primarily in Chapter 3, and dietary intake in Chapter 4. Therefore, the effects of supplementation and nutritional intake have been independently considered. However, if there were no differences based on nutritional intake at baseline it could be inferred that any differences found within the intervention are a response to treatment. If there are positive effects in those with low nutritional intake following multivitamin it can be suggested that this may be due to improved nutritional status, given that other confounding variables have been controlled for.

Vitamin D interactions following multivitamin favoured participants who were below the mean intake, with better social functioning and independent activities of daily living in males and lower levels of pain in females. Similarly, previous research has shown supplementation with vitamin D can improve social functioning and reduce pain in older adults (Huang et al., 2013; Sakalli et al., 2012). The current results extend this by showing positive results following supplements containing lower doses of vitamin D in those who have low dietary intake. At baseline, for both measures participants were scoring very similarly, with similar standard deviations, suggesting no obvious difference based on dietary intake. Furthermore, it has been shown that men are more susceptible to the effect of vitamin D deficiency on the incidence of instrumental activities of daily living disabilities (Luiz et al., 2022). Given men who were below the mean intake at baseline showed improvements in IADLS following multivitamins, it could be suggested that they are also more susceptible to experiencing improvements in this domain following supplementation. Thus, providing a way to combat this detriment in older adult males, to sustain independent living for longer. Those who were above the mean intake may have been at optimum vitamin D level, so did not experience any benefit of supplementation.

An interaction was shown in males whereby those with vitamin D intake above the mean at baseline had higher levels of physical activity following multivitamin when compared to those with intake below the mean. However, there were no differences on this outcome at baseline before supplementation. It has long been established there is a link between vitamin D and physical activity, with clear positive correlations show between the two in older adults (Anand et al., 2011; Raczkiewicz et al., 2015). Higher vitamin D intake at baseline may not have been equivalent to higher vitamin D status, as absorption declines with age (Maurya & Aggarwal, 2017). But it has been shown that consuming a vitamin D supplement with the largest meal of the day improved absorption (Mulligan & Licata, 2010). Therefore, it is being posited that being instructed to take the multivitamin with their largest meal of the day, led to increased physical activity due to increased vitamin D levels.

A range of interactions were found for B-vitamin intake, which were not present at baseline, indicating positive effects of multivitamin supplementation. In males, there were lower levels of depression following multivitamin in those who consumed lower levels of vitamin B2 at baseline. Extensive research has shown vitamin B2 intake to be associated with mood (Wu et al., 2022), however meta-analysis has shown no benefit of  B vitamin supplementation on depressive symptoms (Young et al., 2019). It was suggested from this work that future studies measure baseline dietary habits. This has been addressed in the current research where multivitamin supplementation elicited positive effects on depressive symptoms in males with low dietary intake of vitamin B2. This result adds important knowledge to this area by showing that supplementation needs to be targeted at those with worse dietary patterns to elicit response. Mood improvements were also observed in males who were below the mean intake of folate, following multivitamin supplementation. Low levels of folate have been associated with depressive symptoms in older adults (Petridou et al., 2016; Almeida et al.,2015). No differences in mood at baseline based on folate status were observed in the current study, but this may reflect the small range in values reported. Males also reported lower intake than females, which may explain why these interactions are largely shown in males.

In line with the results found for vitamin D, males who were below the mean intake for vitamin B3 showed greater independent activities of daily living following multivitamin. Although there have been clear associations between risk of poor nutritional status and physical disabilities (Sharkey, 2008), there has been little in terms of vitamin B3 intake and functional ability. Intervention research has shown no beneficial effects of multivitamin supplementation on activities of daily living in older adults (Sun et al., 2007), however the administered treatment did not contain vitamin B3 and the nutritional status of participants was not measured.  More work is needed in this area to fully understand this relationship, but the results of the current study show improvements to IADL in males with lower intakes of vitamin B3 following 12 weeks of multivitamin supplementation, despite no difference between the intake groups at baseline.

Lower levels of vitamin B6 have been associated with higher risk of falls, impairment in mobility and worsened physical performance (Grootswagers et al., 2021; Johnson, 2003; Struijk et al., 2018), although results have been conflicting, with no effects being shown in other research (Bartali et al., 2008). Previous work has shown multivitamin supplementation can have positive effects on bone density and this led to a trend in reduction of falls (Grieger et al., 2009). In the current study, males below the mean vitamin B6 intake had lower fear of falling following multivitamin, which was not shown at baseline. The previous work hypothesised the reductions shown in falls were due to increased serum concentrations of vitamin D, B12 and folate (Grieger et al., 2009). The findings presented here suggest that B6 status may also need to be considered when exploring effects of vitamins and minerals on fear of falling.

At baseline there were no differences on any outcome measures based on vitamin B12 intake. However, following multivitamin intake, females who were below the mean intake at baseline reported lower levels of loneliness. Previous work has found no significant correlations between loneliness scores and vitamin B12 levels (Alshehri et al., 2021), however it has been shown that there are links between nutritional intake and loneliness, when measured as a whole, rather than looking at specific vitamins (Schorr et al., 2021). Vitamins act as cofactors in various processes, so response to treatment in those with lower vitamin B12 intake may be due to a range of interactions. This highlights that the benefits of a multivitamin supplement as single nutrient supplements may not have the ability to elicit the range of effects found here.

There were interactions between mineral intake and multivitamin supplementation, particularly in females. Females with lower iodine intake showed lower anxiety and tension following multivitamin. But as there were no differences at baseline in the current study this would suggest there are minimal mood effects of low iodine intake. There is a lack of published literature on suboptimal iodine intake on mood state in older adults and it has been shown that there is no evidence that higher iodine intake is associated with better mood state in older adults (Buchanan et al., 2015). However, there is evidence iodine intake can affect role functioning.

Multivitamin supplementation led to improved role function in females with lower intake of iodine and selenium. Evidence has shown lower intake of selenium is particularly prevalent in women with higher disability scores, which were computed including measures of role function (Perri et al., 2020). Similarly, subclinical hypothyroidism is more prevalent in older women, especially in those with iodine deficiency and this can affect aspects of role functioning (Chan et al., 2014). The results highlight the potential beneficial effects of multivitamin supplementation in older adult women who have lower dietary mineral intake. This may be due to the role of minerals in the menopause, with mineral status, in particular iodine, being associated with menopausal symptoms (Korkmaz et al., 2015; Valencia et al., 2002). The improvement in role functioning following multivitamin based on selenium intake may also be due to the improvements found in pain in females. Selenium intake has frequently been found to be associated with pain severity, often in patients of fibromyalgia (Batista et al., 2016; Bjørklund et al., 2018). The current study extends this by showing improvements in reported pain in non-clinical samples, suggesting that multivitamin supplementation may be beneficial in those suffering from more severe pain, especially if accompanied by inadequate nutritional intake.

Finally, a range of effects were found based on mineral intake on aspects of social relationships, following multivitamin supplementation, in both males and females. In males, those who had lower intake of zinc and selenium reported fewer number of relationships and worse relationship quality in their social network following multivitamin. Conversely, in females, those who had lower iodine intake reported lower loneliness following multivitamin, but worse relationship quality. Links between mineral intake and response to treatment on measures of loneliness are not well understood with no clear mechanism of effect. However, it would appear there are clear sex differences in response to this and substantial further work is needed to understand this fully.

There were no differences at baseline for any of the measures which were impacted by supplementation. As outlined earlier the participants within this study had good nutritional intake, above national averages based on age and sex. There was also a small range in reported intake across all groups. It may be that participants grouped in both the lower and higher intake group had near to optimal intake and this is why no significant differences were shown on these outcomes at baseline. It is suggested, based on this, that future research conducts prior screening of dietary intake, to ensure a greater variation of reported vitamin and mineral intake. This should be based around the national averages to assess the impact of lower and higher intake on everyday functioning. This would give a clearer indication of how intake in the population impacts these outcomes.

## 6.4 Limitations

The studies outlined in this thesis provide a holistic approach to everyday functioning in older adults, including how this is impacted by multivitamin supplementation and nutritional intake. The use of novel methodologies, such as person-centred qualitative approaches to study design, less restrictive inclusion/exclusion criteria and online adaptation of clinical trials, have addressed limitations and built upon previous research in the field. However, methodological limitations which have arisen throughout the studies presented in this thesis must be considered, some of which have not been addressed fully in previous chapters.

One main aim of the thesis was to explore everyday functioning in 'everyday' older adults, given that most of the previous research in the field utilises 'healthy' older adults (Grodstein et al., 2013; Harris et al., 2011; Harris et al., 2015; Pipingas et al., 2015). There are clear issues with this, as many groups who may see most benefit will have been overlooked in previous trials (Walker et al., 2010) and investigating healthy populations will continually produce null results due to baseline nutrient levels likely already being optimal (Morris & Tangney, 2011). Based on this, for all studies presented in this thesis there were very limited exclusion criteria for participation, aside from being aged 70 and over, and those consuming specific medications had to check with a medical professional before taking part, to avoid any contraindications. Despite this, participants who volunteered to participate could still be categorised as 'healthy' older adults. With lower BMI and alcohol intake than the national average (Conolly & Davies, 2018; Osborne & Cooper, 2018) and higher levels of education which has been consistently linked to better diet quality (Freitas et al., 2017; Thorpe et al., 2019). Therefore, it could be suggested that this aim was not fully met, and the sample included was not reflective of an 'everyday' adult aged 70 or over. Despite this, clear results were found for multivitamin use, interactions between nutritional intake and multivitamin supplementation and the intake of vitamins/minerals alone on everyday functioning. Therefore, it could be suggested that these results may be even more pronounced in older adults who do not already have a good diet, have higher BMI or high alcohol intake. Targeted trials are needed to recruit older adults who are not as healthy and would not usually volunteer to participate in research.

There are other methodological issues within the thesis which must be addressed. The data collection method for the intervention trial was highly unusual. To the authors knowledge this is the first registered clinical trial which has run data collection methods online and administered treatment by post so that participants could complete the full trial from home. This method had clear benefits, such as widening the recruitment pool as participants did not need to be local and being cost and time effective compared to traditional in lab testing. However, there has not been any validation of whether this yields the same results as data collected in the lab. Previous work looking at multivitamin supplementation has found positive effects on mood when measured using at home-mobile phone assessments but no differences when measured in a laboratory setting (Pipingas et al., 2013). Thus, indicating that there may be differences in responses based on the setting in which the participant completes the assessments. Validation of at home assessments for the outcome measures reported is warranted. However, it could be argued that studies conducted at home have greater real-world applicability and if differences do exist between the different settings, it may be that changes to lab studies are needed to increase their generalisability.

Furthermore, there are issues with how participants complete online surveys, with evidence suggesting at least 5 percent or more of respondents answer carelessly (Johnson, 2005). To counter this many researchers have recommended the inclusion of attention check questions in surveys, to allow careless respondents to be identified and screened prior to analysis (Berinsky et al., 2014; Curran, 2016; Maniaci & Rogge, 2014). There has been some concern that attention checks can cause participants to approach subsequent questions differently and potentially pose a threat to scale validity (Hauser & Schwarz, 2015), however further work refuted this showing attention checks did not influence answers to and understanding of the questionnaires administered (Kung et al., 2018). It may have been beneficial to include attention checks throughout the questionnaire, but there were no indications this was an issue in the current study with all responses showing a normal distribution.

Another issue with running the intervention as an online questionnaire is the potential that treatment adherence was not reported accurately. Although participants were asked to self-report the number of tablets remaining in their treatment bottle and this showed excellent levels of adherence this could not be visually confirmed upon completion of the trial as would be usual. This could cause concern regarding whether reported intake is reflective of actual intake, and therefore whether results can be fully attributed to multivitamin consumption.

However, it could also be argued that participants returning treatment bottles at the end of a trial may have removed or lost tablets throughout trial duration. Therefore, this is an issue that must be considered in all trials administering treatment as there is no concrete way in which to confirm whether compliance has been adhered to. Blood biomarkers can be employed to measure changes in nutritional biomarkers, which was originally intended in the current study, however even this cannot fully measure adherence.

As mentioned within the discussion of Chapter 4 one pertinent limitation with this research was the reliance on the FFQ for the measurement of dietary intake. It has been suggested that this technique is prone to error, often leading to over estimation of intake (Bain et al., 2015; Day et al., 1999; McKeown et al., 2001; Riboli et al., 2002). There may, therefore, be implications for the results in this programme if intake has been over estimated. The participants in this study showed particularly high intake compared to the population averages as reported by Scientific Advisory Committee on Nutrition (2021). This could be due to the FFQ measurement, or more likely, these participants may have better diet compared to the general population. Individuals from a higher social class and with better education have been shown to have better diet (Darmon & Drewnowski, 2008; Freitas et al., 2017; Thorpe et al., 2019), with these characteristics being shown in the participants enrolled in this study. Either explanation has implications for interpretation of these results and warrant further research in the area.

## 6.5 Future Research

Despite these limitations, here are several exciting findings which could be investigated in future research. There needs to be an effort by researchers to target specific samples who are most likely to have deficits in everyday functioning and nutritional deficits. The current body of work attempted to do this by employing minimal inclusion/exclusion criteria, although the sample characteristics still suggest some issues with representation. As previously evidenced, there is clear self-selection bias in both nutrition trials, and research in general (Elston, 2021; Young et al., 2020). Many of these characteristics also correlate with nutritional intake, education level, social class and ethnicity are all linked to micronutrient intake (Hayden et al., 2015; Mendonça et al., 2016). Therefore, future research needs to focus on recruiting underrepresented groups, especially those from low socioeconomic areas and diverse ethnic groups. Doing this will provide more valuable information, specifically on the efficacy of multivitamin supplementation on everyday functioning in older adults.

The results presented in Chapter 3 show that multivitamin supplementation does have the potential to improve markers of everyday functioning. However, clear sex differences were found, for both multivitamin alone and response to treatment. Given that both micronutrient requirements and absorption differ by sex (Prentice, 2021), this is not surprising. However little research has considered this in terms of multivitamin supplementation. Secondly, the results relating to improvements in social interaction and loneliness following multivitamin should be investigated further. As loneliness has clear associations with depression, disease, stress, sleep, cognition, and premature mortality (Cacioppo et al., 2010; Hodgson et al., 2020; McHugh & Lawlor, 2013; Park et al., 2020; Winterton et al., 2020), finding ways to alleviate this has clear societal implications. Future work needs to focus on understanding any potential relationship between nutritional intake, supplementation and loneliness, the results reported in this thesis provide a strong rationale for doing this.

One outstanding limitation relates to how diet is measured and the use of relevant biomarker to quantify intake. This was originally planned in the current research, but due to COVID-19 restrictions this aspect of the research could not be completed. Using the FFQ as a measure of dietary intake has clear limitations which have been covered in the previous section of this discussion. Future work may wish to employ newer technologies to measure dietary intake, a range of new apps and methodologies have been developed for dietary assessment (Cade, 2017). As well as developing new and novel technologies to assess diet, the advances in dietary biomarkers such as metabolomics should also be considered (Rollo et al., 2016). It is recommended that biomarkers need to be measured pre and post supplementation to more clearly understand any response to treatments. This will give a deeper understanding of the mechanisms of effect between multivitamin supplementation and everyday functioning.

## 6.6 Overall conclusions and strengths

The aim of this thesis was to assess and improve everyday functioning in older adults aged 70 and over. The qualitative work presented in Chapter 2 clearly identified current and desired levels of everyday functioning in older adults. Importantly, it also provided a novel methodology to aid in intervention design, the benefits of this have been highlighted throughout and it is strongly recommended that researchers consider this in future nutritional intervention trials to bring a more person-centred approach to the area. This also overcomes the issues with previous research focusing on very specific outcome measures, which have limited applicability to the real world. Taking this novel approached ensure meaningful outcome measures which encompass a variety of outcome measures, which have clear implications for daily functioning. The use of this method is considered by the author to be a major strength of this thesis. The results of this study also clearly presented a major issue for supplementation research and pharmaceutical companies going forward. Despite clinical evidence for the benefits of multivitamin supplementation, older adults indicated scepticism of any benefits. It is vital that ways to overcome these views are explored in order that the full impact of findings in this area, including those presented in Chapter 3, can be experienced.

Results of the multivitamin supplement intervention presented in Chapter 3 showed interesting and promising results. Even without considering nutritional intake, 12 weeks of multivitamin supplementation can elicit positive effects in older adults. This is both consistent with previous research in the field and adds new knowledge to the area which has not been shown before. This is the first study to shown differential effects of multivitamin supplementation based on sex in older adults, which has largely been ignored in previous research. Males and females have different nutritional needs, differ in absorption and present different deficits in everyday functioning. Therefore, treating them as a homogenous sample is not an effective technique to understand any benefits of multivitamin supplementation, presenting a strength in this programme of work.

The adaptations made to the trial design due to the COVID-19 pandemic led to some planned outcome measures having to be omitted, such as measures of mobility, cardiovascular response to a multitasking stressor and biological measures of immunity, cardiovascular health, and nutritional biomarkers. It is still important that future work focus on these measures, but the adaptations made to the trial are thought to be advantageous overall. It allowed new and innovative methods for running clinical trials to be explored which could have clear implications going forward for researchers. This may also be an important factor to increase inclusivity in clinical trials. Participants not needing to come into the lab overcomes the issue of the population being intimidated by this aspect and can include those who may have restricted mobility. Similar techniques were employed in the Cocoa Supplement and Multivitamin Outcomes Study for the Mind trial (Baker et al., 2019), in which cognitive testing was employed via telephone. Similarly, the authors concluded using this method is cost effective and allows enrolment to extend beyond circumscribed geography of testing centres, which allows larger cohorts to be studied. The work conducted here extends upon this to show this is feasible for domains other than just cognition.

As already suggested the method employed in the current study allows larger cohorts to be studied. Despite the number of participants completing per protocol being just below the initial target, the sample size of the intervention is considered a strength of this study. Given the restrictions to research during the COVID-19 pandemic, having a sample of 228 older adults aged 70 and over (female N= 124, male N= 104), complete a 12-week intervention per protocol is a success for this trial. Especially due to other large scale vitamin D trials being conducted simultaneously, which attracted large press coverage and attention from the Department of Health (Jolliffe et al., 2022; Martineau, 2022), and the UK government offering free vitamin D supplements to those who were clinically extremely vulnerable, which was predominantly older adults. Both of which made potential participants ineligible for the current trial, adding further difficulties to the recruitment process. Against these difficulties, the sample size is an overall strength and merit of this programme.

The results of Chapter 3 alone added important information to the field but including interactions between dietary intake and supplementation strengthened this further. By independently looking at differences based on nutritional intake at baseline this allowed response to treatment to be explored thoroughly, as well as extending knowledge in the area. Measuring diet at baseline has been a suggestion for future research by most previous work in the area, and as hypothesised there were clear improvements for those below the mean dietary intake of many vitamins and minerals following multivitamin supplementation. Highlighting the need for more future work to consider this and confirming supplementation is more beneficial for those who have worse diet.

Chapter 4 showed that reported nutritional intake impacted a wide range of everyday functioning outcomes. This was often in the opposite direction to that hypothesised, favouring those below the mean intake. Research is needed which intentionally recruits participants with a range of dietary intakes, supported by nutritional biomarkers. By doing this it can be fully explored whether there is an inverted U shape curved explaining the relationship between dietary intake and everyday functioning as suggested in this chapter.

Finally, the adaptation to trial design due to the COVID-19 pandemic allowed a unique opportunity to track participant health and wellbeing, in real time, in response to government-imposed lockdown. Collecting longitudinal data over this time, provided unique data that other rapid research in the area was lacking. This provided clear and critical information on how this was affecting the health and psychosocial wellbeing of older adults in the UK, highlighting both the positive and negative implications of this. This has since been validated by other work in the area and there are clear applications going forward for ways to minimise harmful side effects of stressful situations in older adults.

## APPENDICES

APPENDIX I: Frequency of medical conditions in the sample

Table I.1. Frequency of medical conditions in those enrolled in the main intervention.

| Medical Condition | Number of Participants |
|---|---|
| Acid Reflux | 46 |
| Angina | 2 |
| Anxiety | 2 |
| Arthritis | 20 |
| Asthma | 9 |
| Breast Cancer (in remission) | 4 |
| COPD | 6 |
| Depression | 22 |
| Diabetes | 24 |
| Diverticular Disease | 2 |
| Emphysema | 1 |
| Enlarged Prostate | 26 |
| Glaucoma | 4 |
| Gout | 10 |
| Heart Attack | 4 |
| Heart Bypass | 2 |
| Heart Failure | 3 |
| High Blood Pressure | 95 |
| High Cholesterol | 97 |
| Hypothyroidism | 17 |
| MS | 1 |
| Nerve Damage | 3 |
| Osteoporosis | 7 |
| Overactive Bladder | 3 |
| Prostate cancer (in remission) | 4 |
| Sjogren’s Syndrome | 2 |
| Stroke | 3 |

APPENDIX II: Procedure of face-to-face intervention

Participants arrived at the lab have had a standardised breakfast of cereal and/or toast which had to be eaten at last one hour before arrival, having abstained from alcohol for 24 hours and caffeine for 12 hours. After reading the information sheet and signing consent forms all demographic information was taken including age, sex, ethnicity, years of formal education, medication/supplements, pre-existing medical conditions, smoking status, caregiver status, BMI, portions of fruit/veg per day, average consumption of alcohol per day and average caffeine consumption per day. All questionnaires were completed (except for those being used to measure acute measures of subjective state). Participants then completed the stress reactivity study outlined in figure II.1, using the multi-tasking framework outlined in figure II.2 and then mobility tasks outlined in figure II.3. Upon completion of these tasks, participants were randomised and assigned to either active treatment or placebo, which they were instructed to consume daily for 12 weeks, participant were administered 6 weeks' worth on this visit. Before leaving a venous blood sample was taken from participants. Full study day timeline can be viewed in figure II.4.
After 6 weeks participants returned for a 10-minute visit to return unused treatment and be administered the next 6 weeks' worth of treatment. Any changes in medication, complaints and significant life events were recorded to ensure participants could still be included in the study.

The final visit was completed 12 weeks (+/-5 days) after the first visit and followed the same procedure as visit one. Upon finishing this session participants completed a treatment guess, completed bank details and received a full debrief.

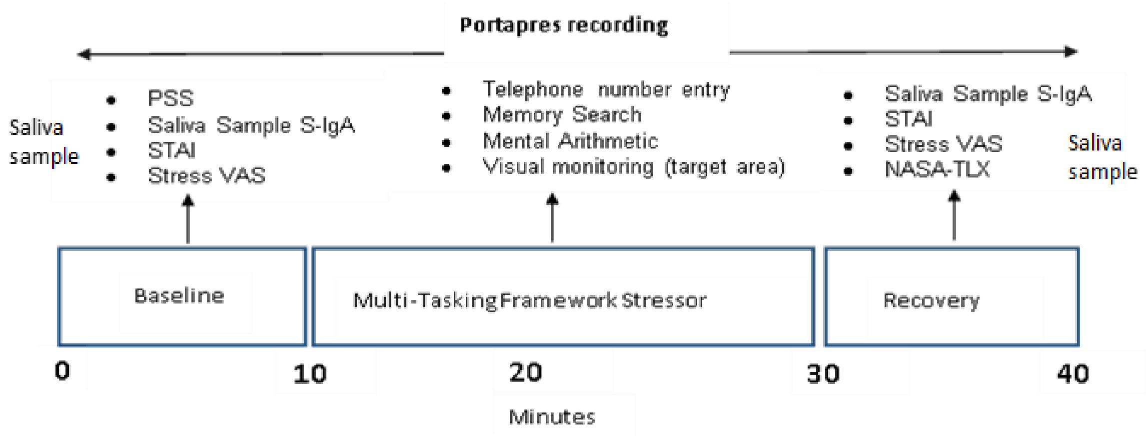


**Figure II.1.** Stress reactivity assessment. Participants will provide a saliva sample and then have a 10-minute rest period whilst wearing the portapres cardiovascular monitoring equipment. During this time, they will provide a complete the Perceived Stress Scale (PSS), STAI and stress VAS. After this rest period, participants will provide another saliva sample and then complete a 20-minute multitasking stress task (figure 2). When this is completed participant will immediately provide a saliva sample, have a 10-minute recovery period, they will again complete the STAI, Stress VAS and additionally the NASA-TLX (a measure of perceived workload). Participants will then provide a final saliva sample.

