Importance of the Caregiver in Lifestyle Interventions for Cognitive Impairment

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Contents

Declaration of Originality

I, the Candidate, Maria Martha Pia Costello, certify that the thesis entitled “Importance of the Caregiver in lifestyle interventions for Cognitive Impairment ":

- is all my own work;
- has not been previously submitted for any degree or qualification at this University or any other institution;
- and where any work in this thesis was conducted in collaboration, appropriate reference to published work by my collaborators has been made and the nature and extent of my contribution has been clearly stated.

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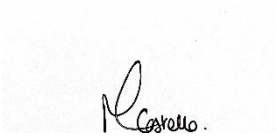

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Maria Martha Pia Costello

Abstract

Lifestyle risk factors have been identified as key targets for dementia prevention strategies, with most clinical trials targeting individual-level interventions. However, many lifestyle behaviours are known to cluster within households (e.g. diet, physical activity), emphasising the need to enhance the role of caregivers (and other members of the household) in the development, evaluation and implementing of interventions for lifestyle risk factor modification.

Beyond the anticipated advantage of improved lifestyle change in patients with cognitive impairment, there may also be potential advantages to caregivers in targeting interventions at the household-level, where there is emerging evidence that certain types of caregiving may be associated with adverse effects on cardiovascular risk factors. The relationship between caregiving and health outcomes is complex, and appears dependent on numerous factors, including the type of caregiving, the needs of the care recipient, intensity of caregiving, support structure and caregiver strain. Some caregivers report little or no strain while others report significant burden and adverse mental and physical health outcomes, often highly prevalent among caregivers of persons with dementia. Therefore, considering the dyadic, or household-based, unit in evaluating interventions for lifestyle risk factors for cognitive decline (and cardiovascular risk) is important.

Employing a number of different methodological and statistical approaches, I report the association of caregiving with cardiovascular risk factors, the association of caregiving and mortality. I report the importance of proxy respondents in observational neurovascular research and quantify the selection bias that may be avoided when proxy respondents are employed in a study of lifestyle risk factors for acute stroke, a condition where many

patients are unable to communicate. In a systematic review, I summarise the evidence for household-level interventions to modify lifestyle risk factors for prevention of cognitive decline. I employ qualitative methodology to explore the attitudes, beliefs and preferences towards lifestyle interventions of household members affected by cognitive impairment. Finally, I discuss the challenges and future opportunity to develop and evaluate novel adaptive clinical trials, which seek to determine the efficacy of household-level interventions to modify lifestyle risk factors, with an emphasis on diet, sleep and physical activity.

The overarching theme of my research thesis is the importance of caregivers, and other members of the household, in developing, evaluating and implementing lifestyle interventions for households with an individual with cognitive impairment.

Acknowledgements

I have been incredibly fortunate to have had the supervision of Professor Martin O'Donnell and Dr Michelle Canavan for this PhD. Thank you both for your support, guidance, and never-ending patience during this process. Both of you have been incredible mentors not only from a research perspective, but throughout my clinical training. I am so fortunate to have worked alongside you both and the passion and skill for patient care and the importance of clinically relevant research is something that continues to inspire me.

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Finally, thank you to my colleagues within the School of Medicine in NUIG, Department of Geriatric Medicine in Galway and Department of Medicine for the Elderly in St James's Hospital, particularly Dr David Robinson who facilitated me in terms of finding time to complete the write up of my thesis.

Dedication

I would like to dedicate this PhD thesis to my husband Marcus and my daughter Margo.

List of Figures

List of Tables

List of Abbreviations

Abbreviation	Definition
3MS	Modified Mini-Mental State
8WT	8 Word Test
aOR	Adjusted Odds Ratio
AARP	American Association of Retired Persons
AD	Alzheimer's Disease
ADLs	Activities of Daily Living
AF	Atrial Fibrillation
AHEI	Alternate Healthy Eating Index
ANOVA	Analysis of Variance
BADS	Behavioural Assessment of Dysexecutive Syndrome
BMI	Body Mass Index
BW	Backwards
CI	Confidence Interval
CON	Control
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
DASH	Dietary Approaches to Stop Hypertension
DM	Diabetes Mellitus
DSM	Diagnostic and Statistical Manual of Mental Disorders
ESKD	End Stage Kidney Disease
FIM	Functional Independence Measure