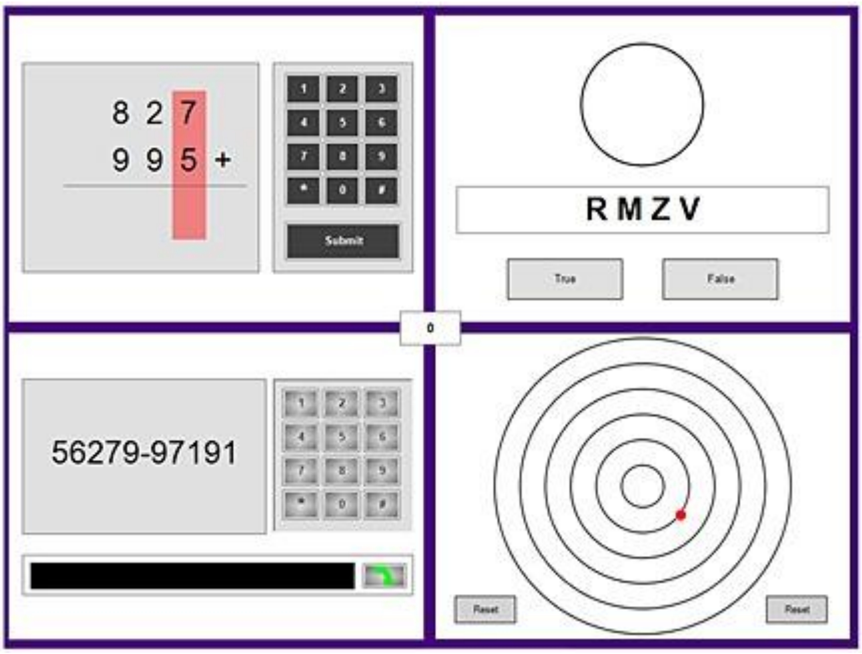


**Figure II.2**. Set up of the MTF. This will compromise four tasks presented simultaneously each on one of four quadrants on a computer screen, whilst monitoring the central counter displaying the score, which is dictated by the accuracy and speed of the response. Clockwise from top left: mental arithmetic (numbers added and answers tapped into an on screen number pad), memory search (a target letter must be identified from a previously memorised string of letters), visual monitoring a target area (a cursor must be reset before it reaches a set perimeter), telephone number entry (a 10 digit number must be entered onto a telephone-style keypad).

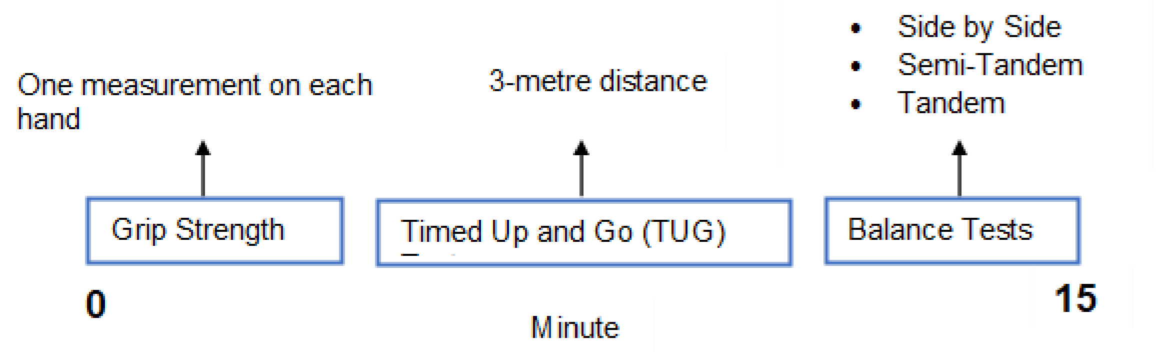


**Figure II.3.** Mobility assessment

Grip Strength: Participants will sit in a chair with fixed back arms, Researcher will demonstrate how to hold and use the dynamometer to the participant. It will be explained the dial registers the best result by squeezing as tightly as possible whilst keeping forearm on the arm of the chair and feet planted on the floor. Maximum force trial will be completed for each hand, participants will have to squeeze as long and tightly as possible whilst being encourage throughout. When the needle stops rising the measurement will be recorded. This will be repeated three times for each hand and the highest measurement being used for analysis.

TUG test: Participant is asked to rise from the chair, walk 3 meters (marked out on floor), turn, walk back and sit down again. The participant is allowed to use the arm rests during the sit – stand and stand – sit movements. Participants may use any gait aid they would usually use, but cannot be assisted by another person. They may stop and rest (but not sit down) if they need to. Participants will get an untimed practice. Timer will start on a countdown and end when participant is sitting back in the chair.

Balance: Side by side, participants asked to stand with feet together for 10 seconds, if this is held they move on to the next balance test. Semi-tandem, participant asked to stand with heel of one foot against the side of the big toe of the other foot for 10 seconds, if this is held they move on to the next balance test. Tandem Stand, feet aligned heel to toe for 10 seconds, time this is held for if less than 10 seconds is recorded.

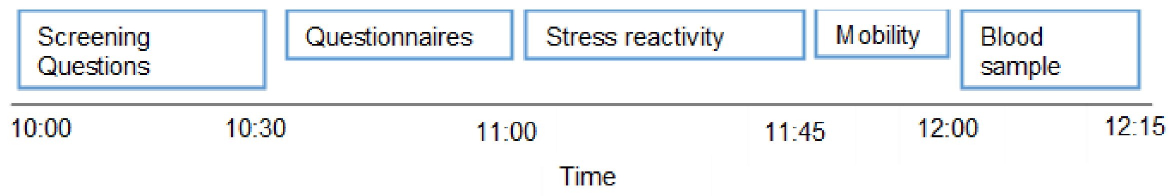


**Figure II.4**. Approximate timings for a full study day per participant.

APPENDIX III: Treatment guess questionnaire

Everyday functioning                                        Date: ____/____/____

Subject ID:

Randomisation No.:

Visit:

Which treatment do you think you were administered? (please circle)

1. Placebo (dummy pill)

2. Multivitamin

What is your reason(s) for thinking this?

_______________________________________________

_______________________________________________

_______________________________________________

APPENDIX IV: Boxplots for reported dietary intake

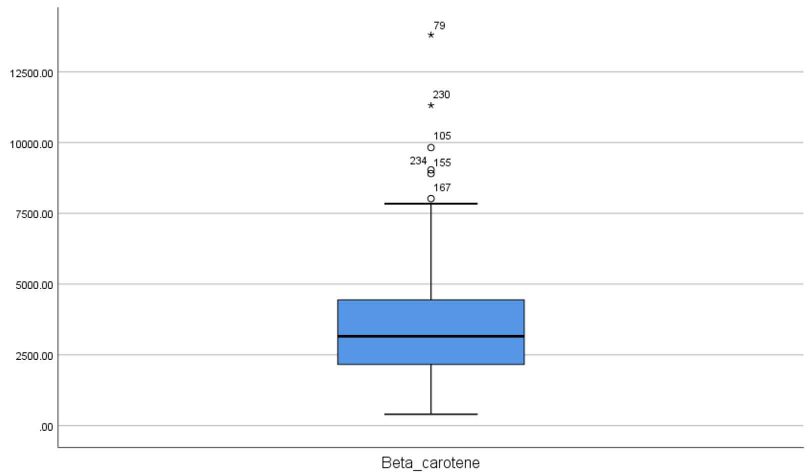


Figure IV.1 Boxplot for reported beta carotene intake. Participant 708 and 667 removed.

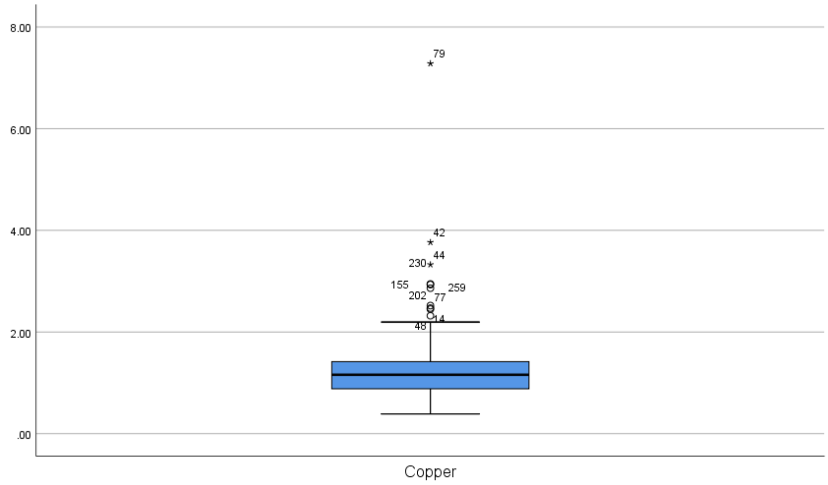


Figure IV.2 Boxplot for reported copper intake. Participant 708, 611, 617 and 667 removed.

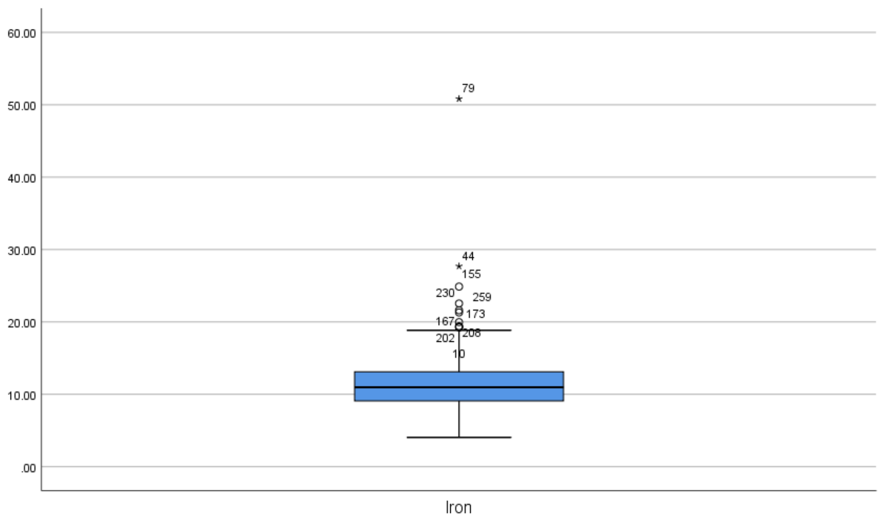

Figure IV.3 Boxplot for reported iron intake. Participant 708 and 617 removed.

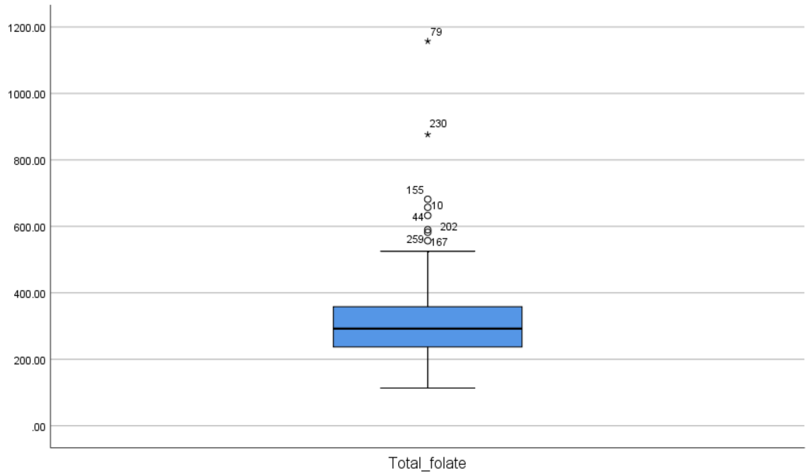


Figure IV.4 Boxplot for reported folate intake. Participant 708 and 667 removed.

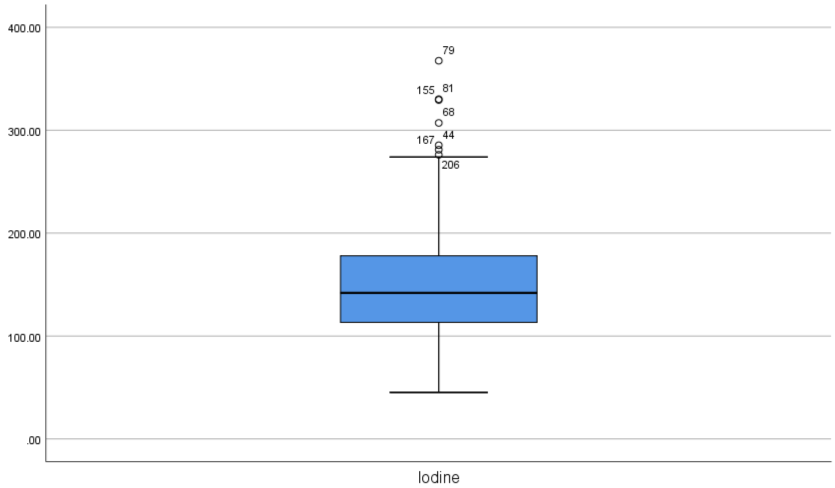


Figure IV.5 Boxplot for reported iodine intake. Participant 708 removed.

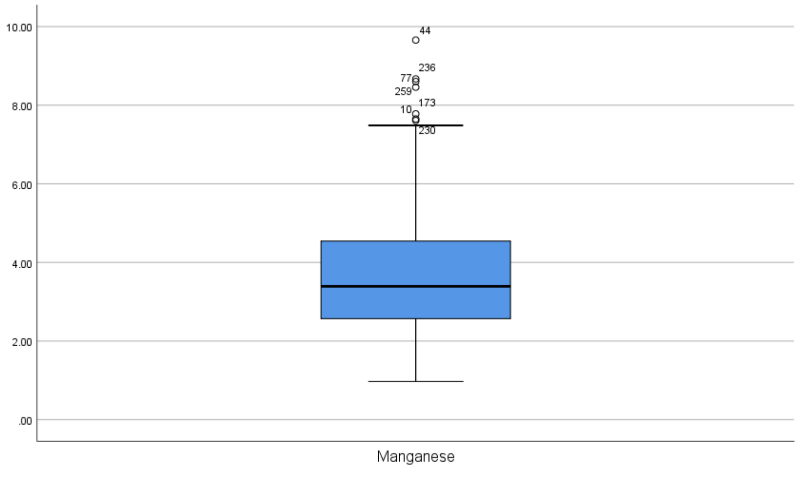


Figure IV.6 Boxplot for reported manganese intake. No participants removed.

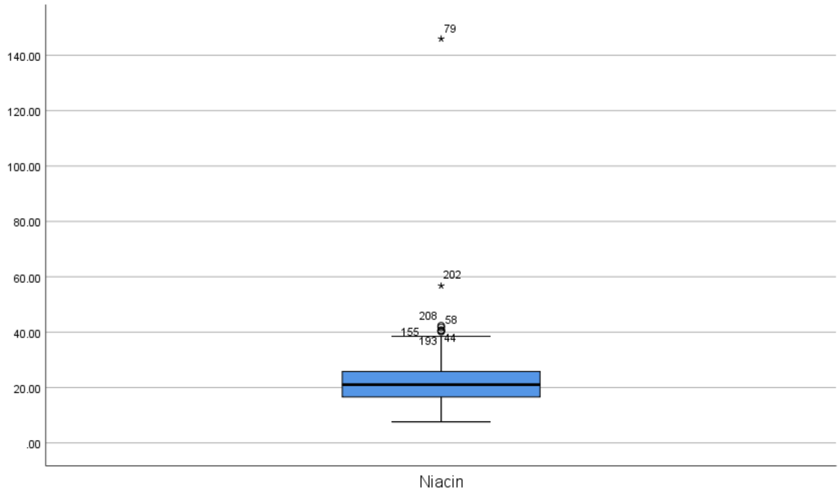


Figure IV.7 Boxplot for reported vitamin B3 intake. Participant 708 and 621 removed.

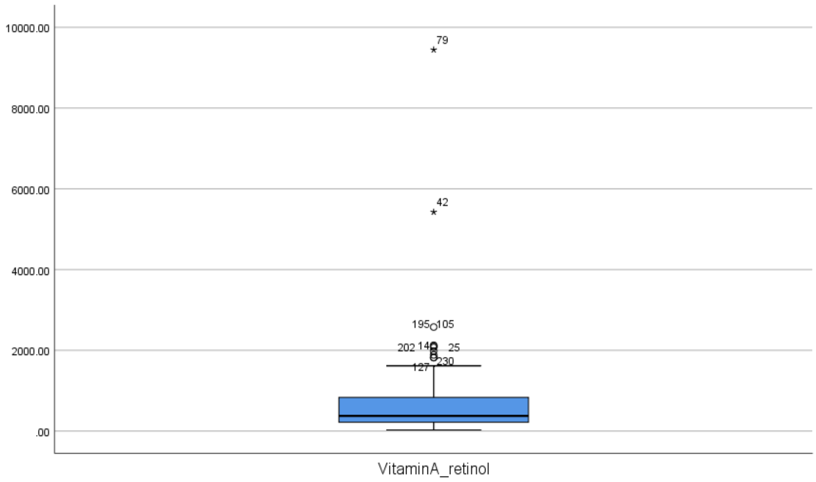


Figure IV.8 Boxplot for reported vitamin A retinol intake. Participant 708, 611, 553, 745, 612, 621, 667, 524 and 506 removed

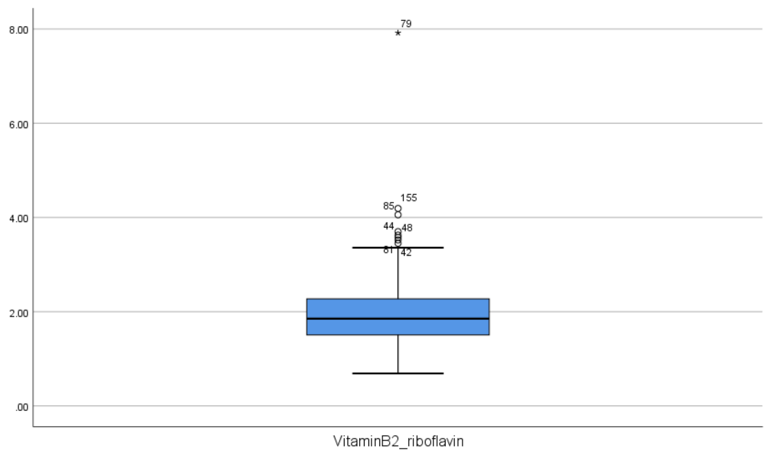

Figure IV.9 Boxplot for reported vitamin B2 intake. Participant 708 removed

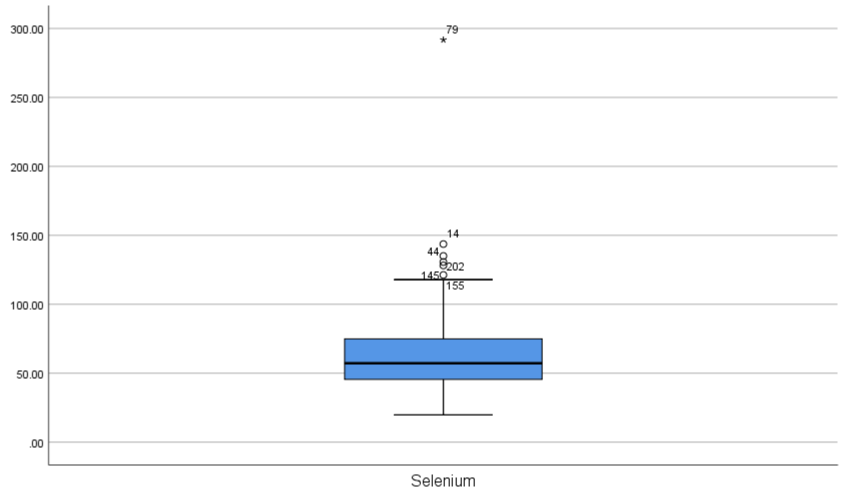


Figure IV.10 Boxplot for reported selenium intake. Participant 708 removed.

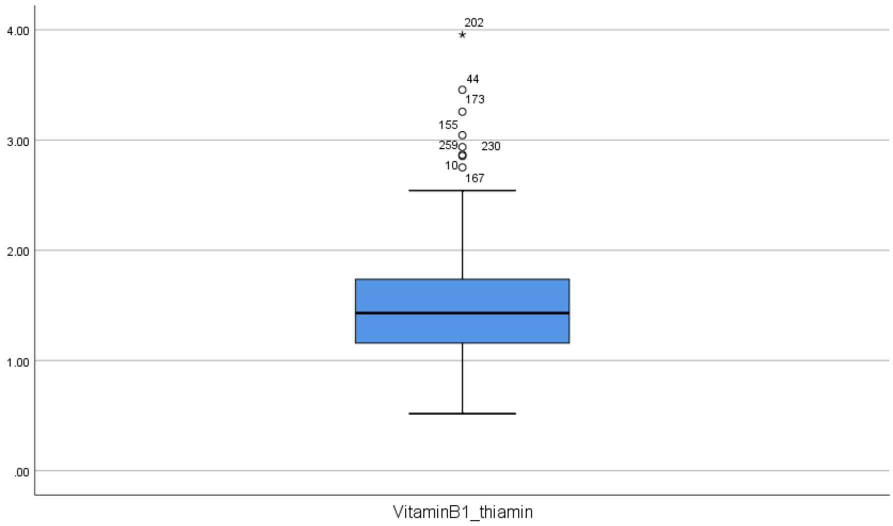


Figure IV.11 Boxplot for reported vitamin B1 intake. Participant 621 removed.

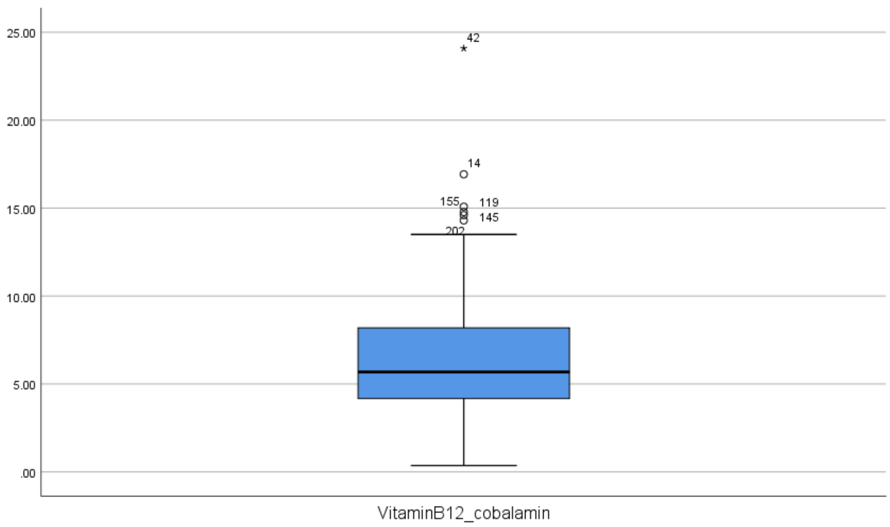

Figure IV.12 Boxplot for reported vitamin B12 intake. Participant 611 removed.

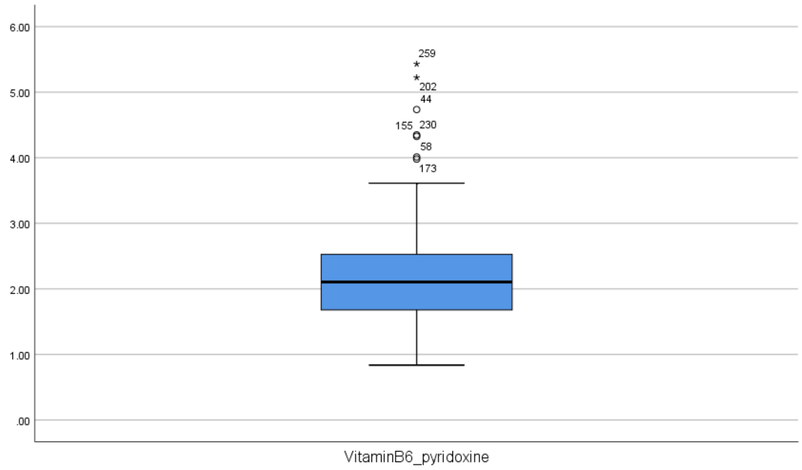


Figure IV.13 Boxplot for reported vitamin B6 intake. Participant 621 and 716 removed.