FU	Follow up
HEI	Healthy Eating Index
HR	Hazard Ratio
HSE	Health Services Executive
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
ICH	Intracerebral Haemorrhage
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Scale
NHS	National Health Service
NIH	National Institute of Health
NR	Not Reported
OCSP	Oxfordshire Community Stroke Project
OR	Odds Ratio
PACI	Partial Anterior Circulation Infarct
PADL	Personal Activities of Daily Living
POCI	Posterior Circulation Infarcts
PPI	Patient and Public Involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSQI	Pittsburgh Sleep Quality Index
PWD	Person with Dementia
RBMT	Rivermead Behavioural Memory Test

RCT	Randomised Controlled Trial
SD	Standard Deviation
SE	Standard Error
SEER	Surveillance, Epidemiology and End Results
TACI	Total Anterior Circulation Infarct
TIA	Transient Ischaemic Attack
UK	United Kingdom
US	United States
WHO	World Health Organisation
WHT	Women's Health Trial
WMS-R	Wechsler Memory Scale Revised
ZBI	Zarit Burden Interview

Chapter 1 Introduction

1.1 Cognitive Impairment: A Condition with a Cascade of Consequences

Cognitive impairment is a broad term referring to difficulty individuals have with cognitive functions such as thinking, reasoning, memory, or attention and can range from mild to severe. There is a spectrum of severity, from subjective memory complaints, to mild cognitive impairment, and then to the clinical syndrome of dementia where impairments in cognition result in impairments in ability to perform activities of daily living. Alzheimer's disease is the most common form of dementia, with other common causes including vascular dementia, frontotemporal dementia, and dementia with Lewy bodies (1). However, there are overlapping features among these subtypes, and mixed forms of dementia are commonly seen clinically.

Globally, it is estimated that over 50 million people are living with dementia, with a projected 10 million new cases annually (2). The prevalence and incidence of dementia worldwide is complex, with the greatest increase in frequency emerging from low- and middle-income countries (3), where the numbers and proportion of older people are rapidly increasing. In contrast, the Cognitive Function and Ageing Studies have demonstrated a reduction in dementia incidence in the United Kingdom which may reflect the impact of investment in public health initiatives on brain health (4). Given the burden of dementia, the absence of clearly effective treatment and complex nature of this condition, developing prevention strategies are of critical importance. With people living longer, cases of dementia will increase exponentially and will place greater burden on individuals, households, communities and health care systems.

1.2 Impact of Dementia on Household Structures and Caregivers

Dementia affects not only the individual but affects the entire family and surrounding social structure. A mandatory diagnostic criteria in establishing a diagnosis of dementia (recently termed major neurocognitive syndrome) is that cognitive deficits impact on social or occupational function (5). Estimating functional impairment in patients with cognitive impairment provides both an estimate of disease severity and meaningful insights into the impact of this condition on the person's household.

Dementia may place significant stress on family members, caregivers and the household. Not only does dementia impact on cognitive function but it can affect emotional control and lead to behavioural issues which can be difficult to manage. Households impacted by cognitive impairment are subject to psychological, physical, and financial stress. Quantifying this impact is difficult due to the unmeasured and underestimated contribution of informal unpaid care being provided within community household settings (6). It is recognised that the impact of this condition extends beyond the individual with dementia, and usually affects the entire household with direct and indirect health consequences for involved household members. The trajectory of caregiving for a person with dementia varies over time, with a typically incremental increase in requirements, and differs from caregiving for patients with other common illnesses (e.g. stroke or malignancy).

One inherent challenge in studies of cognitive and functional impairment is timely and successful recruitment of trial participants (7). Consideration should be given to the role household members and carers have in supporting trial participation. Individuals with cognitive impairment may find it challenging to communicate all details relating to lifestyle habits, medications, medical history, family history and information relating to functional

status. One method to overcome this, is to have family members as a study partner or proxy for the individual with cognitive impairment as proxies have been shown to be reliable for objective parameter measurements e.g. physical activity in those with impaired cognition (8). Incorporating proxy respondents into observational studies can help mitigate the effect of non-response due to cognitive issues, retaining those with more progressive disease states (9). Further exploration is warranted to determine if there are additional benefits to incorporating proxy respondents outside of assisting those with more advanced disease, and to determine if their use can ensure better representation of the population affected by disorders of cognition.