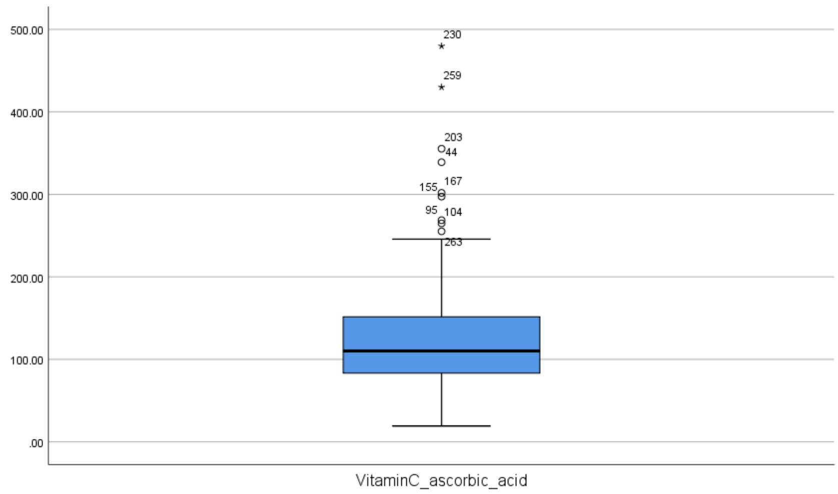


Figure IV.14 Boxplot for reported vitamin C intake. Participant 667, 716 and 625 removed.

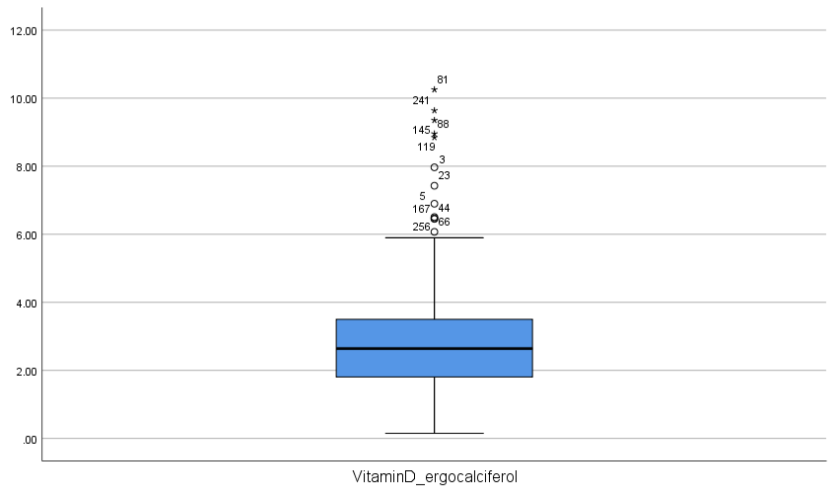


Figure IV.15 Boxplot for reported vitamin D intake. Participant 710, 687, 540, 725 and 758 removed.

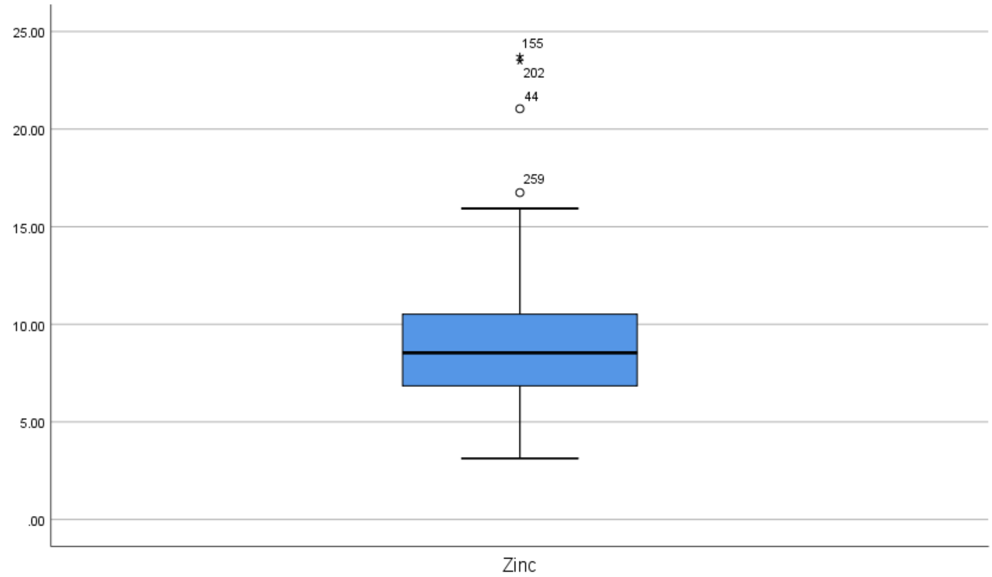


Figure IV.16 Boxplot for reported zinc intake. Participant 553 and 621 removed.

## REFERENCE LIST

Abedi, P., Nikkhah, P., & Najar, S. (2015). Effect of pedometer-based walking on depression, anxiety and insomnia among postmenopausal women. *Climacteric*, *18*(6), 841-845.

Acuff, R. V., Thedford, S. S., Hidiroglou, N. N., Papas, A. M., & Odom Jr, T. A. (1994). Relative bioavailability of RRR-and all-rac-α-tocopheryl acetate in humans: studies using deuterated compounds. *The American Journal of Clinical Nutrition*, *60*(3), 397-402.

Adams, K. B., Leibbrandt, S., & Moon, H. (2011). A critical review of the literature on social and leisure activity and wellbeing in later life. *Ageing & Society*, *31*(4), 683-712.

Agnew-Blais, J. C., Wassertheil-Smoller, S., Kang, J. H., Hogan, P. E., Coker, L. H., Snetselaar, L. G., & Smoller, J. W. (2015). Folate, vitamin B-6, and vitamin B-12 intake and mild cognitive impairment and probable dementia in the Women's Health Initiative Memory Study. *Journal of the Academy of Nutrition and Dietetics*, *115*(2), 231-241.

Ahrenfeldt, L. J., Möller, S., Thinggaard, M., Christensen, K., & Lindahl-Jacobsen, R. (2019). Sex differences in comorbidity and frailty in Europe. *International Journal of Public Health*, *64*(7), 1025-1036.

Albert, P. R. (2015). Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience: JPN*, *40*(4), 219-221.

Alghadir, A. H., Gabr, S. A., Anwer, S., & Li, H. (2021). Associations between vitamin E, oxidative stress markers, total homocysteine levels, and physical activity or cognitive capacity in older adults. *Scientific Reports*, 1-10.

Alisi, L., Cao, R., De Angelis, C., Cafolla, A., Caramia, F., Cartocci, G., Librando, A., & Fiorelli, M. (2019). The relationships between vitamin K and cognition: a review of current evidence. *Frontiers in Neurology*, *10*, 239.

Allam, A. N., El Gamal, S., & Naggar, V. (2011). Bioavailability: A pharmaceutical review. *Int J Novel Drug Deliv Tech*, *1*(1), 77-93.

Allen, S. F., Wetherell, M. A., & Smith, M. A. (2017). The Cohen-Hoberman inventory of physical symptoms: Factor structure, and preliminary tests of reliability and validity in the general population. *Psychology & Health*, *32*(5), 567-587.

Alshehri, K., Algethami, N. E., Algethami, R. A., ALAyyubi, R. H., Alotaibi, G. H., Alotaibi, J. S., & Altawairqi, S. A. (2021). Relationship Between Loneliness and Hypothyroidism. *Cureus*, *13*(11), e19955.

Amarya, S., Singh, K., & Sabharwal, M. (2015). Changes during aging and their association with malnutrition. *Journal of Clinical Gerontology and Geriatrics*, *6*(3), 78-84.

American College of Sports Medicine. (2012). *ACSM's resource manual for guidelines for exercise testing and prescription*. Lippincott Williams & Wilkins.

An, Y., Feng, L., Zhang, X., Wang, Y., Wang, Y., Tao, L., Qin, Z., & Xiao, R. (2019). Dietary intakes and biomarker patterns of folate, vitamin B6, and vitamin B12 can be associated with cognitive impairment by hypermethylation of redox-related genes NUDT15 and TXNRD1. *Clinical Epigenetics*, *11*(1), 1-19.

Anand, S., Kaysen, G. A., Chertow, G. M., Johansen, K. L., Grimes, B., Dalrymple, L. S., & Kurella Tamura, M. (2011). Vitamin D deficiency, self-reported physical activity and health-related quality of life: the Comprehensive Dialysis Study. *Nephrology Dialysis Transplantation*, *26*(11), 3683-3688.

Andreou, E., Alexopoulos, E. C., Lionis, C., Varvogli, L., Gnardellis, C., Chrousos, G. P., & Darviri, C. (2011). Perceived stress scale: reliability and validity study in Greece. *International Journal of Environmental Research and Public Health*, *8*(8), 3287-3298.

Antonucci, T. C., & Akiyama, H. (1987). Social networks in adult life and a preliminary examination of the convoy model. *Journal of Gerontology*, *42*(5), 519-527.

Aretouli, E., & Brandt, J. (2010). Everyday functioning in mild cognitive impairment and its relationship with executive cognition. *International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences*, *25*(3), 224-233.

Aron, J., & Muellbauer, J. (2020). Measuring excess mortality: the case of England during the Covid-19 Pandemic. *Institute for New Economic Thinking, Oxford Working Paper*, *11*.

Aroogh, M. D., & Shahboulaghi, F. M. (2020). Social participation of older adults: A concept analysis. *International Journal of Community Based Nursing and Midwifery*, *8*(1), 55-72.

Arthur, J. R., McKenzie, R. C., & Beckett, G. J. (2003). Selenium in the immune system1, 2. *Journal of Nutrition*, *133*(5), 1457-1457.

Aslam, F., Muhammad, S. M., Aslam, S., & Irfan, J. A. (2017). Vitamins: key role players in boosting up immune response-a mini review. *Vitamins & Minerals*, *6*(01).

Aspy, D. J., Madden, N. A., & Delfabbro, P. (2018). Effects of vitamin B6 (pyridoxine) and a B complex preparation on dreaming and sleep. *Perceptual and Motor Skills*, *125*(3), 451-462.

Austad, S. N., & Fischer, K. E. (2016). Sex differences in lifespan. *Cell Metabolism*, *23*(6), 1022-1033.

Austin, K. G., McGraw, S. M., & Lieberman, H. R. (2014). Multivitamin and Protein Supplement Use Is Associated With Positive Mood States and Health Behaviors in US Military and Coast Guard Personnel. *Journal of Clinical Psychopharmacology*, *34*(5), 595-601.

Avery, H. L. (2021). *Iron Status and Iron-Vitamin C Co-Supplementation Effects on Cognition, Subjective Mood and Fatigue in Menstruating, Non Anaemic Women Aged 18–49 Years* University of Northumbria at Newcastle (United Kingdom)].

Aw, D., Silva, A. B., & Palmer, D. B. (2007). Immunosenescence: emerging challenges for an ageing population. *Immunology*, *120*(4), 435-446.

Azizi-Namini, P., Ahmed, M., Yan, A. T., & Keith, M. (2012). The role of B vitamins in the management of heart failure. *Nutrition in Clinical Practice*, *27*(3), 363-374.

Bain, L. K., Myint, P. K., Jennings, A., Lentjes, M. A., Luben, R. N., Khaw, K.-T., Wareham, N. J., & Welch, A. A. (2015). The relationship between dietary magnesium intake, stroke and its major risk factors, blood pressure and cholesterol, in the EPIC-Norfolk cohort. *International Journal of Cardiology*, *196*, 108-114.

Baker, L. D., Rapp, S. R., Shumaker, S. A., Manson, J. E., Sesso, H. D., Gaussoin, S. A., Harris, D., Caudle, B., Pleasants, D., & Espeland, M. A. (2019). Design and baseline characteristics of the cocoa supplement and multivitamin outcomes study for the Mind: COSMOS-Mind. *Contemporary Clinical Trials*, *83*, 57-63.

Balachandar, R., Pullakhandam, R., Kulkarni, B., & Sachdev, H. S. (2021). Relative Efficacy of Vitamin D2 and Vitamin D3 in improving Vitamin D status: Systematic review and meta-Analysis. *Nutrients*, *13*(10), 3328.

Bales, C. W., & Ritchie, C. S. (2002). Sarcopenia, weight loss, and nutritional frailty in the elderly. *Annual Review of Nutrition*, *22*(1), 309-323.

Baltes, M. M., & Lang, F. R. (1997). Everyday functioning and successful aging: the impact of resources. *Psychology and Aging*, *12*(3), 433-443.

Barone, M., D'Amico, F., Brigidi, P., & Turroni, S. (2022). Gut microbiome–micronutrient interaction: The key to controlling the bioavailability of minerals and vitamins? *BioFactors*, *48*(2), 307-314.

Bartali, B., Frongillo, E. A., Guralnik, J. M., Stipanuk, M. H., Allore, H. G., Cherubini, A., Bandinelli, S., Ferrucci, L., & Gill, T. M. (2008). Serum micronutrient concentrations and decline in physical function among older persons. *Jama*, *299*(3), 308-315.

Bartali, B., Semba, R. D., Frongillo, E. A., Varadhan, R., Ricks, M. O., Blaum, C. S., Ferrucci, L., Guralnik, J. M., & Fried, L. P. (2006). Low micronutrient levels as a predictor of incident disability in older women. *Archives of Internal Medicine*, *166*(21), 2335-2340.

Bates, B., Lennox, A., Prentice, A., Bates, C. J., Page, P., Nicholson, S., & Swan, G. (2014). National diet and nutrition survey: Results from years 1, 2, 3 and 4 (combined) of the rolling programme (2008/2009-2011/2012): A survey carried out on behalf of public health England and the food standards agency. *Public Health England*.

Batista, E. D., Andretta, A., Miranda, R. C. d., Nehring, J., Paiva, E. d. S., & Schieferdecker, M. E. M. (2016). Food intake assessment and quality of life in women with fibromyalgia. *Revista brasileira de Reumatologia*, *56*, 105-110.

Bauer, J., Biolo, G., Cederholm, T., Cesari, M., Cruz-Jentoft, A. J., Morley, J. E., Phillips, S., Sieber, C., Stehle, P., & Teta, D. (2013). Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. *Journal of the American Medical Directors Association*, *14*(8), 542-559.

Bazinet, R. P., & Layé, S. (2014). Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nature Reviews Neuroscience*, *15*(12), 771-785.

Begdache, L., Kianmehr, H., Sabounchi, N., Chaar, M., & Marhaba, J. (2020). Principal component analysis identifies differential gender-specific dietary patterns that may be linked to mental distress in human adults. *Nutritional Neuroscience*, *23*(4), 295-308.

Beierle, I., Meibohm, B., & Derendorf, H. (1999). Gender differences in pharmacokinetics and pharmacodynamics. *International Journal of Clinical Pharmacology and Therapeutics*, *37*(11), 529-547.

Bellows, L., Moore, R., Anderson, J., & Young, L. (2012). Water-soluble vitamins: B-complex and vitamin C. *Food and Nutrition Series. Health; no. 9.312*.

Benton, D. (2002). Selenium intake, mood and other aspects of psychological functioning. *Nutritional Neuroscience*, *5*(6), 363-374.

Benton, D., & Cook, R. (1991). The impact of selenium supplementation on mood. *Biological Psychiatry*, *29*(11), 1092-1098.

Benton, D., & Donohoe, R. T. (1999). The effects of nutrients on mood. *Public Health Nutrition*, *2*(3a), 403-409.

Benton, D., Haller, J., & Fordy, J. (1995). Vitamin supplementation for 1 year improves mood. *Neuropsychobiology*, *32*(2), 98-105.

Ben-Zvi, G. T., & Tidman, M. J. (2012). Be vigilant for scurvy in high-risk groups. *The Practitioner*, *256*(1755), 23-26.

Berinsky, A. J., Margolis, M. F., & Sances, M. W. (2014). Separating the shirkers from the workers? Making sure respondents pay attention on self-administered surveys. *American Journal of Political Science*, *58*(3), 739-753.

Berk, M., Sanders, K. M., Pasco, J. A., Jacka, F. N., Williams, L. J., Hayles, A. L., & Dodd, S. (2007). Vitamin D deficiency may play a role in depression. *Medical Hypotheses*, *69*(6), 1316-1319.

Berkman, L. F., & Syme, S. L. (1979). Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *American Journal of Epidemiology*, *109*(2), 186-204.

Best, L. A., Law, M. A., Roach, S., & Wilbiks, J. M. (2021). The psychological impact of COVID-19 in Canada: Effects of social isolation during the initial response. *Canadian Psychology/Psychologie canadienne*, *62*(1), 143-154.

Bhatti, A. B., & ul Haq, A. (2017). The pathophysiology of perceived social isolation: effects on health and mortality. *Cureus*, *9*(1).

Biesalski, H. K., & Tinz, J. (2017). Multivitamin/mineral supplements: Rationale and safety–A systematic review. *Nutrition*, *33*, 76-82.

Biesalski, H. K., Brummer, R.-J., König, J., O'Connell, M. A., Ovesen, L., Rechkemmer, G., Stos, K., & Thurnham, D. I. (2003). Micronutrient deficiencies. *European Journal of Nutrition*, *42*(6), 353-363.

Bingham, S. A., Gill, C., Welch, A., Cassidy, A., Runswick, S. A., Oakes, S., Lubin, R., Thurnham, D. I., Key, T., & Roe, L. (1997). Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *International Journal of Epidemiology*, *26*(suppl_1), S137.

Bingham, S. A., Welch, A. A., McTaggart, A., Mulligan, A. A., Runswick, S. A., Luben, R., Oakes, S., Khaw, K. T., Wareham, N., & Day, N. E. (2001). Nutritional methods in the European prospective investigation of cancer in Norfolk. *Public Health Nutrition*, *4*(3), 847-858.

Bingham, S., Luben, R., Welch, A., Low, Y. L., Khaw, K. T., Wareham, N., & Day, N. (2008). Associations between dietary methods and biomarkers, and between fruits and vegetables and risk of ischaemic heart disease, in the EPIC Norfolk Cohort Study. *International Journal of Epidemiology*, *37*(5), 978-987.

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *Journal of Psychosomatic Research*, *52*(2), 69-77.

Bjørklund, G., Dadar, M., Chirumbolo, S., & Aaseth, J. (2018). Fibromyalgia and nutrition: Therapeutic possibilities? *Biomedicine & Pharmacotherapy*, *103*, 531-538.

Björnwall, A., Mattsson Sydner, Y., Koochek, A., & Neuman, N. (2021). Eating alone or together among community-living older people—a scoping review. *International journal of environmental research and public health*, *18*(7), 3495.

Blanco-Rojo, R., & Vaquero, M. P. (2019). Iron bioavailability from food fortification to precision nutrition. A review. *Innovative Food Science & Emerging Technologies*, *51*, 126-138.

Blasko, I., Hinterberger, M., Kemmler, G., Jungwirth, S., Krampla, W., Leitha, T., Heinz Tragl, K., & Fischer, P. (2012). Conversion from mild cognitive impairment to dementia: influence of folic acid and vitamin B12 use in the VITA cohort. *The Journal of Nutrition, Health & Aging*, *16*(8), 687-694.

Blot, W. J., Li, J.-Y., Taylor, P. R., Guo, W., Dawsey, S., Wang, G.-Q., Yang, C. S., Zheng, S.-F., Gail, M., & Li, G.-Y. (1993). Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *JNCI: Journal of the National Cancer Institute*, *85*(18), 1483-1491.

Boelaert, K. (2013). Thyroid dysfunction in the elderly. *Nature Reviews Endocrinology*, *9*(4), 194-204.

Bonnefoy, M., Berrut, G., Lesourd, B., Ferry, M., Gilbert, T., Guerin, O., Hanon, O., Jeandel, C., Paillaud, E., & Raynaud-Simon, A. (2015). Frailty and nutrition: searching for evidence. *The Journal of Nutrition, Health & Aging*, *19*(3), 250-257.

Borel, P., Caillaud, D., & Cano, N. (2015). Vitamin D bioavailability: state of the art. *Critical Reviews in Food Science and Nutrition*, *55*(9), 1193-1205.

Bottari, C., Dassa, C., Rainville, C., & Dutil, É. (2010). A generalizability study of the instrumental activities of daily living profile. *Archives of Physical Medicine and Rehabilitation*, *91*(5), 734-742.

Bowling, A., & Grundy, E. (1997). Activities of daily living: changes in functional ability in three samples of elderly and very elderly people. *Age and Ageing*, *26*(2), 107-114.

Boyle, S. E., Fothergill, M. A., Metcalfe, J., Docherty, S., & Haskell-Ramsay, C. F. (2020). The effects of low-intensity multimodal proprioceptive exercise on cognitive function in older adults. *Journal of Physical Activity and Health*, *18*(1), 2-7.

Brewster, G. S., Peterson, L., Roker, R., Ellis, M. L., & Edwards, J. D. (2017). Depressive symptoms, cognition, and everyday function among community-residing older adults. *Journal of Aging and Health*, *29*(3), 367-388.

Brigelius-Flohé, R. (2019). Metabolism of Vitamin E. In *Vitamin E* (pp. 189-207).

Brownie, S. (2006). Why are elderly individuals at risk of nutritional deficiency? *International Journal of Nursing Practice*, *12*(2), 110-118.

Bryant, C., Jackson, H., & Ames, D. (2008). The prevalence of anxiety in older adults: methodological issues and a review of the literature. *Journal of Affective Disorders*, *109*(3), 233-250.

Buchanan, L. M., Charlton, K. E., Roodenrys, S. J., Cocuz, D., Pendergast, T., & Ma, G. (2015). Iodine status not associated with cognitive functioning in older Australians. *Journal of Aging Research and Clinical Practice, 4*(1), 16-24.

Burbridge, C., Randall, J. A., Abraham, L., & Bush, E. N. (2020). Measuring the impact of chronic low back pain on everyday functioning: content validity of the Roland Morris disability questionnaire. *Journal of Patient-Reported Outcomes*, *4*(1), 1-15.

Burke, S. (2020). Stronger together? Intergenerational connection and Covid-19. *Quality in Ageing and Older Adults*.

Buysse, D. J., Reynolds III, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193-213.

Cacioppo, J. T., Hawkley, L. C., & Thisted, R. A. (2010). Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study. *Psychology and Aging*, *25*(2), 453-463.

Cade, J. E. (2017). Measuring diet in the 21st century: use of new technologies. *Proceedings of the Nutrition Society*, *76*(3), 276-282.

Çakır, T., Doğan, G., Subaşı, V., Filiz, M. B., Ülker, N., Doğan, Ş. K., & Toraman, N. F. (2015). An evaluation of sleep quality and the prevalence of restless leg syndrome in vitamin D deficiency. *Acta Neurologica Belgica*, *115*(4), 623-627.

Calder, P. C., Carr, A. C., Gombart, A. F., & Eggersdorfer, M. (2020). Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. *Nutrients*, *12*(4), 1181.

Caluwé, R., Verbeke, F., & De Vriese, A. S. (2020). Evaluation of vitamin K status and rationale for vitamin K supplementation in dialysis patients. *Nephrology Dialysis Transplantation*, *35*(1), 23-33.

Campagne, D. M. (2019). Stress and perceived social isolation (loneliness). *Archives of Gerontology and Geriatrics*, *82*, 192-199.

Cano, R. L. E., & Lopera, H. D. E. (2013). Introduction to T and B lymphocytes. In *Autoimmunity: From Bench to Bedside [Internet]*. El Rosario University Press.

Cao, Q., Guo, Z., Yan, Y., Wu, J., & Song, C. (2019). Exosomal long noncoding RNAs in aging and age-related diseases. *IUBMB life*, *71*(12), 1846-1856.

Cardoso, B. R., Bandeira, V. S., Jacob-Filho, W., & Cozzolino, S. M. F. (2014). Selenium status in elderly: relation to cognitive decline. *Journal of Trace Elements in Medicine and Biology*, *28*(4), 422-426.

Carers UK. (2020). *The rise in the number of unpaid carers during the coronavirus (COVID-19) outbreak*. https://www.carersuk.org/for-professionals/policy/policy-library/carers-week-2020-research-report

Carr, A. C., & Vissers, M. (2013). Synthetic or food-derived vitamin C—are they equally bioavailable? *Nutrients*, *5*(11), 4284-4304.

Carroll, D., Ring, C., Suter, M., & Willemsen, G. (2000). The effects of an oral multivitamin combination with calcium, magnesium, and zinc on psychological well-being in healthy young male volunteers: a double-blind placebo-controlled trial. *Psychopharmacology*, *150*(2), 220-225.

Cénat, J. M., Felix, N., Blais-Rochette, C., Rousseau, C., Bukaka, J., Derivois, D., Noorishad, P.-G., & Birangui, J.-P. (2020). Prevalence of mental health problems in populations affected by the Ebola virus disease: A systematic review and meta-analysis. *Psychiatry Research*, *289*, 113033.

Cesari, M., Fielding, R. A., Pahor, M., Goodpaster, B., Hellerstein, M., Van Kan, G. A., Anker, S. D., Rutkove, S., Vrijbloed, J. W., & Isaac, M. (2012). Biomarkers of sarcopenia in clinical trials—recommendations from the International Working Group on Sarcopenia. *Journal of Cachexia, Sarcopenia and Muscle*, *3*(3), 181-190.

Chan, I. T., Lobo Santos, M. A., Cohen, M., de La Roque P Araujo, M., da Silva Almeida, J., Simões, A., Givigi, H. R. B., Vaisman, M., Paixão, C. M., & de Fatima dos S Teixeira, P. (2014). Impact of thyroid status and age on comprehensive geriatric assessment. *Endocrine*, *47*(1), 255-265.

Chandra, R. K. (1992). Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. *Lancet (London, England)*, *340*(8828), 1124-1127.

Chauhan, B., Kumar, G., Kalam, N., & Ansari, S. H. (2013). Current concepts and prospects of herbal nutraceutical: A review. *Journal of Advanced Pharmaceutical Technology & Research*, *4*(1), 4-8.

Chen, S., Honda, T., Chen, T., Narazaki, K., Haeuchi, Y., Supartini, A., & Kumagai, S. (2015). Screening for frailty phenotype with objectively-measured physical activity in a west Japanese suburban community: evidence from the Sasaguri Genkimon Study. *BMC Geriatrics*, *15*(1), 1-10.

Chiao, C., Weng, L.-J., & Botticello, A. L. (2011). Social participation reduces depressive symptoms among older adults: an 18-year longitudinal analysis in Taiwan. *BMC public health*, *11*(1), 1-9.

Chien, M.-H., & Guo, H.-R. (2014). Nutritional status and falls in community-dwelling older people: a longitudinal study of a population-based random sample. *PLoS One*, *9*(3), e91044.

Chien, M.-Y., & Chen, H.-C. (2015). Poor sleep quality is independently associated with physical disability in older adults. *Journal of Clinical Sleep Medicine*, *11*(3), 225-232.

Choi, J. E., & Ainsworth, B. E. (2016). Associations of food consumption, serum vitamins and metabolic syndrome risk with physical activity level in middle-aged adults: the National Health and Nutrition Examination Survey (NHANES) 2005–2006. *Public Health Nutrition*, *19*(9), 1674-1683.

Christiansen, J., Lund, R., Qualter, P., Andersen, C. M., Pedersen, S. S., & Lasgaard, M. (2021). Loneliness, social isolation, and chronic disease outcomes. *Annals of Behavioral Medicine*, *55*(3), 203-215.

Chrysant, S. G., & Chrysant, G. S. (2018). The current status of homocysteine as a risk factor for cardiovascular disease: a mini review. *Expert Review of Cardiovascular Therapy*, *16*(8), 559-565.

Clarke, R., Smith, A. D., Jobst, K. A., Refsum, H., Sutton, L., & Ueland, P. M. (1998). Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. *Archives of Neurology*, *55*(11), 1449-1455.

Classon, E., Fällman, K., Wressle, E., & Marcusson, J. (2016). Relations between concurrent longitudinal changes in cognition, depressive symptoms, self-rated health and everyday function in normally aging octogenarians. *PLoS One*, *11*(8), e0160742.

Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. *The Lancet*, *381*(9868), 752-762.

Clegg, M. E., & Williams, E. A. (2018). Optimizing nutrition in older people. *Maturitas*, *112*, 34-38.

Cockle, S., Haller, J., Kimber, S., Dawe, R., & Hindmarch, I. (2000). The influence of multivitamins on cognitive function and mood in the elderly. *Aging & Mental Health*, *4*(4), 339-353.

Cohen, S., & Hoberman, H. M. (1983). Positive events and social supports as buffers of life change stress 1. *Journal of Applied Social Psychology*, *13*(2), 99-125.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, 385-396.

Cohen-Mansfield, J., Hazan, H., Lerman, Y., & Shalom, V. (2016). Correlates and predictors of loneliness in older-adults: a review of quantitative results informed by qualitative insights. *International Psychogeriatrics*, *28*(4), 557-576.

Cole, M. G., & Dendukuri, N. (2003). Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *American Journal of Psychiatry*, *160*(6), 1147-1156.

Combs Jr, G. F., & McClung, J. P. (2016). *The vitamins: fundamental aspects in nutrition and health*. Academic press.

Comerford, K. B. (2013). Recent developments in multivitamin/mineral research. *Advances in Nutrition*, *4*(6), 644-656.

Conklin, S. M., Harris, J. I., Manuck, S. B., Yao, J. K., Hibbeln, J. R., & Muldoon, M. F. (2007). Serum ω-3 fatty acids are associated with variation in mood, personality and behavior in hypercholesterolemic community volunteers. *Psychiatry Research*, *152*(1), 1-10.

Conklin, S. M., Manuck, S. B., Yao, J. K., Flory, J. D., Hibbeln, J. R., & Muldoon, M. F. (2007). High ω-6 and low ω-3 fatty acids are associated with depressive symptoms and neuroticism. *Psychosomatic Medicine*, *69*(9), 932-934.

Connolly, D., Garvey, J., & McKee, G. (2017). Factors associated with ADL/IADL disability in community dwelling older adults in the Irish longitudinal study on ageing (TILDA). *Disability and Rehabilitation*, *39*(8), 809-816.

Conolly, A., & Davies, B. (2018). Health survey for England 2017: adult and child overweight and obesity. *NHS Digital*, *1*, 1-30.

Cosgrove, M. C., Franco, O. H., Granger, S. P., Murray, P. G., & Mayes, A. E. (2007). Dietary nutrient intakes and skin-aging appearance among middle-aged American women. *The American Journal of Clinical Nutrition*, *86*(4), 1225-1231.

Costa, A., Pereira, E. S. P., Assumpção, E. C., Dos Santos, F. B. C., Ota, F. S., de Oliveira Pereira, M., Fidelis, M. C., Fávaro, R., Langen, S. S. B., & de Arruda, L. H. F. (2015). Assessment of clinical effects and safety of an oral supplement based on marine protein, vitamin C, grape seed extract, zinc, and tomato extract in the improvement of visible signs of skin aging in men. *Clinical, Cosmetic and Investigational Dermatology*, *8*, 319-328.

Cousins, R. J., Blanchard, R. K., Popp, M. P., Liu, L., Cao, J., Moore, J. B., & Green, C. L. (2003). A global view of the selectivity of zinc deprivation and excess on genes expressed in human THP-1 mononuclear cells. *Proceedings of the National Academy of Sciences*, *100*(12), 6952-6957.

Cowan, A. E., Jun, S., Gahche, J. J., Tooze, J. A., Dwyer, J. T., Eicher-Miller, H. A., Bhadra, A., Guenther, P. M., Potischman, N., & Dodd, K. W. (2018). Dietary supplement use differs by socioeconomic and health-related characteristics among US adults, NHANES 2011–2014. *Nutrients*, *10*(8), 1114.

Cox, K. H., Pipingas, A., & Scholey, A. B. (2015). Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. *Journal of Psychopharmacology*, *29*(5), 642-651.

Craske, M. G. (2012). Transdiagnostic treatment for anxiety and depression. *Depression and anxiety*.

Crawford, J., Smith, G., Maylor, E., Della Sala, S., & Logie, R. (2003). The Prospective and Retrospective Memory Questionnaire (PRMQ): Normative data and latent structure in a large non-clinical sample. *Memory*, *11*(3), 261-275.

Crimmins, E. M., Kim, J. K., & Solé-Auró, A. (2011). Gender differences in health: results from SHARE, ELSA and HRS. *European Journal of Public Health*, *21*(1), 81-91.

Crimmins, E. M., Shim, H., Zhang, Y. S., & Kim, J. K. (2019). Differences between men and women in mortality and the health dimensions of the morbidity process. *Clinical Chemistry*, *65*(1), 135-145.

Crooke, S. N., Ovsyannikova, I. G., Poland, G. A., & Kennedy, R. B. (2019). Immunosenescence and human vaccine immune responses. *Immunity & Ageing*, *16*(1), 1-16.

Crowley, K. (2011). Sleep and sleep disorders in older adults. *Neuropsychology Review*, *21*(1), 41-53.

Curran, P. G. (2016). Methods for the detection of carelessly invalid responses in survey data. *Journal of Experimental Social Psychology*, *66*, 4-19.

Curtis, A. B., Karki, R., Hattoum, A., & Sharma, U. C. (2018). Arrhythmias in patients≥ 80 years of age: pathophysiology, management, and outcomes. *Journal of the American College of Cardiology*, *71*(18), 2041-2057.

Dankner, R., Chetrit, A., Ken Dror, G., & Sela, B.-A. (2007). Physical activity is inversely associated with total homocysteine levels, independent of C677T MTHFR genotype and plasma B vitamins. *Age*, *29*(4), 219-227.

Darmon, N., & Drewnowski, A. (2008). Does social class predict diet quality? *The American Journal of Clinical Nutrition*, *87*(5), 1107-1117.

Das, A., Cumming, R. G., Naganathan, V., Blyth, F., Ribeiro, R. V., Le Couteur, D. G., Handelsman, D. J., Waite, L. M., Simpson, S. J., & Hirani, V. (2020). Prospective associations between dietary antioxidant intake and frailty in older Australian men: The concord health and ageing in men project. *The Journals of Gerontology: Series A*, *75*(2), 348-356.

Davies, N. (2011). Promoting healthy ageing: the importance of lifestyle. *Nursing Standard (through 2013)*, *25*(19), 43-49.

Davison, K. M., & Kaplan, B. J. (2012). Nutrient intakes are correlated with overall psychiatric functioning in adults with mood disorders. *The Canadian Journal of Psychiatry*, *57*(2), 85-92.

Day, N., Oakes, S., Luben, R., Khaw, K., Bingham, S. a., Welch, A., & Wareham, N. (1999). EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *British Journal of Cancer*, *80*, 95-103.

De Groot, C., Van Den Broek, T., & Van Staveren, W. (1999). Energy intake and micronutrient intake in elderly Europeans: seeking the minimum requirement in the SENECA study. *Age and Ageing*, *28*(5), 469-474.

De Jong-Gierveld, J., & Kamphuls, F. (1985). The development of a Rasch-type loneliness scale. *Applied Psychological Measurement*, *9*(3), 289-299.

De Jong-Gierveld, J., & Van Tilburg, T. (1990). *Manual of the loneliness scale*. Vrije Universiteit Amsterdam, Netherlands.

de Leon, C. F. M. (2005). Social engagement and successful aging. *European Journal of Ageing*, *1*(2), 64-66.

de Leon, C., Gold, D., Glass, T., Kaplan, L., & George, L. (2001). Disability as a function of social networks and support in elderly African Americans and Whites: The duke EPESE 1986-1992. *Journals of Gerontology. Series B: Psychological Sciences & Social Sciences*, *56*, S179-S190.

de Souza, R. O. B., de Faria Marcon, L., de Arruda, A. S. F., Junior, F. L. P., & de Melo, R. C. (2018). Effects of mat pilates on physical functional performance of older adults: a meta-analysis of randomized controlled trials. *American Journal of Physical Medicine & Rehabilitation*, *97*(6), 414-425.

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., Penke, L., Rafnsson, S. B., & Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin*, *92*(1), 135-152.

Debes, C., Merentitis, A., Sukhanov, S., Niessen, M., Frangiadakis, N., & Bauer, A. (2016). Monitoring activities of daily living in smart homes: Understanding human behavior. *IEEE Signal Processing Magazine*, *33*(2), 81-94.

Del Valle, H. B., Yaktine, A. L., Taylor, C. L., & Ross, A. C. (2011). Dietary reference intakes for calcium and vitamin D.

Delbaere, K., Close, J. C., Mikolaizak, A. S., Sachdev, P. S., Brodaty, H., & Lord, S. R. (2010). The Falls Efficacy Scale International (FES-I). A comprehensive longitudinal validation study. *Age and Ageing*, *39*(2), 210-216.

Delgado, P. L. (2000). Depression: the case for a monoamine deficiency. *Journal of clinical Psychiatry*, *61*(6), 7-11.

Denison, H., Jameson, K., Syddall, H., Dennison, E., Cooper, C., Sayer, A. A., & Robinson, S. (2012). Patterns of dietary supplement use among older men and women in the UK: findings from the Hertfordshire Cohort Study. *The Journal of Nutrition, Health & Aging*, *16*(4), 307-311.

Depp, C. A., Mausbach, B. T., Harmell, A. L., Savla, G. N., Bowie, C. R., Harvey, P. D., & Patterson, T. L. (2012). Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disorders*, *14*(3), 217-226.

Derry, H. M., Johnston, C. D., Burchett, C. O., Brennan-Ing, M., Karpiak, S., Zhu, Y.-S., Siegler, E. L., & Glesby, M. J. (2022). Links between inflammation, mood, and physical function among older adults with HIV. *The Journals of Gerontology: Series B*, *77*(1), 50-60.

Devore, E. E., Grodstein, F., van Rooij, F. J., Hofman, A., Stampfer, M. J., Witteman, J. C., & Breteler, M. M. (2010). Dietary antioxidants and long-term risk of dementia. *Archives of Neurology*, *67*(7), 819-825.

Dickinson, A., Blatman, J., El-Dash, N., & Franco, J. C. (2014). Consumer usage and reasons for using dietary supplements: report of a series of surveys. *Journal of the American College of Nutrition*, *33*(2), 176-182.

Dipietro, L., Caspersen, C. J., Ostfeld, A. M., & Nadel, E. R. (1993). A survey for assessing physical activity among older adults. *Medicine & Science in Sports & Exercise*.

Divers, R., Robinson, A., Miller, L., De Vito, A. N., Pugh, E., & Calamia, M. (2022). Beyond depression: examining the role of anxiety and anxiety sensitivity on subjective cognition and functioning in older adults. *Aging & Mental Health*, *26*(11), 2300-2306.

Dodd, F., Kennedy, D., Stevenson, E., Veasey, R., Walker, K., Reed, S., Jackson, P., & Haskell-Ramsay, C. (2020). Acute and chronic effects of multivitamin/mineral supplementation on objective and subjective energy measures. *Nutrition & Metabolism*, *17*(1), 1-14.

Doets, E. L., Ueland, P. M., Tell, G. S., Vollset, S. E., Nygård, O. K., Van't Veer, P., de Groot, L. C., Nurk, E., Refsum, H., & Smith, A. D. (2014). Interactions between plasma concentrations of folate and markers of vitamin B12 status with cognitive performance in elderly people not exposed to folic acid fortification: the Hordaland Health Study. *British Journal of Nutrition*, *111*(6), 1085-1095.

Dombrowsky, T. A. (2017). Relationship between engagement and level of functional status in older adults. *SAGE Open Medicine*, *5*, 2050312117727998.

Donhowe, E. G., & Kong, F. (2014). Beta-carotene: digestion, microencapsulation, and in vitro bioavailability. *Food and Bioprocess Technology*, *7*(2), 338-354.

Doyle, Y., McKee, M., Rechel, B., & Grundy, E. (2009). Meeting the challenge of population ageing. *Bmj*, *339*.

Du, J., Cullen, J. J., & Buettner, G. R. (2012). Ascorbic acid: chemistry, biology and the treatment of cancer. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, *1826*(2), 443-457.

Dupuy, L., N'kaoua, B., Dehail, P., & Sauzéon, H. (2020). Role of cognitive resources on everyday functioning among oldest-old physically frail. *Aging Clinical and Experimental Research*, *32*(10), 2021-2029.

Durga, J., van Boxtel, M. P., Schouten, E. G., Kok, F. J., Jolles, J., Katan, M. B., & Verhoef, P. (2007). Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *The Lancet*, *369*(9557), 208-216.

Dyer, O. (2006). UK is urged to rethink funding of long term care of elderly people. *Bmj*, *332*(7549), 1052.

Edney, L. C., Burns, N. R., & Danthiir, V. (2015). Subjective well-being in older adults: folate and vitamin B12 independently predict positive affect. *British Journal of Nutrition*, *114*(8), 1321-1328.

Elia, M., & Russell, C. (2009). *Combating malnutrition: recommendations for action. report from the advisory group on malnutrition, led by BAPEN*. BAPEN.

Elia, M., Normand, C., Laviano, A., & Norman, K. (2016). A systematic review of the cost and cost effectiveness of using standard oral nutritional supplements in community and care home settings. *Clinical Nutrition*, *35*(1), 125-137.

El-Kadiki, A., & Sutton, A. J. (2005). Role of multivitamins and mineral supplements in preventing infections in elderly people: systematic review and meta-analysis of randomised controlled trials. *Bmj*, *330*(7496), 871.

Elstgeest, L., Brouwer, I., Penninx, B. W., Van Schoor, N., & Visser, M. (2017). Vitamin B12, homocysteine and depressive symptoms: a longitudinal study among older adults. *European Journal of Clinical Nutrition*, *71*(4), 468-475.

Elston, D. (2021). Participation Bias, Self-selection Bias and Response Bias. *Journal of the American Academy of Dermatology*.

Englard, S., & Seifter, S. (1986). The biochemical functions of ascorbic acid. *Annual Review of Nutrition*, *6*(1), 365-406.

Eskelinen, K., Hartikainen, S., & Nykänen, I. (2016). Is loneliness associated with malnutrition in older people? *International Journal of Gerontology*, *10*(1), 43-45.

Evans, H. M., Howe, P. R., & Wong, R. H. (2017). Effects of resveratrol on cognitive performance, mood and cerebrovascular function in post-menopausal women; a 14-week randomised placebo-controlled intervention trial. *Nutrients*, *9*(1), 27.

Evans, I., Llewellyn, D., Matthews, F., Woods, R., Brayne, C., & Clare, L. (2018). Social isolation, cognitive reserve, and cognition in healthy older people. *PLoS One*, *13*(8), e0201008.

Everard, K. M., Lach, H. W., Fisher, E. B., & Baum, M. C. (2000). Relationship of activity and social support to the functional health of older adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *55*(4), S208-S212.

Fairweather-Tait, S. J., & Teucher, B. (2002). Iron and calcium bioavailability of fortified foods and dietary supplements. *Nutrition Reviews*, *60*(11), 360-367.

Farias, S. T., Mungas, D., Reed, B. R., Harvey, D., Cahn-Weiner, D., & Decarli, C. (2006). MCI is associated with deficits in everyday functioning. *Alzheimer Disease and Associated Disorders*, *20*(4), 217-223.

Feart, C., Helmer, C., Merle, B., Herrmann, F. R., Annweiler, C., Dartigues, J.-F., Delcourt, C., & Samieri, C. (2017). Associations of lower vitamin D concentrations with cognitive decline and long-term risk of dementia and Alzheimer's disease in older adults. *Alzheimer's & Dementia*, *13*(11), 1207-1216.

Feger, D. M., Willis, S. L., Thomas, K. R., Marsiske, M., Rebok, G. W., Felix, C., & Gross, A. L. (2020). Incident instrumental activities of daily living difficulty in older adults: Which comes first? Findings from the advanced cognitive training for independent and vital elderly study. *Frontiers in Neurology*, *11*, 550577.

Fenech, M., El-Sohemy, A., Cahill, L., Ferguson, L. R., French, T.-A. C., Tai, E. S., Milner, J., Koh, W.-P., Xie, L., & Zucker, M. (2011). Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. *Lifestyle Genomics*, *4*(2), 69-89.

Fernandez, A., Santi, A., & Torres Aleman, I. (2018). Insulin Peptides as Mediators of the Impact of Life Style in Alzheimer's disease. *Brain Plasticity*, *4*(1), 3-15.

Ferro-Luzzi, A., Toth, M., Elia, M., & Schurch, B. (2000). Report of the IDECG Working Group on body weight and body composition of the elderly. *European Journal of Clinical Nutrition*, *54*(S3), S160-S160.

Ford, A. H., & Almeida, O. P. (2019). Effect of vitamin B supplementation on cognitive function in the elderly: a systematic review and meta-analysis. *Drugs & Aging*, *36*(5), 419-434.

Ford, A. H., Flicker, L., Singh, U., Hirani, V., & Almeida, O. P. (2013). Homocysteine, depression and cognitive function in older adults. *Journal of Affective Disorders*, *151*(2), 646-651.

Fratiglioni, L., Wang, H.-X., Ericsson, K., Maytan, M., & Winblad, B. (2000). Influence of social network on occurrence of dementia: a community-based longitudinal study. *The Lancet*, *355*(9212), 1315-1319.

Freak-Poli, R., Ryan, J., Tran, T., Owen, A., McHugh Power, J., Berk, M., Stocks, N., Gonzalez-Chica, D., Lowthian, J. A., & Fisher, J. (2022). Social isolation, social support and loneliness as independent concepts, and their relationship with health-related quality of life among older women. *Aging & Mental Health*, *26*(7), 1335-1344.

Freitas, T. I. d., Previdelli, A. N., Ferreira, M. P. d. N., Marques, K. M., Goulart, R. M. M., & Aquino, R. d. C. d. (2017). Factors associated with diet quality of older adults. *Revista de Nutrição*, *30*, 297-306.

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *59*(3), M255-M263.

Gadie, A., Shafto, M., Leng, Y., & Kievit, R. A. (2017). How are age-related differences in sleep quality associated with health outcomes? An epidemiological investigation in a UK cohort of 2406 adults. *BMJ open*, *7*(7), e014920.

Galan, P., Viteri, F., Bertrais, S., Czernichow, S., Faure, H., Arnaud, J., Ruffieux, D., Chenal, S., Arnault, N., & Favier, A. (2005). Serum concentrations of β-carotene, vitamins C and E, zinc and selenium are influenced by sex, age, diet, smoking status, alcohol consumption and corpulence in a general French adult population. *European Journal of Clinical Nutrition*, *59*(10), 1181-1190.

Galli, F., Azzi, A., Birringer, M., Cook-Mills, J. M., Eggersdorfer, M., Frank, J., Cruciani, G., Lorkowski, S., & Özer, N. K. (2017). Vitamin E: Emerging aspects and new directions. *Free Radical Biology and Medicine*, *102*, 16-36.

Gameiro, S., Boivin, J., Canavarro, M. C., Moura-Ramos, M., & Soares, I. (2010). Social nesting: Changes in social network and support across the transition to parenthood in couples that conceived spontaneously or through assisted reproductive technologies. *Journal of Family Psychology*, *24*(2), 175.

Gao, Q., Kou, T., Zhuang, B., Ren, Y., Dong, X., & Wang, Q. (2018). The association between vitamin D deficiency and sleep disorders: a systematic review and meta-analysis. *Nutrients*, *10*(10), 1395.

Garatachea, N., Molinero, O., Martínez-García, R., Jimenez-Jimenez, R., Gonzalez-Gallego, J., & Marquez, S. (2009). Feelings of well being in elderly people: relationship to physical activity and physical function. *Archives of Gerontology and Geriatrics*, *48*(3), 306-312.

Garber, A. K., Binkley, N., Krueger, D. C., & Suttie, J. (1999). Comparison of phylloquinone bioavailability from food sources or a supplement in human subjects. *The Journal of Nutrition*, *129*(6), 1201-1203.

Gariballa, S. (2014). Poor vitamin C status is associated with increased depression symptoms following acute illness in older people. *International Journal for Vitamin and Nutrition Research*, *84*(1-2), 12-17.

Gaziano, J. M., Sesso, H. D., Christen, W. G., Bubes, V., Smith, J. P., MacFadyen, J., Schvartz, M., Manson, J. E., Glynn, R. J., & Buring, J. E. (2012). Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. *Jama*, *308*(18), 1871-1880.

Gensous, N., Bacalini, M. G., Pirazzini, C., Marasco, E., Giuliani, C., Ravaioli, F., Mengozzi, G., Bertarelli, C., Palmas, M. G., & Franceschi, C. (2017). The epigenetic landscape of age-related diseases: the geroscience perspective. *Biogerontology*, *18*(4), 549-559.

Gholipour Baradari, A., Alipour, A., Mahdavi, A., Sharifi, H., Nouraei, S. M., & Emami Zeydi, A. (2018). The effect of zinc supplementation on sleep quality of ICU nurses: a double blinded randomized controlled trial. *Workplace Health & Safety*, *66*(4), 191-200.

Gibson, R. S. (2007). Role of Diet-and Host-Related Factors in Nutrient Bioavailability and Thus in Nutrient-Based Dietary Requirement Estimates. *Food and nutrition bulletin*.

Gilbert-Johns, S., Mason, R., Ward, M., & Humby, P. (2020). *Overview of the UK population: 2020*. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/2020

Gill, H., & Walker, G. (2008). Selenium, immune function and resistance to viral infections. *Nutrition & Dietetics*, *65*, S41-S47.

Gill, T. M., Gahbauer, E. A., Allore, H. G., & Han, L. (2006). Transitions between frailty states among community-living older persons. *Archives of Internal Medicine*, *166*(4), 418-423.

Glass, T. A., De Leon, C. F. M., Bassuk, S. S., & Berkman, L. F. (2006). Social engagement and depressive symptoms in late life: longitudinal findings. *Journal of Aging and Health*, *18*(4), 604-628.

Glass, T. A., De Leon, C. M., Marottoli, R. A., & Berkman, L. F. (1999). Population based study of social and productive activities as predictors of survival among elderly Americans. *Bmj*, *319*(7208), 478-483.

Godin, J., Armstrong, J. J., Rockwood, K., & Andrew, M. K. (2017). Dynamics of frailty and cognition after age 50: why it matters that cognitive decline is mostly seen in old age. *Journal of Alzheimer's Disease*, *58*(1), 231-242.

Gombart, A. F., Pierre, A., & Maggini, S. (2020). A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. *Nutrients*, *12*(1), 236.

González-Sarrías, A., Larrosa, M., García-Conesa, M. T., Tomás-Barberán, F. A., & Espín, J. C. (2013). Nutraceuticals for older people: Facts, fictions and gaps in knowledge. *Maturitas*, *75*(4), 313-334.

Gott, M., & Hinchliff, S. (2003). How important is sex in later life? The views of older people. *Social Science & Medicine*, *56*(8), 1617-1628.

Gott, M., Hinchliff, S., & Galena, E. (2004). General practitioner attitudes to discussing sexual health issues with older people. *Social Science & Medicine*, *58*(11), 2093-2103.

Graf, C. (2009). The Lawton instrumental activities of daily living (IADL) scale. *The Gerontologist*, *9*(3), 179-186.

Grandner, M. A., Jackson, N., Gerstner, J. R., & Knutson, K. L. (2014). Sleep symptoms associated with intake of specific dietary nutrients. *Journal of Sleep Research*, *23*(1), 22-34.

Grant, B. C. (2001). 'You're never too old': beliefs about physical activity and playing sport in later life. *Ageing & Society*, *21*(6), 777-798.

Greer, F. R. (2010). Vitamin K the basics—What's new? *Early Human Development*, *1*(86), 43-47.

Grieger, J., Nowson, C., Jarman, H., Malon, R., & Ackland, L. (2009). Multivitamin supplementation improves nutritional status and bone quality in aged care residents. *European Journal of Clinical Nutrition*, *63*(4), 558-565.

Grodstein, F., O'Brien, J., Kang, J. H., Dushkes, R., Cook, N. R., Okereke, O., Manson, J. E., Glynn, R. J., Buring, J. E., & Gaziano, J. M. (2013). Long-term multivitamin supplementation and cognitive function in men: a randomized trial. *Annals of Internal Medicine*, *159*(12), 806-814.

Grootswagers, P., Mensink, M., Berendsen, A. A., Deen, C. P., Kema, I. P., Bakker, S. J., Santoro, A., Franceschi, C., Meunier, N., & Malpuech-Brugère, C. (2021). Vitamin B-

6 intake is related to physical performance in European older adults: results of the New Dietary Strategies Addressing the Specific Needs of the Elderly Population for Healthy Aging in Europe (NU-AGE) study. *The American Journal of Clinical Nutrition*, *113*(4), 781-789.

Grune, T., Lietz, G., Palou, A., Ross, A. C., Stahl, W., Tang, G., Thurnham, D., Yin, S.-a., & Biesalski, H. K. (2010). β-Carotene is an important vitamin A source for humans. *The Journal of Nutrition*, *140*(12), 2268S-2285S.

Gupta, C., & Prakash, D. (2015). Nutraceuticals for geriatrics. *Journal of Traditional and Complementary Medicine*, *5*(1), 5-14.

Haan, M. N., Miller, J. W., Aiello, A. E., Whitmer, R. A., Jagust, W. J., Mungas, D. M., Allen, L. H., & Green, R. (2007). Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging. *The American Journal of Clinical Nutrition*, *85*(2), 511-517.

Haase, H., Mazzatti, D. J., White, A., Ibs, K. H., Engelhardt, G., Hebel, S., Powell, J. R., & Rink, L. (2007). Differential gene expression after zinc supplementation and deprivation in human leukocyte subsets. molecular medicine,

Hajek, A., Brettschneider, C., Mallon, T., Ernst, A., Mamone, S., Wiese, B., Weyerer, S., Werle, J., Pentzek, M., & Fuchs, A. (2017). The impact of social engagement on health-related quality of life and depressive symptoms in old age-evidence from a multicenter prospective cohort study in Germany. *Health and Quality of Life Outcomes*, *15*(1), 1-8.

Han, O. (2011). Molecular mechanism of intestinal iron absorption. *Metallomics*, *3*(2), 103-109.

Han, S. (2018). *The Impact of Age on Acute Bioavailability of Minerals from a Multivitamin and Mineral Supplement* ResearchSpace@ Auckland].

Han, S. N., & Meydani, S. N. (2006). Impact of vitamin E on immune function and its clinical implications. *Expert Review of Clinical Immunology*, *2*(4), 561-567.

Hargittai, E., Piper, A. M., & Morris, M. R. (2019). From internet access to internet skills: digital inequality among older adults. *Universal Access in the Information Society*, *18*(4), 881-890.

Harris, E., Kirk, J., Rowsell, R., Vitetta, L., Sali, A., Scholey, A. B., & Pipingas, A. (2011). The effect of multivitamin supplementation on mood and stress in healthy older men. *Human Psychopharmacology: Clinical and Experimental*, *26*(8), 560-567.

Harris, E., Macpherson, H., & Pipingas, A. (2015). Improved blood biomarkers but no cognitive effects from 16 weeks of multivitamin supplementation in healthy older adults. *Nutrients*, *7*(5), 3796-3812.

Harris, E., Macpherson, H., Vitetta, L., Kirk, J., Sali, A., & Pipingas, A. (2012). Effects of a multivitamin, mineral and herbal supplement on cognition and blood biomarkers in older men: a randomised, placebo-controlled trial. *Human Psychopharmacology: Clinical and Experimental*, *27*(4), 370-377.

Haskell, C. F., Robertson, B., Jones, E., Forster, J., Jones, R., Wilde, A., Maggini, S., & Kennedy, D. O. (2010). Effects of a multi-vitamin/mineral supplement on cognitive function and fatigue during extended multi-tasking. *Human Psychopharmacology: Clinical and Experimental*, *25*(6), 448-461.

Haskell, M. J. (2012). The challenge to reach nutritional adequacy for vitamin A: β-carotene bioavailability and conversion—evidence in humans. *The American Journal of Clinical Nutrition*, *96*(5), 1193S-1203S.

Hauser, D. J., & Schwarz, N. (2015). It'sa trap! Instructional manipulation checks prompt systematic thinking on “tricky” tasks. *Sage Open*, *5*(2), 2158244015584617.

Hawkley, L. C., & Cacioppo, J. T. (2004). Stress and the aging immune system. *Brain, Behavior, and Immunity*, *18*(2), 114-119.

Hawkley, L. C., & Capitanio, J. P. (2015). Perceived social isolation, evolutionary fitness and health outcomes: a lifespan approach. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *370*(1669), 20140114.

Hayden, K., Sandle, L., & Berry, J. (2015). Ethnicity and social deprivation contribute to vitamin D deficiency in an urban UK population. *The Journal of Steroid Biochemistry and Molecular Biology*, *148*, 253-255.

Haynes, L. (2020). Aging of the immune system: research challenges to enhance the health span of older adults. *Frontiers in Aging*, *1*, 602108.

Heaney, R. P. (2001). Factors influencing the measurement of bioavailability, taking calcium as a model. *The Journal of Nutrition*, *131*(4), 1344S-1348S.

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nature Reviews Neuroscience*, *5*(2), 87-96.

Hercberg, S., Galan, P., Preziosi, P., Bertrais, S., Mennen, L., Malvy, D., Roussel, A.-M., Favier, A., & Briançon, S. (2004). The SU. VI. MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Archives of Internal Medicine*, *164*(21), 2335-2342.

Hernandez, M. E., Goldberg, A., & Alexander, N. B. (2010). Decreased muscle strength relates to self-reported stooping, crouching, or kneeling difficulty in older adults. *Physical Therapy*, *90*(1), 67-74.

Hinchliff, S., Tetley, J., Lee, D., & Nazroo, J. (2018). Older adults' experiences of sexual difficulties: qualitative findings from the English Longitudinal Study on Ageing (ELSA). *The Journal of Sex Research*, *55*(2), 152-163.

Hodgson, S., Watts, I., Fraser, S., Roderick, P., & Dambha-Miller, H. (2020). Loneliness, social isolation, cardiovascular disease and mortality: a synthesis of the literature and conceptual framework. *Journal of the Royal Society of Medicine*, *113*(5), 185-192.

Houston, D. K., Cesari, M., Ferrucci, L., Cherubini, A., Maggio, D., Bartali, B., Johnson, M. A., Schwartz, G. G., & Kritchevsky, S. B. (2007). Association between vitamin D status and physical performance: the InCHIANTI study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62*(4), 440-446.

Howdon, D., & Rice, N. (2018). Health care expenditures, age, proximity to death and morbidity: Implications for an ageing population. *Journal of Health Economics*, *57*, 60-74.

Howes, M.-J., Perry, N., Vasquez-Londono, C., & Perry, E. (2020). Role of phytochemicals as nutraceuticals for cognitive functions affected in ageing. *British Journal of Pharmacology*.

Huang, C.-J., Webb, H. E., Zourdos, M. C., & Acevedo, E. O. (2013). Cardiovascular reactivity, stress, and physical activity. *Frontiers in Physiology*, *4*, 314.

Huang, W., Shah, S., Long, Q., Crankshaw, A. K., & Tangpricha, V. (2013). Improvement of pain, sleep, and quality of life in chronic pain patients with vitamin D supplementation. *The Clinical Journal of Pain*, *29*(4), 341-347.

Hurrell, R., & Egli, I. (2010). Iron bioavailability and dietary reference values. *The American Journal of Clinical Nutrition*, *91*(5), 1461S-1467S.

Huskisson, E., Maggini, S., & Ruf, M. (2007). The role of vitamins and minerals in energy metabolism and well-being. *Journal of International Medical Research*, *35*(3), 277-289.

Hwang, E. J.-L., Rivas, J. G., Fremming, R., Rivas, M. M., & Crane, K. R. (2009). Relationship between perceived burden of caring for a family member with Alzheimer's disease and decreased participation in meaningful activities. *Occupational Therapy in Health Care*, *23*(4), 249-266.

Hwang, T.-J., Rabheru, K., Peisah, C., Reichman, W., & Ikeda, M. (2020). Loneliness and social isolation during the COVID-19 pandemic. *International Psychogeriatrics*, *32*(10), 1217-1220.

Ikonte, C. J., Mun, J. G., Reider, C. A., Grant, R. W., & Mitmesser, S. H. (2019). Micronutrient inadequacy in short sleep: analysis of the NHANES 2005–2016. *Nutrients*, *11*(10), 2335.

Jacobsen, D. W. (1998). Homocysteine and vitamins in cardiovascular disease. *Clinical Chemistry*, *44*(8), 1833-1843.

Jain, A. L. (2002). Influence of vitamins and trace-elements on the incidence of respiratory infection in the elderly. *Nutrition Research*, *22*(1-2), 85-87.

Jayaprasad, N., & Francis, J. (2005). Atrial fibrillation and hyperthyroidism. *Indian Pacing and Electrophysiology Journal*, *5*(4), 305-311.

Jernerén, F., Elshorbagy, A. K., Oulhaj, A., Smith, S. M., Refsum, H., & Smith, A. D. (2015). Brain atrophy in cognitively impaired elderly: the importance of long-chain ω-3 fatty acids and B vitamin status in a randomized controlled trial. *The American Journal of Clinical Nutrition*, *102*(1), 215-221.

Jessen, F., Amariglio, R. E., Buckley, R. F., van der Flier, W. M., Han, Y., Molinuevo, J. L., Rabin, L., Rentz, D. M., Rodriguez-Gomez, O., & Saykin, A. J. (2020). The characterisation of subjective cognitive decline. *The Lancet Neurology*, *19*(3), 271-278.

Ji, X., Grandner, M. A., & Liu, J. (2017). The relationship between micronutrient status and sleep patterns: a systematic review. *Public Health Nutrition*, *20*(4), 687-701.

Jia, J., Hu, J., Huo, X., Miao, R., Zhang, Y., & Ma, F. (2019). Effects of vitamin D supplementation on cognitive function and blood Aβ-related biomarkers in older adults with Alzheimer's disease: a randomised, double-blind, placebo-controlled trial. *Journal of Neurology, Neurosurgery & Psychiatry*, *90*(12), 1347-1352.

Johnson, C. (2003). The association between nutritional risk and falls among frail elderly. *The Journal of Nutrition, Health & Aging*, *7*(4), 247-250.

Johnson, J. A. (2005). Ascertaining the validity of individual protocols from web-based personality inventories. *Journal of Research in Personality*, *39*(1), 103-129.

Johnston, C. S., Barkyoumb, G. M., & Schumacher, S. S. (2014). Vitamin C supplementation slightly improves physical activity levels and reduces cold incidence in men with marginal vitamin C status: a randomized controlled trial. *Nutrients, 6*(7), 2572-2583.

Jolliffe, D. A., Holt, H., Greenig, M., Talaei, M., Perdek, N., Pfeffer, P., Vivaldi, G., Maltby, S., Symons, J., & Barlow, N. L. (2022). Effect of a test-and-treat approach to vitamin D supplementation on risk of all cause acute respiratory tract infection and covid-19: phase 3 randomised controlled trial (CORONAVIT). *Bmj*, *378*.

Jorde, R., Mathiesen, E. B., Rogne, S., Wilsgaard, T., Kjærgaard, M., Grimnes, G., & Schirmer, H. (2015). Vitamin D and cognitive function: the Tromsø Study. *Journal of the Neurological Sciences*, *355*(1-2), 155-161.

Kaplan, B. J., Crawford, S. G., Field, C. J., & Simpson, J. S. A. (2007). Vitamins, minerals, and mood. *Psychological Bulletin*, *133*(5), 747-760.

Kaźmierczak-Barańska, J., Boguszewska, K., Adamus-Grabicka, A., & Karwowski, B. T. (2020). Two faces of vitamin C—antioxidative and pro-oxidative agent. *Nutrients*, *12*(5), 1501.

Kehoe, L., Walton, J., & Flynn, A. (2019). Nutritional challenges for older adults in Europe: current status and future directions. *Proceedings of the Nutrition Society*, *78*(2), 221-233.

Keilich, S. R., Bartley, J. M., & Haynes, L. (2019). Diminished immune responses with aging predispose older adults to common and uncommon influenza complications. *Cellular Immunology*, *345*, 103992.

Kendrick, D., Kumar, A., Carpenter, H., Zijlstra, G. R., Skelton, D. A., Cook, J. R., Stevens, Z., Belcher, C. M., Haworth, D., & Gawler, S. J. (2014). Exercise for reducing fear of falling in older people living in the community. *Cochrane Database of Systematic Reviews*(11).

Kennedy, D. O. (2016). B vitamins and the brain: mechanisms, dose and efficacy—a review. *Nutrients*, *8*(2), 68.

Kennedy, D. O., & Haskell, C. F. (2011). Vitamins and cognition. *Drugs*, *71*(15), 1957-1971.

Kennedy, D. O., Stevenson, E. J., Jackson, P. A., Dunn, S., Wishart, K., Bieri, G., Barella, L., Carne, A., Dodd, F. L., & Robertson, B. C. (2016). Multivitamins and minerals modulate whole-body energy metabolism and cerebral blood-flow during cognitive task performance: a double-blind, randomised, placebo-controlled trial. *Nutrition & Metabolism*, *13*(1), 1-16.

Kennedy, D. O., Veasey, R., Watson, A., Dodd, F., Jones, E., Maggini, S., & Haskell, C. F. (2010). Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males. *Psychopharmacology*, *211*(1), 55-68.

Kennel, K. A., Drake, M. T., & Hurley, D. L. (2010, August). Vitamin D deficiency in adults: when to test and how to treat. In *mayo clinic proceedings* (Vol. 85, No. 8, pp. 752-758). Elsevier.

Kim, J. G., Moon, K. H., Lim, E. S., & Yoo, J. H. (2016). A Study on IADL, Stress and Motivation on Healthy Lifestyle among Elderly People with Arthritis. *Journal of the Korea Academia-Industrial Cooperation Society*, *17*(3), 209-217.

Kim, J., Choi, J., Kwon, S. Y., McEvoy, J. W., Blaha, M. J., Blumenthal, R. S., Guallar, E., Zhao, D., & Michos, E. D. (2018). Association of multivitamin and mineral supplementation and risk of cardiovascular disease: a systematic review and meta-analysis. *Circulation: Cardiovascular Quality and Outcomes*, *11*(7), e004224.

Kiyose, C., Muramatsu, R., Kameyama, Y., Ueda, T., & Igarashi, O. (1997). Biodiscrimination of alpha-tocopherol stereoisomers in humans after oral administration. *The American Journal of Clinical Nutrition*, *65*(3), 785-789.

Kiyoshige, E., Kabayama, M., Gondo, Y., Masui, Y., Inagaki, H., Ogawa, M., Nakagawa, T., Yasumoto, S., Akasaka, H., & Sugimoto, K. (2019). Age group differences in association between IADL decline and depressive symptoms in community-dwelling elderly. *BMC Geriatrics*, *19*(1), 1-8.

Korkmaz, V., Ozkaya, E., Cekmez, Y., Leblebıcı, D., Dagdevıren, G., Cınar, M., Kara, F., & Kucukozkan, T. (2015). Relationship between the body iodine status and menopausal symptoms during postmenopausal period. *Gynecological Endocrinology*, *31*(1), 61-64.

Kozakai, R. (2017). Grip strength and healthy aging. *The Journal of Physical Fitness and Sports Medicine*, *6*(3), 145-149.

Krause, D., & Roupas, P. (2015). Effect of vitamin intake on cognitive decline in older adults: evaluation of the evidence. *The journal of Nutrition, Health & Aging*, *19*(7), 745-753.

Kuh, D., & Shlomo, Y. B. (2004). *A life course approach to chronic disease epidemiology*. Oxford university press.

Kumrungsee, T., Zhang, P., Chartkul, M., Yanaka, N., & Kato, N. (2020). Potential role of vitamin B6 in ameliorating the severity of COVID-19 and its complications. *Frontiers in Nutrition*, 220.

Kung, F. Y., Kwok, N., & Brown, D. J. (2018). Are attention check questions a threat to scale validity? *Applied Psychology*, *67*(2), 264-283.

Kuster, P. A., & Merkle, C. J. (2004). Caregiving stress, immune function, and health: implications for research with parents of medically fragile children. *Issues in Comprehensive Pediatric Nursing*, *27*(4), 257-276.

Landvik, S. (2004). Vitamin E from supplements has good bioavailability. *The American Journal of Clinical Nutrition*, *80*(3), 784-785; author reply 785.

Lara, E., Martín-María, N., De la Torre-Luque, A., Koyanagi, A., Vancampfort, D., Izquierdo, A., & Miret, M. (2019). Does loneliness contribute to mild cognitive impairment and dementia? A systematic review and meta-analysis of longitudinal studies. *Ageing Research Reviews*, *52*, 7-16.

Laurberg, P., Cerqueira, C., Ovesen, L., Rasmussen, L. B., Perrild, H., Andersen, S., Pedersen, I. B., & Carlé, A. (2010). Iodine intake as a determinant of thyroid disorders in populations. *Best Practice & Research Clinical Endocrinology & Metabolism*, *24*(1), 13-27.

Lavie, C. J., Lee, J. H., & Milani, R. V. (2011). Vitamin D and cardiovascular disease: will it live up to its hype? *Journal of the American College of Cardiology*, *58*(15), 1547-1556.

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist*, *9*(3_Part_1), 179-186.

Lee, G. Y., & Han, S. N. (2018). The role of vitamin E in immunity. *Nutrients*, *10*(11), 1614.

Lee, S. H., Kang, Y., & Cho, S.-J. (2017). Subjective cognitive decline in patients with migraine and its relationship with depression, anxiety, and sleep quality. *The Journal of Headache and Pain*, *18*(1), 1-8.

Lentjes, M. A. (2019). The balance between food and dietary supplements in the general population. *Proceedings of the Nutrition Society*, *78*(1), 97-109.

Leonard, S. W., Good, C. K., Gugger, E. T., & Traber, M. G. (2004). Vitamin E bioavailability from fortified breakfast cereal is greater than that from encapsulated supplements. *The American Journal of Clinical Nutrition*, *79*(1), 86-92.

Lewis, E. D., Meydani, S. N., & Wu, D. (2019). Regulatory role of vitamin E in the immune system and inflammation. *IUBMB life*, *71*(4), 487-494.

Lichstein, K. L., Payne, K. L., Soeffing, J. P., Durrence, H. H., Taylor, D. J., Riedel, B. W., & Bush, A. J. (2007). Vitamins and sleep: an exploratory study. *Sleep Medicine*, *9*(1), 27-32.

Limm, H., Angerer, P., Heinmueller, M., Marten-Mittag, B., Nater, U. M., & Guendel, H. (2010). Self-perceived stress reactivity is an indicator of psychosocial impairment at the workplace. *BMC Public Health*, *10*(1), 1-10.

Lin, M.-H., Chen, L.-J., Huang, S.-T., Meng, L.-C., Lee, W.-J., Peng, L.-N., Hsiao, F.-Y., & Chen, L.-K. (2022). Age and sex differences in associations between self-reported health, physical function, mental function and mortality. *Archives of Gerontology and Geriatrics*, *98*, 104537.

Lindschinger, M., Tatzber, F., Schimetta, W., Schmid, I., Lindschinger, B., Cvirn, G., Stanger, O., Lamont, E., & Wonisch, W. (2019). A randomized pilot trial to evaluate the bioavailability of natural versus synthetic vitamin B complexes in healthy humans and their effects on homocysteine, oxidative stress, and antioxidant levels. *Oxidative Medicine and Cellular Longevity*, *2019*.

Liu, B., Floud, S., Pirie, K., Green, J., Peto, R., Beral, V., & Collaborators, M. W. S. (2016). Does happiness itself directly affect mortality? The prospective UK Million Women Study. *The Lancet*, *387*(10021), 874-881.

Liu, Y., Sun, Q., Zhang, M., Ren, M., Chen, P., & Liang, T. (2021). Association between thyroid hormone levels and frailty in an older inpatient cohort: a cross-sectional study. *Ann Palliat Med*, *10*(6), 6678-6686.

Long, S.-J., & Benton, D. (2013). Effects of vitamin and mineral supplementation on stress, mild psychiatric symptoms, and mood in nonclinical samples: a meta-analysis. *Psychosomatic Medicine*, *75*(2), 144-153.

Lorem, G. F., Schirmer, H., Wang, C. E., & Emaus, N. (2017). Ageing and mental health: changes in self-reported health due to physical illness and mental health status with consecutive cross-sectional analyses. *BMJ open*, *7*(1), e013629.

Lotto, V., Choi, S.-W., & Friso, S. (2011). Vitamin B6: a challenging link between nutrition and inflammation in CVD. *British Journal of Nutrition*, *106*(2), 183-195.

Lovell, B., & Wetherell, M. A. (2011). The cost of caregiving: endocrine and immune implications in elderly and non elderly caregivers. *Neuroscience & Biobehavioral Reviews*, *35*(6), 1342-1352.

Lubben, J. E. (1988). Assessing social networks among elderly populations. *Family and Community Health*, *11*(3), 42-52.

Luchesi, B. M., Souza, É. N., Gratão, A. C. M., de Oliveira Gomes, G. A., Inouye, K., da Silva Alexandre, T., Marques, S., & Pavarini, S. C. I. (2016). The evaluation of perceived stress and associated factors in elderly caregivers. *Archives of Gerontology and Geriatrics*, *67*, 7-13.

Luiz, M. M., Máximo, R. d. O., De Oliveira, D. C., Ramírez, P. C., De Souza, A. F., Delinocente, M. L. B., Steptoe, A., De Oliveira, C., & Alexandre, T. d. S. (2022). Sex Differences in Vitamin D Status as a Risk Factor for Incidence of Disability in Instrumental Activities of Daily Living: Evidence from the ELSA Cohort Study. *Nutrients*, *14*(10), 2012.

Lupien, S. J., Ouellet-Morin, I., Hupbach, A., Tu, M. T., Buss, C., Walker, D., Pruessner, J., & Mcewen, B. S. (2006). Beyond the stress concept: Allostatic load--a developmental biological and cognitive perspective.

Mackenzie, C. S., & Abdulrazaq, S. (2021). Social engagement mediates the relationship between participation in social activities and psychological distress among older adults. *Aging & mental health*, *25*(2), 299-305.

Macpherson, H., Ellis, K. A., Sali, A., & Pipingas, A. (2012). Memory improvements in elderly women following 16 weeks treatment with a combined multivitamin, mineral and herbal supplement. *Psychopharmacology*, *220*(2), 351-365.

Macpherson, H., Pipingas, A., & Pase, M. P. (2013). Multivitamin-multimineral supplementation and mortality: a meta-analysis of randomized controlled trials. *The American Journal of Clinical Nutrition*, *97*(2), 437-444.

Macpherson, H., Rowsell, R., Cox, K. H., Reddan, J., Meyer, D., Scholey, A., & Pipingas, A. (2016). The effects of four-week multivitamin supplementation on mood in healthy older women: A randomized controlled trial. *Evidence-Based Complementary and Alternative Medicine*, *2016*.

Macpherson, H., Rowsell, R., Cox, K., Scholey, A., & Pipingas, A. (2015). Acute mood but not cognitive improvements following administration of a single multivitamin and mineral supplement in healthy women aged 50 and above: a randomised controlled trial. *Age*, *37*(3), 1-10.

Major, G. C., Doucet, E., Jacqmain, M., St-Onge, M., Bouchard, C., & Tremblay, A. (2008). Multivitamin and dietary supplements, body weight and appetite: results from a cross-sectional and a randomised double-blind placebo-controlled study. *British Journal of Nutrition*, *99*(5), 1157-1167.

Mak, I. W. C., Chu, C. M., Pan, P. C., Yiu, M. G. C., & Chan, V. L. (2009). Long-term psychiatric morbidities among SARS survivors. *General Hospital Psychiatry*, *31*(4), 318-326.

Makkar, R., Behl, T., Bungau, S., Zengin, G., Mehta, V., Kumar, A., Uddin, M., Ashraf, G. M., Abdel-Daim, M. M., & Arora, S. (2020). Nutraceuticals in neurological disorders. *International Journal of Molecular Sciences*, *21*(12), 4424.

Makovski, T. T., Schmitz, S., Zeegers, M. P., Stranges, S., & van den Akker, M. (2019). Multimorbidity and quality of life: systematic literature review and meta-analysis. *Ageing research reviews*, *53*, 100903.

Malhotra, R., Tareque, M. I., Saito, Y., Ma, S., Chiu, C. T., & Chan, A. (2021). Loneliness and health expectancy among older adults: A longitudinal population-based study. *Journal of the American Geriatrics Society*, *69*(11), 3092-3102.

Mangialasche, F., Solomon, A., Kåreholt, I., Hooshmand, B., Cecchetti, R., Fratiglioni, L., Soininen, H., Laatikainen, T., Mecocci, P., & Kivipelto, M. (2013). Serum levels of vitamin E forms and risk of cognitive impairment in a Finnish cohort of older adults. *Experimental Gerontology*, *48*(12), 1428-1435.

Maniaci, M. R., & Rogge, R. D. (2014). Caring about carelessness: Participant inattention and its effects on research. *Journal of Research in Personality*, *48*, 61-83.

Maraini, G., Williams, S. L., Sperduto, R. D., Ferris, F. L., Milton, R. C., Clemons, T. E., Rosmini, F., & Ferrigno, L. (2009). Effects of multivitamin/mineral supplementation on plasma levels of nutrients. Report No. 4 of the Italian-American clinical trial of nutritional supplements and age-related cataract. *Annali Dell'Istituto Superiore di Sanità*, *45*(2), 119-127.

Maric, D., Brkic, S., Mikic, A. N., Tomic, S., Cebovic, T., & Turkulov, V. (2014). Multivitamin mineral supplementation in patients with chronic fatigue syndrome. *Medical Science Monitor: international medical journal of experimental and clinical research*, *20*, 47-53.

Marra, M. V., & Wellman, N. S. (2008). Multivitamin–Mineral Supplements in the Older Americans Act Nutrition Program: Not a One-Size-Fits-All Quick Fix. *American Journal of Public Health*, *98*(7), 1171-1176.

Martineau, A. (2022). Behind the scenes at the Coronavit trial. In (Vol. 378): British Medical Journal Publishing Group.

Mason, P. (2007). One is okay, more is better? Pharmacological aspects and safe limits of nutritional supplements. *Proceedings of the Nutrition Society*, *66*(4), 493-507.

Massa, J., Stone, K. L., Wei, E. K., Harrison, S. L., Barrett-Connor, E., Lane, N. E., Paudel, M., Redline, S., Ancoli-Israel, S., & Orwoll, E. (2015). Vitamin D and actigraphic sleep outcomes in older community-dwelling men: the MrOS sleep study. *Sleep*, *38*(2), 251-257.

Mastroiacovo, D., Kwik-Uribe, C., Grassi, D., Necozione, S., Raffaele, A., Pistacchio, L., Righetti, R., Bocale, R., Lechiara, M. C., & Marini, C. (2015). Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study—a randomized controlled trial. *The American Journal of Clinical Nutrition*, *101*(3), 538-548.

Mathieu, M. A. (1999). The surgeon general's report and leisure services for older adults. *Journal of Physical Education, Recreation & Dance*, *70*(3), 28-31.

Matteini, A. M., Walston, J. D., Fallin, M., Bandeen-Roche, K., Kao, W., Semba, R., Allen, R., Guralnik, J., Fried, L., & Stabler, S. (2008). Markers of B-vitamin deficiency and frailty in older women. *The Journal of Nutrition Health and Aging*, *12*(5), 303-308.

Maurya, V. K., & Aggarwal, M. (2017). Factors influencing the absorption of vitamin D in GIT: an overview. *Journal of Food Science and Technology*, *54*(12), 3753-3765.

McCann, J. C., & Ames, B. N. (2009). Vitamin K, an example of triage theory: is micronutrient inadequacy linked to diseases of aging? *The American Journal of Clinical Nutrition*, *90*(4), 889-907.

McDougall, F. A., Kvaal, K., Matthews, F. E., Paykel, E., Jones, P. B., Dewey, M. E., & Brayne, C. (2007). Prevalence of depression in older people in England and Wales: the MRC CFA Study. *Psychological Medicine*, *37*(12), 1787-1795.

McElhaney, J. E., & Effros, R. B. (2009). Immunosenescence: what does it mean to health outcomes in older adults? *Current Opinion in Immunology*, *21*(4), 418-424.

McEwen, B. S. (2004). Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Annals of the New York Academy of Sciences*, *1032*(1), 1-7.

McGrath, R., Stastny, S., Casperson, S., Jahns, L., Roemmich, J., & Hackney, K. J. (2020). Daily protein intake and distribution of daily protein consumed decreases odds for functional disability in older Americans. *Journal of Aging and Health*, *32*(9), 1075-1083.

McHugh, J. E., & Lawlor, B. A. (2013). Perceived stress mediates the relationship between emotional loneliness and sleep quality over time in older adults. *British Journal of Health Psychology*, *18*(3), 546-555.

McIntosh, W. A., Shifflett, P. A., & Picou, J. S. (1989). Social Support, Stressful Events, Strain, Dietary Intake, and the Elderly. *Medical Care*, *27*(2), 140-153.

McKay, D. L., Perrone, G., Rasmussen, H., Dallal, G., Hartman, W., Cao, G., Prior, R. L., Roubenoff, R., & Blumberg, J. B. (2000). The effects of a multivitamin/mineral supplement on micronutrient status, antioxidant capacity and cytokine production in healthy older adults consuming a fortified diet. *Journal of the American College of Nutrition*, *19*(5), 613-621.

McKeown, N. M., Day, N. E., Welch, A. A., Runswick, S. A., Luben, R. N., Mulligan, A. A., McTaggart, A., & Bingham, S. A. (2001). Use of biological markers to validate self-reported dietary intake in a random sample of the European Prospective Investigation into Cancer United Kingdom Norfolk cohort. *The American Journal of Clinical Nutrition*, *74*(2), 188-196.

McKinlay, A., Fancourt, D., & Burton, A. (2021). A qualitative study about the mental health and wellbeing of older adults in the UK during the COVID-19 pandemic. *BMC Geriatrics*, *21*(1), 1-10.

McNair, D. M., Lorr, M., & Droppleman, L. F. (1971). Manual profile of mood states.

McNamara, R. K., Kalt, W., Shidler, M. D., McDonald, J., Summer, S. S., Stein, A. L., Stover, A. N., & Krikorian, R. (2018). Cognitive response to fish oil, blueberry, and combined supplementation in older adults with subjective cognitive impairment. *Neurobiology of Aging*, *64*, 147-156.

McNeill, G., Avenell, A., Campbell, M. K., Cook, J. A., Hannaford, P. C., Kilonzo, M. M., Milne, A. C., Ramsay, C. R., Seymour, D. G., & Stephen, A. I. (2007). Effect of multivitamin and multimineral supplementation on cognitive function in men and women aged 65 years and over: a randomised controlled trial. *Nutrition Journal*, *6*(1), 1-5.

McNulty, H., Pentieva, K., Hoey, L., & Ward, M. (2008). Homocysteine, B-vitamins and CVD. *Proceedings of the Nutrition Society*, *67*, 232-237.

Mehrabi, F., & Béland, F. (2020). Effects of social isolation, loneliness and frailty on health outcomes and their possible mediators and moderators in community-dwelling older adults: A scoping review. *Archives of Gerontology and Geriatrics*, *90*, 104119.

Mendonça, N., Hill, T. R., Granic, A., Davies, K., Collerton, J., Mathers, J. C., Siervo, M., Wrieden, W. L., Seal, C. J., & Kirkwood, T. B. (2016). Micronutrient intake and food sources in the very old: analysis of the Newcastle 85+ Study. *British Journal of Nutrition*, *116*, 751-761.

Mène-Saffrané, L., & DellaPenna, D. (2010). Biosynthesis, regulation and functions of tocochromanols in plants. *Plant Physiology and Biochemistry*, *48*(5), 301-309.

Metz, D. H. (2000). Mobility of older people and their quality of life. *Transport policy*, *7*(2), 149-152.

Meydani, M. (2004). Vitamin E modulation of cardiovascular disease. *Annals of the New York Academy of Sciences*, *1031*(1), 271-279.

Meydani, S. N., Lewis, E. D., & Wu, D. (2018). Perspective: Should vitamin E recommendations for older adults be increased? *Advances in Nutrition*, *9*(5), 533-543.

Meydani, S., Ribaya-Mercado, J., Russell, R., Sahyoun, N., Morrow, F., & Gershoff, S. (1991). Vitamin B-6 deficiency impairs interleukin 2 production and lymphocyte proliferation in elderly adults. *The American Journal of Clinical Nutrition*, *53*(5), 1275-1280.

Miaskowski, C., Zimmer, E. F., Barrett, K. M., Dibble, S. L., & Wallhagen, M. (1997). Differences in patients' and family caregivers' perceptions of the pain experience influence patient and caregiver outcomes. *Pain*, *72*(1-2), 217-226.

Michaelson, J., Mahony, S., & Schifferes, J. (2012). Measuring wellbeing: a guide for practitioners. *New Economics Foundation, London*.

Mikkelsen, K., & Apostolopoulos, V. (2018). B vitamins and ageing. *Biochemistry and Cell Biology of Ageing: Part I Biomedical Science*, 451-470.

Mikkelsen, K., Stojanovska, L., Polenakovic, M., Bosevski, M., & Apostolopoulos, V. (2017). Exercise and mental health. *Maturitas*, *106*, 48-56.

Miller, K. J., Mesagno, C., McLaren, S., Grace, F., Yates, M., & Gomez, R. (2019). Exercise, mood, self-efficacy, and social support as predictors of depressive symptoms in older adults: Direct and interaction effects. *Frontiers in Psychology*, *10*, 2145.

Miller, K. J., Parsons, T. D., Whybrow, P. C., Herle, K. V., Rasgon, N., Herle, A. V., Martinez, D., Silverman, D. H., & Bauer, M. (2006). Memory improvement with treatment of hypothyroidism. *International journal of neuroscience*, *116*(8), 895-906.

Milte, C. M., Sinn, N., Street, S. J., Buckley, J. D., Coates, A. M., & Howe, P. R. (2011). Erythrocyte polyunsaturated fatty acid status, memory, cognition and mood in older adults with mild cognitive impairment and healthy controls. *Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA)*, *84*(5-6), 153-161.

Mitchell, B. L., Ulrich, C. M., & McTiernan, A. (2003). Supplementation with vitamins or minerals and immune function: can the elderly benefit? *Nutrition Research*, *23*(8), 1117-1139.

Mocchegiani, E., Romeo, J., Malavolta, M., Costarelli, L., Giacconi, R., Diaz, L.-E., & Marcos, A. (2013). Zinc: dietary intake and impact of supplementation on immune function in elderly. *Age*, *35*(3), 839-860.

Moitra, E., Herbert, J. D., & Forman, E. M. (2008). Behavioral avoidance mediates the relationship between anxiety and depressive symptoms among social anxiety disorder patients. *Journal of Anxiety Disorders*, *22*(7), 1205-1213.

Mollayeva, T., Thurairajah, P., Burton, K., Mollayeva, S., Shapiro, C. M., & Colantonio, A. (2016). The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *25*, 52-73.

Morelli, M. B., Gambardella, J., Castellanos, V., Trimarco, V., & Santulli, G. (2020). Vitamin C and cardiovascular disease: an update. *Antioxidants*, *9*(12), 1227.

Morris, M. C., & Tangney, C. C. (2011). A potential design flaw of randomized trials of vitamin supplements. *Jama*, *305*(13), 1348-1349.

Mosekilde, L. (2005). Vitamin D and the elderly. *Clinical Endocrinology*, *62*(3), 265-281.

Mugica-Errazquin, I., Zarrazquin, I., Seco-Calvo, J., Gil-Goikouria, J., Rodriguez-Larrad, A., Virgala, J., Arizaga, N., Matilla-Alejos, B., Irazusta, J., & Kortajarena, M. (2021). The Nutritional Status of Long-Term Institutionalized Older Adults Is Associated with Functional Status, Physical Performance and Activity, and Frailty. *Nutrients*, *13*(11), 3716.

Mulder, A. M. (2011). *An exploration of the acute stress response to psychological and physical stressors, utilising biomarkers of the cardiovascular, HPA, SAM and secretory immune systems* (Doctoral dissertation, Southern Cross University).

Mulero, J., Zafrilla, P., & Martinez-Cacha, A. (2011). Oxidative stress, frailty and cognitive decline. *The Journal of Nutrition, Health & Aging*, *15*(9), 756-760.

Mulligan, A. A., Luben, R. N., Bhaniani, A., Parry-Smith, D. J., O'Connor, L., Khawaja, A. P., Forouhi, N. G., & Khaw, K.-T. (2014). A new tool for converting food frequency questionnaire data into nutrient and food group values: FETA research methods and availability. *BMJ Open*, *4*(3), e004503.

Mulligan, G. B., & Licata, A. (2010). Taking vitamin D with the largest meal improves absorption and results in higher serum levels of 25-hydroxyvitamin D. *Journal of Bone and Mineral Research*, *25*(4), 928-930.

Mullins, C. D., Vandigo, J., Zheng, Z., & Wicks, P. (2014). Patient-centeredness in the design of clinical trials. *Value in Health*, *17*(4), 471-475.

National Academies of Sciences, E., & Medicine. (2020). *Social isolation and loneliness in older adults: Opportunities for the health care system*. National Academies Press.

Navarro, M., & Wood, R. (2003). Plasma changes in micronutrients following a multivitamin and mineral supplement in healthy adults. *Journal of the American College of Nutrition*, *22*(2), 124-132.

Naylor, R., Baker, D., & Van Deursen, J. (2013). Senescent cells: a novel therapeutic target for aging and age-related diseases. *Clinical Pharmacology & Therapeutics*, *93*(1), 105-116.

Neuhouser, M. L., Wassertheil-Smoller, S., Thomson, C., Aragaki, A., Anderson, G. L., Manson, J. E., Patterson, R. E., Rohan, T. E., Van Horn, L., & Shikany, J. M. (2009). Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. *Archives of Internal Medicine*, *169*(3), 294-304.

Neupert, S. D., Almeida, D. M., Mroczek, D. K., & Spiro III, A. (2006). Daily stressors and memory failures in a naturalistic setting: findings from the VA Normative Aging Study. *Psychology and Aging*, *21*(2), 424-429.

NHS England. (2017). *Half of adults aged 55 and over have experienced common mental health problems, say Age UK.* . https://www.england.nhs.uk/2017/10/half-of-adults-aged-55-and-over-have-experienced-common-mental-health-problems-say-age-uk/

NIH State-of-the Science Panel. (2007). National Institutes of Health State-of-the-Science Conference Statement: multivitamin/mineral supplements and chronic disease prevention. *The American Journal of Clinical Nutrition*, *85*(1), 257S-264S.

Noorwali, E. A., Cade, J. E., Burley, V. J., & Hardie, L. J. (2018). The relationship between sleep duration and fruit/vegetable intakes in UK adults: a cross-sectional study from the National Diet and Nutrition Survey. *BMJ open*, *8*(4), e020810.

Norton, J., Ancelin, M. L., Stewart, R., Berr, C., Ritchie, K., & Carriere, I. (2012). Anxiety symptoms and disorder predict activity limitations in the elderly. *Journal of Affective Disorders*, *141*(2-3), 276-285.

O'Connor, D., Scarlett, S., De Looze, C., O'Halloran, A. M., Laird, E., Molloy, A. M., Clarke, R., McGarrigle, C. A., & Kenny, R. A. (2022). Low folate predicts accelerated cognitive decline: 8-year follow-up of 3140 older adults in Ireland. *European Journal of Clinical Nutrition*, 1-8.

Office National Statistics. (2018). Living longer: how our population is changing and why it matters.

Ofoedu, C. E., Iwouno, J. O., Ofoedu, E. O., Ogueke, C. C., Igwe, V. S., Agunwah, I. M., Ofoedum, A. F., Chacha, J. S., Muobike, O. P., & Agunbiade, A. O. (2021). Revisiting food-sourced vitamins for consumer diet and health needs: a perspective review, from vitamin classification, metabolic functions, absorption, utilization, to balancing nutritional requirements. *PeerJ*, *9*, e11940.

Oishi, J., & Kawakami, N. (2009). Nutrition and depressive symptoms in community-dwelling elderly persons in Japan. *Acta Medica Okayama*, *63*(1), 9-17.

Oksuzyan, A., Brønnum-Hansen, H., & Jeune, B. (2010). Gender gap in health expectancy. In (Vol. 7, pp. 213-218): Springer.

Olivties, M., Fernando Pizarro, M., Walter, T., Arredondo, M., & Hertrampf, E. (1999). Bioavailbility of iron supplements consumed daily is not different from that of iron supplements consumed weekly. *Nutrition Research*, *19*(2), 179-190.

Omran, M., & Morley, J. (2000). Assessment of protein energy malnutrition in older persons, part I: History, examination, body composition, and screening tools. *Nutrition*, *16*(1), 50-63.

Ortega, R. M., Requejo, A. M., Andrés, P., López-Sobaler, A. M., Quintas, M. E., Redondo, M. R., Navia, B., & Rivas, T. (1997). Dietary intake and cognitive function in a group of elderly people. *The American Journal of Clinical Nutrition*, *66*(4), 803-809.

Örücü, M. Ç., & Demir, A. (2009). Psychometric evaluation of perceived stress scale for Turkish university students. *Stress and Health: Journal of the International Society for the Investigation of Stress*, *25*(1), 103-109.

Osborne, B., & Cooper, V. (2018). Health Survey for England 2017 Adult health related behaviours. *NHS Digital: Leeds, UK*.

Oulhaj, A., Jernerén, F., Refsum, H., Smith, A. D., & de Jager, C. A. (2016). Omega-3 fatty acid status enhances the prevention of cognitive decline by B vitamins in mild cognitive impairment. *Journal of Alzheimer's Disease*, *50*(2), 547-557.

Owen, A., Batterham, M., Probst, Y., Grenyer, B., & Tapsell, L. (2005). Low plasma vitamin E levels in major depression: diet or disease? *European Journal of Clinical Nutrition*, *59*(2), 304-304.

Özkaya, M. O., Nazıroğlu, M., Barak, C., & Berkkanoglu, M. (2011). Effects of multivitamin/mineral supplementation on trace element levels in serum and follicular fluid of women undergoing in vitro fertilization (IVF). *Biological Trace Element Research*, *139*(1), 1-9.

Padayatty, S. J., & Levine, M. (2016). Vitamin C: the known and the unknown and Goldilocks. *Oral Diseases*, *22*(6), 463-493.

Pae, M., Meydani, S. N., & Wu, D. (2012). The role of nutrition in enhancing immunity in aging. *Aging and Aisease*, *3*(1), 91-129.

Pansarasa, O., Pistono, C., Davin, A., Bordoni, M., Mimmi, M. C., Guaita, A., & Cereda, C. (2019). Altered immune system in frailty: genetics and diet may influence inflammation. *Ageing Research Reviews*, *54*, 100935.

Park, C., Majeed, A., Gill, H., Tamura, J., Ho, R. C., Mansur, R. B., Nasri, F., Lee, Y., Rosenblat, J. D., & Wong, E. (2020). The effect of loneliness on distinct health outcomes: a comprehensive review and meta-analysis. *Psychiatry Research*, *294*, 113514.

Park, H. L., O'Connell, J. E., & Thomson, R. G. (2003). A systematic review of cognitive decline in the general elderly population. *International Journal of Geriatric Psychiatry*, *18*(12), 1121-1134.

Park, K. (2015). Role of micronutrients in skin health and function. *Biomolecules & Therapeutics*, *23*(3), 207-217.

Park, N. S., Lee, B. S., Chiriboga, D. A., & Chung, S. (2019). Loneliness as a mediator in the relationship between social engagement and depressive symptoms: Age differences among community-dwelling Korean adults. *Health & Social Care in the Community*, *27*(3), 706-716.

Pata, R. W., Lord, K., & Lamb, J. (2014). The effect of Pilates based exercise on mobility, postural stability, and balance in order to decrease fall risk in older adults. *Journal of Bodywork and Movement Therapies*, *18*(3), 361-367.

Patrick, R. P., & Ames, B. N. (2014). Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. *The FASEB Journal*, *28*(6), 2398-2413.

Patterson, E., Wall, R., Fitzgerald, G., Ross, R., & Stanton, C. (2012). Health implications of high dietary omega-6 polyunsaturated fatty acids. *Journal of Nutrition and Metabolism*, *2012*.

Patterson, T. L., Goldman, S., McKibbin, C. L., Hughs, T., & Jeste, D. V. (2001). UCSD Performance-Based Skills Assessment: development of a new measure of everyday functioning for severely mentally ill adults. *Schizophrenia Bulletin*, *27*(2), 235-245.

Pawelec, G. (2018). Age and immunity: what is “immunosenescence”? *Experimental Gerontology*, *105*, 4-9.

Peeri, N. C., Egan, K. M., Chai, W., & Tao, M.-H. (2021). Association of magnesium intake and vitamin D status with cognitive function in older adults: an analysis of US National Health and Nutrition Examination Survey (NHANES) 2011 to 2014. *European Journal of Nutrition*, *60*(1), 465-474.

Pek, K., Chew, J., Lim, J. P., Yew, S., Tan, C. N., Yeo, A., Ding, Y. Y., & Lim, W. S. (2020). Social frailty is independently associated with mood, nutrition, physical performance, and physical activity: Insights from a theory-guided approach. *International Journal of Environmental Research and Public Health*, *17*(12), 4239.

Penninx, B. W., Guralnik, J. M., Ferrucci, L., Fried, L. P., Allen, R. H., & Stabler, S. P. (2000). Vitamin B12 deficiency and depression in physically disabled older women: epidemiologic evidence from the Women’s Health and Aging Study. *American Journal of Psychiatry*, *157*(5), 715-721.

Perez, R. (2011). Vitamin supplements: Hope vs. hype. *Tufts University Health & Nutrition Letter*, *29*(6), S1.

Perissinotto, C., Holt-Lunstad, J., Periyakoil, V. S., & Covinsky, K. (2019). A practical approach to assessing and mitigating loneliness and isolation in older adults. *Journal of the American Geriatrics Society*, *67*(4), 657-662.

Perri, G., Mendonça, N., Jagger, C., Walsh, J., Eastell, R., Mathers, J. C., & Hill, T. R. (2020). Dietary Selenium Intakes and Musculoskeletal Function in Very Old Adults: Analysis of the Newcastle 85+ Study. *Nutrients*, *12*(7), 2068.

Peuhkuri, K., Sihvola, N., & Korpela, R. (2012). Diet promotes sleep duration and quality. *Nutrition Research*, *32*(5), 309-319.

Pezdirc, K., Hutchesson, M., Whitehead, R., Ozakinci, G., Perrett, D., & Collins, C. E. (2015). Can dietary intake influence perception of and measured appearance? A systematic review. *Nutrition Research*, *35*(3), 175-197.

Pfeifer, M., Begerow, B., & Minne, H. (2002). Vitamin D and muscle function. *Osteoporosis International*, *13*(3), 187-194.

Philip, K. E., Polkey, M. I., Hopkinson, N. S., Steptoe, A., & Fancourt, D. (2020). Social isolation, loneliness and physical performance in older-adults: fixed effects analyses of a cohort study. *Scientific Reports*, *10*(1), 1-9.

Phillips, C. (2017). Lifestyle modulators of neuroplasticity: how physical activity, mental engagement, and diet promote cognitive health during aging. *Neural plasticity*.

Phillips, F. (2003). Nutrition for healthy ageing. *Nutrition Bulletin*, *28*(3), 253-263.

Pinheiro, H. A., Cerceau, V. R., Pereira, L. C., Funghetto, S. S., & Menezes, R. L. d. (2020). Nutritional intervention and functional exercises improve depression, loneliness and quality of life in elderly women with sarcopenia: a randomized clinical trial. *Fisioterapia em Movimento*, *33*.

Pinquart, M., & Sorensen, S. (2001). Influences on loneliness in older adults: A meta-analysis. *Basic and Applied Social Psychology*, *23*(4), 245-266.

Pipingas, A., Camfield, D., Stough, C., Cox, K., Fogg, E., Tiplady, B., Sarris, J., White, D. J., Sali, A., & Wetherell, M. A. (2013). The effects of multivitamin supplementation on mood and general well-being in healthy young adults. A laboratory and at-home mobile phone assessment. *Appetite*, *69*, 123-136.

Pipingas, A., Silberstein, R. B., Vitetta, L., Rooy, C. V., Harris, E. V., Young, J. M., Frampton, C. M., Sali, A., & Nastasi, J. (2008). Improved cognitive performance after dietary supplementation with a Pinus radiata bark extract formulation. *Phytotherapy Research*, *22*(9), 1168-1174.

Pipingas, A., Sinclair, A., Croft, K. D., Januszewski, A. S., Jenkins, A. J., Mori, T. A., Cockerell, R., Grima, N. A., Stough, C., & Scholey, A. (2015). Fish oil and multivitamin supplementation reduces oxidative stress but not inflammation in healthy older adults: a randomised controlled trial. *Journal of Functional Foods*, *19*, 949-957.

Pistollato, F., Sumalla Cano, S., Elio, I., Masias Vergara, M., Giampieri, F., & Battino, M. (2016). Associations between sleep, cortisol regulation, and diet: possible implications for the risk of Alzheimer disease. *Advances in Nutrition*, *7*(4), 679-689.

Polder, J. J., Bonneux, L., Meerding, W. J., & Van Der Maas, P. J. (2002). Age-specific increases in health care costs. *The European Journal of Public Health*, *12*(1), 57-62.

Prakash, V., & van Boekel, M. A. (2010). Nutraceuticals: possible future ingredients and food safety aspects. In *Ensuring Global Food Safety* (pp. 333-338). Elsevier.

Prasad, A., Fitzgerald, J., Hess, J., Kaplan, J., Pelen, F., & Dardenne, M. (1993). Zinc deficiency in elderly patients. *Nutrition (Burbank, Los Angeles County, Calif.)*, *9*(3), 218-224.

Prentice, A. (2021). Sex differences in requirements for micronutrients across the lifecourse. *Proceedings of the Nutrition Society*, *80*(3), 356-364.

Prohaska, T., Burholt, V., Burns, A., Golden, J., Hawkley, L., Lawlor, B., Leavey, G., Lubben, J., O'Sullivan, R., & Perissinotto, C. (2020). Consensus statement: loneliness in older adults, the 21st century social determinant of health? *BMJ open*, *10*(8), e034967.

Pullar, J. M., Carr, A. C., Bozonet, S. M., & Vissers, M. C. (2018). High vitamin C status is associated with elevated mood in male tertiary students. *Antioxidants*, *7*(7), 91.

Qian, B., Shen, S., Zhang, J., & Jing, P. (2017). Effects of vitamin B6 deficiency on the composition and functional potential of T cell populations. *Journal of immunology research*, *2017*.

Raczkiewicz, A., Kisiel, B., Kulig, M., & Tlustochowicz, W. (2015). Vitamin D status and its association with quality of life, physical activity, and disease activity in rheumatoid arthritis patients. *JCR: Journal of Clinical Rheumatology*, *21*(3), 126-130.

Radimer, K., Bindewald, B., Hughes, J., Ervin, B., Swanson, C., & Picciano, M. F. (2004). Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999–2000. *American Journal of Epidemiology*, *160*(4), 339-349.

Ramsay, R. R. (2019). Electron carriers and energy conservation in mitochondrial respiration. *ChemTexts*, *5*(2), 1-14.

Rautiainen, S., Rist, P. M., Glynn, R. J., Buring, J. E., Gaziano, J. M., & Sesso, H. D. (2016). Multivitamin use and the risk of cardiovascular disease in men. *The Journal of Nutrition*, *146*(6), 1235-1240.

Reay, J. L., Smith, M. A., & Riby, L. (2013). B vitamins and cognitive performance in older adults. *International Scholarly Research Notices*, *2013*.

Redman, K., Ruffman, T., Fitzgerald, P., & Skeaff, S. (2016). Iodine deficiency and the brain: effects and mechanisms. *Critical Reviews in Food Science and Nutrition*, *56*(16), 2695-2713.

Refsum, H., Smith, A. D., Ueland, P. M., Nexo, E., Clarke, R., McPartlin, J., Johnston, C., Engbaek, F., Schneede, J., & McPartlin, C. (2004). Facts and recommendations about total homocysteine determinations: an expert opinion. *Clinical Chemistry*, *50*(1), 3-32.

Reichenberg, A., Feo, C., Prestia, D., Bowie, C. R., Patterson, T. L., & Harvey, P. D. (2014). The course and correlates of everyday functioning in schizophrenia. *Schizophrenia Research: Cognition*, *1*(1), e47-e52.

Rein, M. J., Renouf, M., Cruz-Hernandez, C., Actis-Goretta, L., Thakkar, S. K., & da Silva Pinto, M. (2013). Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. *British Journal of Clinical Pharmacology*, *75*(3), 588-602.

Remes, O., Brayne, C., Van Der Linde, R., & Lafortune, L. (2016). A systematic review of reviews on the prevalence of anxiety disorders in adult populations. *Brain and Behavior*, *6*(7), e00497.

Ribeiro, O., Teixeira, L., Araújo, L., Rodríguez-Blázquez, C., Calderón-Larrañaga, A., & Forjaz, M. J. (2020). Anxiety, depression and quality of life in older adults: Trajectories of influence across age. *International Journal of Environmental Research and Public Health*, *17*(23), 9039.

Riboli, E., Hunt, K., Slimani, N., Ferrari, P., Norat, T., Fahey, M., Charrondiere, U., Hemon, B., Casagrande, C., & Vignat, J. (2002). European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutrition*, *5*(6b), 1113-1124.

Rickenbach, E. H., Almeida, D. M., Seeman, T. E., & Lachman, M. E. (2014). Daily stress magnifies the association between cognitive decline and everyday memory problems: an integration of longitudinal and diary methods. *Psychology and Aging*, *29*(4), 852-862.

Ried, K., Sullivan, T. R., Fakler, P., Frank, O. R., & Stocks, N. P. (2012). Effect of cocoa on blood pressure. *Cochrane Database of Systematic Reviews*(8).

Rimando, A. M., & Suh, N. (2008). Natural products and dietary prevention of cancer. *Molecular Nutrition & Food Research*, *52*(1), S5.

Rimm, E. B., Stampfer, M. J., Ascherio, A., Giovannucci, E., Colditz, G. A., & Willett, W. C. (1993). Vitamin E consumption and the risk of coronary heart disease in men. *New England Journal of Medicine*, *328*(20), 1450-1456.

Roberta, M., Federica, G., Stefano, K., Fabiola, F., Gioacchino, L., Antonio, N., Francesca, V., & Gian, L. d. A. (2018). Thyroid and celiac disease in pediatric age: a literature review. *Acta Bio Medica: Atenei Parmensis*, *89*(Suppl 9), 11.

Roberts, C., Steer, T., Maplethorpe, N., Cox, L., Meadows, S., Nicholson, S., Page, P., & Swan, G. (2018). National diet and nutrition survey: results from years 7 and 8 (combined) of the rolling programme (2014/2015–2015/2016).

Rock, C. (2007). Multivitamin-multimineral supplements: who uses them? *The American Journal of Clinical Nutrition*, *85*(1), 277S-279S.

Rollo, M. E., Williams, R. L., Burrows, T., Kirkpatrick, S. I., Bucher, T., & Collins, C. E. (2016). What are they really eating? A review on new approaches to dietary intake assessment and validation. *Current Nutrition Reports*, *5*(4), 307-314.

Romano, F., Muscogiuri, G., Di Benedetto, E., Zhukouskaya, V. V., Barrea, L., Savastano, S., Colao, A., & Di Somma, C. (2020). Vitamin D and sleep regulation: is there a role for vitamin D? *Current Pharmaceutical Design*, *26*(21), 2492-2496.

Roubenoff, R., Scrimshaw, N., Shetty, P., & Woo, J. (2000). Report of the IDECG Working Group on the role of lifestyle including nutrition for the health of the elderly. *European Journal of Clinical Nutrition*, *54*(S3), S164-S164.

Rowe, J. W., & Kahn, R. L. (1987). Human aging: usual and successful. *Science*, *237*(4811), 143-149.

Russell, R. M. (2000). The aging process as a modifier of metabolism. *The American Journal of Clinical Nutrition*, *72*(2), 529S-532S.

Rutherford, T., & Socio, A. (2012). Population ageing: statistics. *House of Commons library (Standard not. Retrieved Jan 2, 2013, from: www. parliament. uk/topics/PopulationArchive*.

Ryu, S. Y., Lee, S. B., Kim, T. W., & Lee, T. J. (2016). Subjective memory complaints, depressive symptoms and instrumental activities of daily living in mild cognitive impairment. *International Psychogeriatrics*, *28*(3), 487-494.

Sahyoun, N. R., Pratt, C. A., & Anderson, A. (2004). Evaluation of nutrition education interventions for older adults: a proposed framework. *Journal of the American Dietetic Association*, *104*(1), 58-69.

Said, H. M. (2011). Intestinal absorption of water-soluble vitamins in health and disease. *Biochemical Journal*, *437*(3), 357-372.

Saini, R. K., & Keum, Y.-S. (2018). Omega-3 and omega-6 polyunsaturated fatty acids: Dietary sources, metabolism, and significance—A review. *Life sciences*, *203*, 255-267.

Sajatovic, M., Strejilevich, S. A., Gildengers, A. G., Dols, A., Al Jurdi, R. K., Forester, B. P., Kessing, L. V., Beyer, J., Manes, F., & Rej, S. (2015). A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disorders*, *17*(7), 689-704.

Sakakeeny, L., Roubenoff, R., Obin, M., Fontes, J. D., Benjamin, E. J., Bujanover, Y., Jacques, P. F., & Selhub, J. (2012). Plasma pyridoxal-5-phosphate is inversely associated with systemic markers of inflammation in a population of US adults. *The Journal of Nutrition*, *142*(7), 1280-1285.

Sakalli, H., Arslan, D., & Yucel, A. E. (2012). The effect of oral and parenteral vitamin D supplementation in the elderly: a prospective, double-blinded, randomized, placebo-controlled study. *Rheumatology International*, *32*(8), 2279-2283.

Salminen, K., Suominen, M., Kautiainen, H., & Pitkälä, K. (2020). Associations between nutritional status, frailty and health-related quality of life among older long-term care residents in Helsinki. *The journal of Nutrition, Health & Aging*, *24*(3), 319-324.

Salthouse, T. (2012). Consequences of age-related cognitive declines. *Annual Review of Psychology*, *63*, 201-226.

Sánchez-Villegas, A., Doreste, J., Schlatter, J., Pla, J., Bes-Rastrollo, M., & Martinez-Gonzalez, M. (2009). Association between folate, vitamin B6 and vitamin B12 intake and depression in the SUN cohort study. *Journal of Human Nutrition and Dietetics*, *22*(2), 122-133.

Sandstead, H. H. (1994). Understanding zinc: recent observations and interpretations. *The Journal of Laboratory and Clinical Medicine*, *124*(3), 322-327.

Sandström, B. (2001). Micronutrient interactions: effects on absorption and bioavailability. *The British Journal of Nutrition*, *85*(S2), S181.

Santini, A., Tenore, G. C., & Novellino, E. (2017). Nutraceuticals: A paradigm of proactive medicine. *European Journal of Pharmaceutical Sciences*, *96*, 53-61.

Santini, Z. I., & Koyanagi, A. (2021). Loneliness and its association with depressed mood, anxiety symptoms, and sleep problems in Europe during the COVID-19 pandemic. *Acta Neuropsychiatrica*, *33*(3), 160-163.

Sarris, J., Cox, K. H., Camfield, D. A., Scholey, A., Stough, C., Fogg, E., Kras, M., White, D. J., Sali, A., & Pipingas, A. (2012). Participant experiences from chronic administration of a multivitamin versus placebo on subjective health and wellbeing: a double-blind qualitative analysis of a randomised controlled trial. *Nutrition Journal*, *11*(1), 1-10.

Scheel-Hincke, L. L., Möller, S., Lindahl-Jacobsen, R., Jeune, B., & Ahrenfeldt, L. J. (2020). Cross-national comparison of sex differences in ADL and IADL in Europe: findings from SHARE. *European Journal of Ageing*, *17*(1), 69-79.

Schiborr, C., Kocher, A., Behnam, D., Jandasek, J., Toelstede, S., & Frank, J. (2014). The oral bioavailability of curcumin from micronized powder and liquid micelles is significantly increased in healthy humans and differs between sexes. *Molecular Nutrition & Food Research*, *58*(3), 516-527.

Schlotz, W., Yim, I. S., Zoccola, P. M., Jansen, L., & Schulz, P. (2011). The Perceived Stress Reactivity Scale: measurement invariance, stability, and validity in three countries. *Psychological Assessment*, *23*(1), 80-94.

Schmidt, N. (2011). Marketing Dietary Supplements: Public Relations and the Ability of Pharmaceutical Companies to Retain and Develop Consumer Relationships.

Schneider, C. (2005). Chemistry and biology of vitamin E. *Molecular Nutrition & Food Research*, *49*(1), 7-30.

Scholey, A., Bauer, I., Neale, C., Savage, K., Camfield, D., White, D., Maggini, S., Pipingas, A., Stough, C., & Hughes, M. (2013). Acute effects of different multivitamin mineral preparations with and without guaraná on mood, cognitive performance and functional brain activation. *Nutrients*, *5*(9), 3589-3604.

Scholey, A., Kennedy, D., Zangara, A., Robertson, B., Reay, J., Luedemann, J., Maggini, S., & Ruf, M. (2008). A multivitamin–mineral preparation with guaraná positively effects cognitive performance and reduces mental fatigue during sustained mental demand. *Appetite*, *50*(2-3), 565.

Schorr, A. V., Yehuda, I., & Tamir, S. (2021). Ethnic differences in loneliness, depression, and malnutrition among older adults during COVID-19 quarantine. *The Journal of Nutrition, Health & Aging*, *25*(3), 311-317.

Schünemann, J., Strulik, H., & Trimborn, T. (2017). The gender gap in mortality: How much is explained by behavior? *Journal of Health Economics*, *54*, 79-90.

Schwartz, B. (2014). New criteria for supplementation of selected micronutrients in the era of nutrigenetics and nutrigenomics. *International Journal of Food Sciences and Nutrition*, *65*(5), 529-538.

Schwartz, J. B. (2003). The influence of sex on pharmacokinetics. *Clinical Pharmacokinetics*, *42*(2), 107-121.

Scientific Advisory Committee on Nutrition. (2021). *SACN statement on nutrition and older adults*.

Segger, D., & Schönlau, F. (2004). Supplementation with Evelle® improves skin smoothness and elasticity in a double-blind, placebo-controlled study with 62 women. *Journal of Dermatological Treatment*, *15*(4), 222-226.

Seidel, D., Brayne, C., & Jagger, C. (2011). Limitations in physical functioning among older people as a predictor of subsequent disability in instrumental activities of daily living. *Age and Ageing*, *40*(4), 463-469.

Seifert, N., Seddig, D., & Eckhard, J. (2022). Does social isolation affect physical and mental health? A test of the social causation hypothesis using dynamic panel models with fixed effects. *Aging & Mental Health*, *26*(7), 1353-1367.

Sekhri, K., & Kaur, K. (2014). Public knowledge, use and attitude toward multivitamin supplementation: A cross-sectional study among general public. *International Journal of Applied and Basic Medical Research*, *4*(2), 77-80.

Sepúlveda-Loyola, W., Rodríguez-Sánchez, I., Pérez-Rodríguez, P., Ganz, F., Torralba, R., Oliveira, D., & Rodríguez-Mañas, L. (2020). Impact of social isolation due to COVID-19 on health in older people: mental and physical effects and recommendations. *The Journal of Nutrition, Health & Aging*, *24*(9), 938-947.

Shah, R. (2013). The role of nutrition and diet in Alzheimer disease: a systematic review. *Journal of the American Medical Directors Association*, *14*(6), 398-402.

Shan, Z.-y., Li, Y.-s., Wang, Z.-y., Jin, Y., Guan, H.-x., Hu, F.-n., Teng, X.-c., Yang, F., Gao, T.-s., & Wang, W.-b. (2005). Effect of different iodine intake on the prevalence of hypothyroidism in 3 counties in China. *Chinese Medical Journal*, *118*(22), 1918-1920.

Shankar, A., McMunn, A., Banks, J., & Steptoe, A. (2011). Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychology*, *30*(4), 377-385.

Sharkey, J. R. (2008). Diet and health outcomes in vulnerable populations. *Annals of the New York Academy of Sciences*, *1136*, 210-217.

Shayeghi, M., Latunde-Dada, G. O., Oakhill, J. S., Laftah, A. H., Takeuchi, K., Halliday, N., Khan, Y., Warley, A., McCann, F. E., & Hider, R. C. (2005). Identification of an intestinal heme transporter. *Cell*, *122*(5), 789-801.

Shea, M. K., & Booth, S. L. (2022). Vitamin K. *Advances in Nutrition*, *13*(1), 350-351.

Shearer, M. J., Fu, X., & Booth, S. L. (2012). Vitamin K Nutrition, Metabolism, and Requirements: Current Concepts and Future Research. *Advance in Nutrition, 3*(2), 182-195.

Shields, G. S., Doty, D., Shields, R. H., Gower, G., Slavich, G. M., & Yonelinas, A. P. (2017). Recent life stress exposure is associated with poorer long-term memory, working memory, and self-reported memory. *Stress*, *20*(6), 598-607.

Shlisky, J., Bloom, D. E., Beaudreault, A. R., Tucker, K. L., Keller, H. H., Freund-Levi, Y., Fielding, R. A., Cheng, F. W., Jensen, G. L., & Wu, D. (2017). Nutritional considerations for healthy aging and reduction in age-related chronic disease. *Advances in Nutrition*, *8*(1), 17-26.

Simes, D. C., Viegas, C. S., Araújo, N., & Marreiros, C. (2020). Vitamin K as a diet supplement with impact in human health: current evidence in age-related diseases. *Nutrients*, *12*(1), 138.

Šimoliūnas, E., Rinkūnaitė, I., Bukelskienė, Ž., & Bukelskienė, V. (2019). Bioavailability of different vitamin D Oral supplements in laboratory animal model. *Medicina*, *55*(6), 265.

Singh, A., Moses, F. M., & Deuster, P. A. (1992). Chronic multivitamin-mineral supplementation does not enhance physical performance. *Medicine and Science in Sports and Exercise*, *24*(6), 726-732.

Singh, F., Bernstein, M., Ryan, A., O'neill, E., Clements, K., & Evans, W. J. (2000). The effect of oral nutritional supplements on habitual dietary quality and quantity in frail elders. *The Journal of Nutrition, Health & Aging*, *4*(1), 5-12.

Singh, R., Vishwakarma, S., & Singh, P. (2014). 19 Vitamins and Minerals: Roles and Plant Sources. *Phytochemicals of Nutraceutical Importance*, 310.

Skikne, B., & Hershko, C. (2012). Iron deficiency. In *Iron physiology and Pathophysiology in Humans* (pp. 251-282). Springer.

Slinin, Y., Paudel, M., Taylor, B., Fink, H., Ishani, A., Canales, M., Yaffe, K., Barrett-Connor, E., Orwoll, E., & Shikany, J. (2010). 25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men. *Neurology*, *74*(1), 33-41.

Smagula, S. F., Stone, K. L., Fabio, A., & Cauley, J. A. (2016). Risk factors for sleep disturbances in older adults: evidence from prospective studies. *Sleep Medicine Reviews*, *25*, 21-30.

Small, B. J., Rawson, K. S., Martin, C., Eisel, S. L., Sanberg, C. D., McEvoy, C. L., Sanberg, P. R., Shytle, R. D., Tan, J., & Bickford, P. C. (2014). Nutraceutical intervention improves older adults' cognitive functioning. *Rejuvenation Research*, *17*(1), 27-32.

Smirnoff, N., Conklin, P. L., & Loewus, F. A. (2001). Biosynthesis of ascorbic acid in plants: a renaissance. *Annual Review of Plant Biology*, *52*(1), 437-467.

Smith, J. M. (2012). Toward a better understanding of loneliness in community-dwelling older adults. *The Journal of Psychology*, *146*(3), 293-311.

Sohl, E., De Jongh, R., Heijboer, A., Swart, K., Brouwer-Brolsma, E., Enneman, A., De Groot, C., van der Velde, N., Dhonukshe-Rutten, R., & Lips, P. (2013). Vitamin D status is associated with physical performance: the results of three independent cohorts. *Osteoporosis International*, *24*(1), 187-196.

Sokoll, L. J., Booth, S. L., O'Brien, M. E., Davidson, K. W., Tsaioun, K. I., & Sadowski, J. A. (1997). Changes in serum osteocalcin, plasma phylloquinone, and urinary gamma-carboxyglutamic acid in response to altered intakes of dietary phylloquinone in human subjects. *The American Journal of Clinical Nutrition*, *65*(3), 779-784.

Sokoll, L. J., Russell, R. M., Sadowski, J. A., & Morrow, F. D. (1994). Establishment of creatinine clearance reference values for older women. *Clinical Chemistry*, *40*(12), 2276-2281.

Song, C.-H., Kim, Y.-H., & Jung, K.-I. (2012). Associations of zinc and copper levels in serum and hair with sleep duration in adult women. *Biological Trace Element esearch*, *149*(1), 16-21.

Song, E. K., & Wu, J.-R. (2018). Associations of vitamin D intake and sleep quality with cognitive dysfunction in older adults with heart failure. *Journal of Cardiovascular Nursing*, *33*(4), 392-399.

Sousa, R. D. d., Rodrigues, A. M., Gregório, M. J., Branco, J. D. C., Gouveia, M. J., Canhão, H., & Dias, S. S. (2017). Anxiety and depression in the Portuguese older adults: prevalence and associated factors. *Frontiers in Medicine*, *4*, 196.

Soysal, P., Veronese, N., Thompson, T., Kahl, K. G., Fernandes, B. S., Prina, A. M., Solmi, M., Schofield, P., Koyanagi, A., & Tseng, P.-T. (2017). Relationship between depression and frailty in older adults: a systematic review and meta-analysis. *Ageing Research Reviews*, *36*, 78-87.

Spallholz, J. E., Boylan, L. M., & Larsen, H. S. (1990). Advances in understanding selenium's role in the immune system. *Annals of the New York Academy of Sciences*, *587*(1), 123-139.

Spijker, J., & MacInnes, J. (2013). Population ageing: the timebomb that isn't? *Bmj*, *347*.

Srinivasan, V. S. (2001). Bioavailability of nutrients: a practical approach to in vitro demonstration of the availability of nutrients in multivitamin-mineral combination products. *The Journal of Nutrition*, *131*(4), 1349S-1350S.

Stahl, E. C., & Brown, B. N. (2015). Cell therapy strategies to combat immunosenescence. *Organogenesis*, *11*(4), 159-172.

Stampfer, M. J., Hennekens, C. H., Manson, J. E., Colditz, G. A., Rosner, B., & Willett, W. C. (1993). Vitamin E consumption and the risk of coronary disease in women. *New England Journal of Medicine*, *328*(20), 1444-1449.

Stanger, O., Fowler, B., Piertzik, K., Huemer, M., Haschke-Becher, E., Semmler, A., Lorenzl, S., & Linnebank, M. (2009). Homocysteine, folate and vitamin B12 in neuropsychiatric diseases: review and treatment recommendations. *Expert Review of Neurotherapeutics*, *9*(9), 1393-1412.

Stanisławska, M., Szkup-Jabłońska, M., Jurczak, A., Wieder-Huszla, S., Samochowiec, A., Jasiewicz, A., Noceń, I., Augustyniuk, K., Brodowska, A., & Karakiewicz, B. (2014). The severity of depressive symptoms vs. serum Mg and Zn levels in postmenopausal women. *Biological Trace Element Research*, *157*(1), 30-35.

Stanner, S. (2009). Healthy ageing: the role of nutrition and lifestyle. *Nursing And Residential Care*, *11*(5), 239-242.

Steenman, M., & Lande, G. (2017). Cardiac aging and heart disease in humans. *Biophysical Reviews*, *9*(2), 131-137.

Steptoe, A., Shankar, A., Demakakos, P., & Wardle, J. (2013). Social isolation, loneliness, and all-cause mortality in older men and women. *Proceedings of the National Academy of Sciences*, *110*(15), 5797-5801.

Stern, S., Behar, S., & Gottlieb, S. (2003). Aging and diseases of the heart. *Circulation*, *108*(14), e99-e101.

Stern, Y., Hesdorffer, D., Sano, M., & Mayeux, R. (1990). Measurement and prediction of functional capacity in Alzheimer's disease. *Neurology*, *40*(1), 8-8.

Sternberg, S., & Roberts, S. (2006). Nutritional supplements and infection in the elderly: why do the findings conflict? *Nutrition Journal*, *5*(1), 1-7.

Stewart, A. L., Hays, R. D., & Ware Jr, J. E. (1988). The MOS short-form general health survey: reliability and validity in a patient population. *Medical Care*, 724-735.

Stokes, J. P. (1985). The relation of social network and individual difference variables to loneliness. *Journal of Personality and Social Psychology*, *48*(4), 981.

St-Onge, M.-P., Mikic, A., & Pietrolungo, C. E. (2016). Effects of diet on sleep quality. *Advances in Nutrition*, *7*(5), 938-949.

Strike, S. C., Carlisle, A., Gibson, E. L., & Dyall, S. C. (2016). A high omega-3 fatty acid multinutrient supplement benefits cognition and mobility in older women: a randomized, double-blind, placebo-controlled pilot study. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, *71*(2), 236-242.

Strine, T. W., Lesesne, C. A., Okoro, C. A., McGuire, L. C., Chapman, D. P., Balluz, L. S., & Mokdad, A. H. (2006). Emotional and Behavioral Difficulties and Impairments in Everyday Functioning Among Children With a History of Attention-Deficit/Hyperactivity Disorder. *Preventing Chronic Disease*, *3*(2).

Struijk, E. A., Lana, A., Guallar-Castillón, P., Rodríguez-Artalejo, F., & Lopez-Garcia, E. (2018). Intake of B vitamins and impairment in physical function in older adults. *Clinical Nutrition*, *37*(4), 1271-1278.

Sun, Y., Lu, C.-J., Chien, K.-L., Chen, S.-T., & Chen, R.-C. (2007). Efficacy of multivitamin supplementation containing vitamins B6 and B12 and folic acid as adjunctive treatment with a cholinesterase inhibitor in Alzheimer's disease: a 26-week, randomized, double-blind, placebo-controlled study in Taiwanese patients. *Clinical Therapeutics*, *29*(10), 2204-2214.

Sunkara, A., & Raizner, A. (2019). Supplemental vitamins and minerals for cardiovascular disease prevention and treatment. *Methodist Debakey Cardiovascular Journal*, *15*(3), 179.

Swaminathan, A., & Jicha, G. A. (2014). Nutrition and prevention of Alzheimer's dementia. *Frontiers in Aging Neuroscience*, *6*, 282.

Taekema, D. G., Gussekloo, J., Maier, A. B., Westendorp, R. G., & de Craen, A. J. (2010). Handgrip strength as a predictor of functional, psychological and social health. A prospective population-based study among the oldest old. *Age and Ageing*, *39*(3), 331-337.

Tahmasebi, K., Amani, R., Nazari, Z., Ahmadi, K., Moazzen, S., & Mostafavi, S.-A. (2017). Association of mood disorders with serum zinc concentrations in adolescent female students. *Biological Trace Element Research*, *178*(2), 180-188.

Tan, S.-Y., Tey, S. L., & Brown, R. (2021). Nuts and older adults' health: A narrative review. *International Journal of Environmental Research and Public Health*, *18*(4), 1848.

Tardy, A.-L., Pouteau, E., Marquez, D., Yilmaz, C., & Scholey, A. (2020). Vitamins and minerals for energy, fatigue and cognition: A narrative review of the biochemical and clinical evidence. *Nutrients*, *12*(1), 228.

Tarleton, E. K., & Littenberg, B. (2015). Magnesium intake and depression in adults. *The Journal of the American Board of Family Medicine*, *28*(2), 249-256.

Tetley, J., Lee, D. M., Nazroo, J., & Hinchliff, S. (2018). Let's talk about sex–what do older men and women say about their sexual relations and sexual activities? A qualitative analysis of ELSA Wave 6 data. *Ageing & Society*, *38*(3), 497-521.

Thacher, T. D., & Clarke, B. L. (2011). Vitamin D insufficiency. Mayo Clinic Proceedings,

Theuwissen, E., Magdeleyns, E., Braam, L., Teunissen, K., Knapen, M., Binnekamp, I., van Summeren, M., & Vermeer, C. (2014). Vitamin K status in healthy volunteers. *Food & Function*, *5*(2), 229-234.

Thomas, D. R. (2006). Vitamins in aging, health, and longevity. *Clinical Interventions in Aging*, *1*(1), 81.

Thorpe, M. G., Milte, C. M., Crawford, D., & McNaughton, S. A. (2019). Education and lifestyle predict change in dietary patterns and diet quality of adults 55 years and over. *Nutrition Journal*, *18*(1), 1-13.

Tinkler, L., & Hicks, S. (2011). Measuring subjective well-being. Office for National Statistics, United Kingdom.

Toffanello, E. D., Perissinotto, E., Sergi, G., Zambon, S., Musacchio, E., Maggi, S., Coin, A., Sartori, L., Corti, M.-C., & Baggio, G. (2012). Vitamin D and physical performance in elderly subjects: the Pro. VA study. *PLoS One*, *7*(4), e34950.

Tolmunen, T., Voutilainen, S., Hintikka, J., Rissanen, T., Tanskanen, A., Viinamäki, H., Kaplan, G. A., & Salonen, J. T. (2003). Dietary folate and depressive symptoms are associated in middle-aged Finnish men. *The Journal of Nutrition*, *133*(10), 3233-3236.

Tomaszewski Farias, S., Cahn-Weiner, D. A., Harvey, D. J., Reed, B. R., Mungas, D., Kramer, J. H., & Chui, H. (2009). Longitudinal changes in memory and executive functioning are associated with longitudinal change in instrumental activities of daily living in older adults. *The Clinical Neuropsychologist*, *23*(3), 446-461.

Tomioka, K., Kurumatani, N., & Hosoi, H. (2016). Relationship of having hobbies and a purpose in life with mortality, activities of daily living, and instrumental activities of daily living among community-dwelling elderly adults. *Journal of Epidemiology*, *26*(7), 361-370.

Tong, A., Scholes-Robertson, N., Hawley, C., Viecelli, A. K., Carter, S. A., Levin, A., Hemmelgarn, B. R., Harris, T., & Craig, J. C. (2022). Patient-centred clinical trial design. *Nature Reviews Nephrology*, 1-10.

Travica, N., Ried, K., Sali, A., Scholey, A., Hudson, I., & Pipingas, A. (2017). Vitamin C status and cognitive function: a systematic review. *Nutrients*, *9*(9), 960.

Tritter, J. Q. (2009). Revolution or evolution: the challenges of conceptualizing patient and public involvement in a consumerist world. *Health Expectations*, *12*(3), 275-287.

Trombetti, A., Reid, K., Hars, M., Herrmann, F., Pasha, E., Phillips, E., & Fielding, R. (2016). Age-associated declines in muscle mass, strength, power, and physical performance: impact on fear of falling and quality of life. *Osteoporosis International*, *27*(2), 463-471.

Tso, P., & Fujimoto, K. (1991). The absorption and transport of lipids by the small intestine. *Brain Research Bulletin*, *27*(3-4), 477-482.

Tucker-Drob, E. M. (2019). Cognitive aging and dementia: a life span perspective. *Annual Review of Developmental Psychology*, *1*, 177-196.

Unger, J. M., Hershman, D. L., Albain, K. S., Moinpour, C. M., Petersen, J. A., Burg, K., & Crowley, J. J. (2013). Patient income level and cancer clinical trial participation. *Journal of Clinical Oncology*, *31*(5), 536-542.

Valencia, E., Marin, A., & Hardy, G. (2002). Can antioxidant nutraceuticals benefit the menopause? *British Menopause Society Journal*, *8*(3), 98-101.

Valiathan, R., Ashman, M., & Asthana, D. (2016). Effects of ageing on the immune system: infants to elderly. *Scandinavian Journal of Immunology*, *83*(4), 255-266.

Valtorta, N. K., Kanaan, M., Gilbody, S., & Hanratty, B. (2018). Loneliness, social isolation and risk of cardiovascular disease in the English Longitudinal Study of Ageing. *European Journal of Preventive Cardiology*, *25*(13), 1387-1396.

Valtueña, J., Gracia-Marco, L., Huybrechts, I., Breidenassel, C., Ferrari, M., Gottrand, F., Dallongeville, J., Sioen, I., Gutierrez, A., & Kersting, M. (2013). Cardiorespiratory fitness in males, and upper limbs muscular strength in females, are positively related with 25-hydroxyvitamin D plasma concentrations in European adolescents: the HELENA study. *QJM: monthly journal of the Association of Physicians*, *106*(9), 809-821.

Van Den Berg, P., Kemperman, A., De Kleijn, B., & Borgers, A. (2016). Ageing and loneliness: the role of mobility and the built environment. *Travel Behaviour and Society*, *5*, 48-55.

van Dijk, M., Cullum, A., Swan, G., Peacock, E., Fine, G., Robinson, S., McArdle, H., Walls, A., & Walsh, S. (2021). An overview of the Scientific Advisory Committee on Nutrition's position statement on nutrition and older adults living in the community. *British Journal of Nutrition*, *126*(8), 1164-1167.

Van Soest, A. P., Van De Rest, O., Witkamp, R. F., Cederholm, T., & De Groot, L. C. (2022). DHA status influences effects of B-vitamin supplementation on cognitive ageing: a post-hoc analysis of the B-proof trial. *European Journal of Nutrition*, *61*(7), 3731-3739.

Vance, D. E., Fazeli, P. L., & Gakumo, C. A. (2013). The impact of neuropsychological performance on everyday functioning between older and younger adults with and without HIV. *Journal of the Association of Nurses in AIDS Care*, *24*(2), 112-125.

Vance, D. E., Heaton, K., Eaves, Y., & Fazeli, P. L. (2011). Sleep and cognition on everyday functioning in older adults: implications for nursing practice and research. *Journal of Neuroscience Nursing*, *43*(5), 261-271.

Vasiliadis, H.-M., Desjardins, F., Roberge, P., & Grenier, S. (2020). Sex differences in anxiety disorders in older adults. *Current Psychiatry Reports*, *22*(12), 1-9.

Vega-Cabello, V., Caballero, F. F., Lana, A., Arias-Fernandez, L., Banegas, J. R., Rodríguez-Artalejo, F., Lopez-Garcia, E., & Struijk, E. A. (2022). Association of zinc intake with risk of impaired physical function and frailty among older adults. *The Journals of Gerontology: Series A*.

Vellas, B. J., Wayne, S. J., Romero, L. J., Baumgartner, R. N., & Garry, P. J. (1997). Fear of falling and restriction of mobility in elderly fallers. *Age and Ageing*, *26*(3), 189-193.

Veronese, N., Stubbs, B., Punzi, L., Soysal, P., Incalzi, R. A., Saller, A., & Maggi, S. (2019). Effect of nutritional supplementations on physical performance and muscle strength parameters in older people: a systematic review and meta-analysis. *Ageing Research reviews*, *51*, 48-54.

Victor, C., & Scharf, T. (2005). Social isolation and loneliness. *Understanding quality of life in old age. Open University Press, Buckingham*, 100-116.

Viñas, B. R., Barba, L. R., Ngo, J., Gurinovic, M., Novakovic, R., Cavelaars, A., De Groot, L. C., van't Veer, P., Matthys, C., & Majem, L. S. (2011). Projected prevalence of inadequate nutrient intakes in Europe. *Annals of Nutrition and Metabolism*, *59*(2-4), 84-95.

Vivanti, A., Ward, N., & Haines, T. (2011). Nutritional status and associations with falls, balance, mobility and functionality during hospital admission. *The Journal of Nutrition, Health & Aging*, *15*(5), 388-391.

Walker, D., & Beauchene, E., Roy. (1991). The relationship of loneliness, social isolation, and physical health to dietary adequacy of independently living elderly. *Journal of the American Dietetic Association*, *91*(3), 300-304.

Walker, J. G., Mackinnon, A. J., Batterham, P., Jorm, A. F., Hickie, I., McCarthy, A., Fenech, M., & Christensen, H. (2010). Mental health literacy, folic acid and vitamin B12, and physical activity for the prevention of depression in older adults: randomised controlled trial. *The British Journal of Psychiatry*, *197*(1), 45-54.

Walston, J., Hadley, E. C., Ferrucci, L., Guralnik, J. M., Newman, A. B., Studenski, S. A., Ershler, W. B., Harris, T., & Fried, L. P. (2006). Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *Journal of the American Geriatrics Society*, *54*(6), 991-1001.

Wang, G.-Q., Dawsey, S. M., Li, J.-Y., Taylor, P. R., Li, B., Blot, W. J., Weinstein, W. M., Liu, F.-S., Lewin, K. J., & Wang, H. (1994). Effects of vitamin/mineral supplementation on the prevalence of histological dysplasia and early cancer of the esophagus and stomach: results from the General Population Trial in Linxian, China. *Cancer Epidemiology and Prevention Biomarkers*, *3*(2), 161-166.

Wang, L., Song, Y., Manson, J. E., Pilz, S., März, W., Michaëlsson, K., Lundqvist, A., Jassal, S. K., Barrett-Connor, E., & Zhang, C. (2012). Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circulation: Cardiovascular Quality and Outcomes*, *5*(6), 819-829.

Wang, X., Ouyang, Y., Liu, J., Zhu, M., Zhao, G., Bao, W., & Hu, F. B. (2014). Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. *Bmj*, *349*.

Weber, D., & Grune, T. (2012). The contribution of β-carotene to vitamin A supply of humans. *Molecular Nutrition & Food Research*, *56*(2), 251-258.

Weih, M., Wiltfang, J., & Kornhuber, J. (2007). Non-pharmacologic prevention of Alzheimer's disease: nutritional and life-style risk factors. *Journal of Neural Transmission*, *114*(9), 1187-1197.

Wells, J. L., & Dumbrell, A. C. (2006). Nutrition and aging: assessment and treatment of compromised nutritional status in frail elderly patients. *Clinical Interventions in Aging*, *1*(1), 67-79.

Wengreen, H., Munger, R. G., Cutler, A., Quach, A., Bowles, A., Corcoran, C., Tschanz, J. T., Norton, M. C., & Welsh-Bohmer, K. A. (2013). Prospective study of Dietary Approaches to Stop Hypertension–and Mediterranean-style dietary patterns and age-related cognitive change: the Cache County Study on Memory, Health and Aging. *The American Journal of Clinical Nutrition*, *98*(5), 1263-1271.

Weyand, C. M., & Goronzy, J. J. (2021). The immunology of rheumatoid arthritis. *Nature Immunology*, *22*(1), 10-18.

Whitehead, B. R. (2021). COVID-19 as a stressor: pandemic expectations, perceived stress, and negative affect in older adults. *The Journals of Gerontology: Series B*, *76*(2), e59-e64.

Whyte, A. R., Cheng, N., Fromentin, E., & Williams, C. M. (2018). A randomized, double-blinded, placebo-controlled study to compare the safety and efficacy of low dose enhanced wild blueberry powder and wild blueberry extract (ThinkBlue™) in maintenance of episodic and working memory in older adults. *Nutrients*, *10*(6), 660.

Wilkins, C. H., Sheline, Y. I., Roe, C. M., Birge, S. J., & Morris, J. C. (2006). Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *The American Journal of Geriatric Psychiatry*, *14*(12), 1032-1040.

Wilson, J. X. (2005). Regulation of vitamin C transport. *Annu. Rev. Nutr.*, *25*, 105-125.

Winterton, A., Rødevand, L., Westlye, L. T., Steen, N. E., Andreassen, O. A., & Quintana, D. S. (2020). Associations of loneliness and social isolation with cardiovascular and metabolic health: a systematic review and meta-analysis protocol. *Systematic Reviews*, *9*(1), 1-7.

Wohlgemuth, K. J., Arieta, L. R., Brewer, G. J., Hoselton, A. L., Gould, L. M., & Smith-Ryan, A. E. (2021). Sex differences and considerations for female specific nutritional strategies: a narrative review. *Journal of the International Society of Sports Nutrition*, *18*(1), 1-20.

World Health Organization. (2017). *Mental health of older adults* http://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults

Wouters-Wesseling, W., Van Hooijdonk, C., Wagenaar, L., Bindels, J., De Groot, L., & Van Staveren, W. (2003). The effect of a liquid nutrition supplement on body composition and physical functioning in elderly people. *Clinical Nutrition*, *22*(4), 371-377.
Wouters-Wesseling, W., Van Hooijdonk, C., Wagenaar, L., Bindels, J., De Groot, L., & Van Staveren, W. (2003). The effect of a liquid nutrition supplement on body composition and physical functioning in elderly people. *Clinical Nutrition*, *22*(4), 371-377.
Wu, X.-Y., & Lu, L. (2012). Vitamin B6 deficiency, genome instability and cancer. *Asian Pacific Journal of Cancer Prevention*, *13*(11), 5333-5338.

Wu, Y., Zhang, L., Li, S., & Zhang, D. (2022). Associations of dietary vitamin B1, vitamin B2, vitamin B6, and vitamin B12 with the risk of depression: a systematic review and meta-analysis. *Nutrition Reviews*, *80*(3), 351-366.

Yamashima, T., Ota, T., Mizukoshi, E., Nakamura, H., Yamamoto, Y., Kikuchi, M., Yamashita, T., & Kaneko, S. (2020). Intake of ω-6 polyunsaturated fatty acid-rich vegetable oils and risk of lifestyle diseases. *Advances in Nutrition*, *11*(6), 1489-1509.

Yanachkova, V., Staynova, R., Stoev, S., & Naseva, E. (2021). Benefits of using a microencapsulated vitamin D delivery system in women with polycystic ovary syndrome. *European Journal of Hospital Pharmacy*.

Yang, Z., Matteson, E. L., Goronzy, J. J., & Weyand, C. M. (2015). T-cell metabolism in autoimmune disease. *Arthritis Research & Therapy*, *17*(1), 1-10.

Yardley, L., Beyer, N., Hauer, K., Kempen, G., Piot-Ziegler, C., & Todd, C. (2005). Development and initial validation of the Falls Efficacy Scale-International (FES-I). *Age and Ageing*, *34*(6), 614-619.

Yazdanyar, A., & Newman, A. B. (2009). The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. *Clinics in Geriatric Medicine*, *25*(4), 563-577.

Yeom, H. A., Fleury, J., & Keller, C. (2008). Risk factors for mobility limitation in community-dwelling older adults: a social ecological perspective. *Geriatric Nursing*, *29*(2), 133-140.

Yetley, E. A. (2007). Multivitamin and multimineral dietary supplements: definitions, characterization, bioavailability, and drug interactions. *The American Journal of Clinical Nutrition*, *85*(1), 269S-276S.

Yonezawa, K., Kusumoto, Y., Kanchi, N., Kinoshita, H., Kanegae, S., Yamaguchi, N., & Ozawa, H. (2020). Recent trends in mental illness and omega-3 fatty acids. *Journal of Neural Transmission*, *127*(11), 1491-1499.

Young, L. M., Gauci, S., Scholey, A., White, D. J., & Pipingas, A. (2020). Self-selection bias: an essential design consideration for nutrition trials in healthy populations. *Frontiers in Nutrition*, *7*, 587983.

Young, L. M., Pipingas, A., White, D. J., Gauci, S., & Scholey, A. (2019). A systematic review and meta-analysis of B vitamin supplementation on depressive symptoms, anxiety, and stress: Effects on healthy and 'at-risk'individuals. *Nutrients*, *11*(9), 2232.

Yuan, M., Pickering, R. T., Bradlee, M. L., Mustafa, J., Singer, M. R., & Moore, L. L. (2021). Animal protein intake reduces risk of functional impairment and strength loss in older adults. *Clinical Nutrition*, *40*(3), 919-927.

Yuan, S., Mason, A. M., Carter, P., Burgess, S., & Larsson, S. C. (2021). Homocysteine, B vitamins, and cardiovascular disease: a Mendelian randomization study. *BMC Medicine*, *19*(1), 1-9.

Zabransky, D. J., Jaffee, E. M., & Weeraratna, A. T. (2022). Shared genetic and epigenetic changes link aging and cancer. *Trends in Cell Biology*, *32*(4) , 338-350.

Zengarini, E., Ruggiero, C., Pérez-Zepeda, M. U., Hoogendijk, E. O., Vellas, B., Mecocci, P., & Cesari, M. (2015). Fatigue: relevance and implications in the aging population. *Experimental Gerontology*, *70*, 78-83.

Zhang, D.-M., Ye, J.-X., Mu, J.-S., & Cui, X.-P. (2017). Efficacy of vitamin B supplementation on cognition in elderly patients with cognitive-related diseases: a systematic review and meta-analysis. *Journal of Geriatric Psychiatry and Neurology*, *30*(1), 50-59.

Zhang, Y., & Ma, Z. F. (2020). Impact of the COVID-19 pandemic on mental health and quality of life among local residents in Liaoning Province, China: A cross-sectional study. *International Journal of Environmental Research and Public Health*, *17*(7), 2381.

Zhu, L. N., Mei, X., Zhang, Z. G., Xie, Y. p., & Lang, F. (2019). Curcumin intervention for cognitive function in different types of people: A systematic review and meta-analysis. *Phytotherapy Research*, *33*(3), 524-533.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361-370.

Zylberstein, D. E., Lissner, L., Björkelund, C., Mehlig, K., Thelle, D. S., Gustafson, D., Östling, S., Waern, M., Guo, X., & Skoog, I. (2011). Midlife homocysteine and late-life dementia in women. A prospective population study. *Neurobiology of Aging*, *32*(3), 380-386.