1.3 Association of Caregiving with Health Outcomes

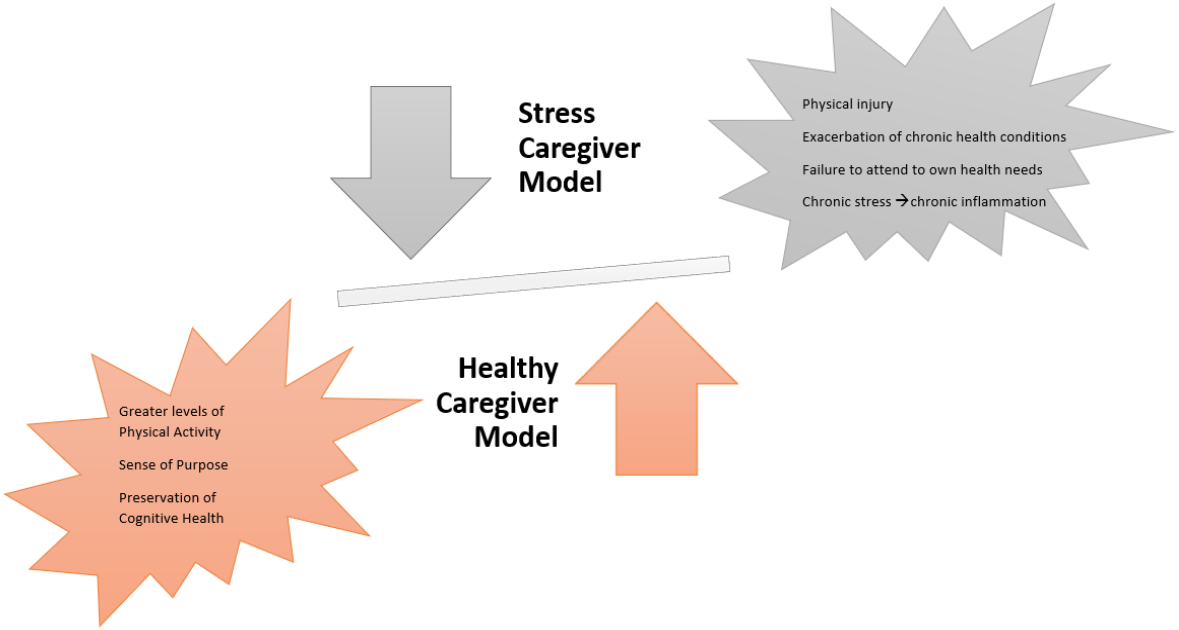
The definition of caregiving for adults varies across the literature with most definitions encompassing that care delivered is unpaid, that there is a pre-existing relationship with the person requiring care (family, friendship) and that assistance is delivered with personal (e.g. bathing, dressing, toileting, eating) or instrumental (e.g. cooking, using public transport, using mobile telephones, housework) activities of daily living (PADLs and IADLs) (10,11). Other definitions that have emerged are the concepts of “primary caregivers” (being most responsible for the care recipient), “secondary caregivers” (provide care in conjunction with and at a similar level to primary caregivers but are not responsible for decision making for the care recipient) and “tertiary caregivers” (complete specific tasks such as gardening, shopping but do not carry any responsibility for making decisions on behalf of the care recipient) (12). Studies have also defined caregiving by living arrangements, relationship type and illness type (13). The term “caregiver burden” is often applied without context of cultural difference and caregiver profile and the spectrum of definitions have made it a

challenging area for systematic review and critical appraisal (14). Some studies have provided breakdown of caregiving by quantity of time (11,15), which may act as a surrogate for strain placed on caregivers with those caregiving for greater durations likely to be delivering a high level of functional support.

Given the spectrum of definitions, there is considerable variation among prevalence of caregiving with US estimates ranging from 2.7 to 36.1 million (16), and European estimates ranging from 8.2% to 43.5% across 20 different countries (17). This variation is reflective of people living longer and differences in detection and access to early diagnostic evaluation. In Ireland, it is estimated there are 180,000 people who are, or previously have been caregivers for persons with dementia (18). These figures do not account for informal caregiving and supports which friends, family and neighbours willingly provide on a regular basis.

There have been conflicting findings in studies exploring the relationship between caregiving and mortality. Some observational studies have reported an association of caregiving with increased mortality, most notably when caregiving for persons with significant functional and behavioural issues (19,20). Other longitudinal studies, however, have demonstrated a reduction in mortality associated with caregiving (21,22) leading to two theoretical models; the stress process model and the healthy caregivers model. This is reflective of the complex relationship between caregiving, health outcomes and mortality with several factors to consider: the level of dependency of the care recipient, the relationship between them and pre-existing health status of the caregiver (Figure 1-1).

Figure 1-1 Theoretical Models of Impact of Caregiving



There have been fewer studies reporting on cause-specific morbidity and mortality among caregivers. One US study demonstrated higher incidence of coronary heart disease among women caregiving for spouses (23), and caregiving has also been associated with increased risk of incident hypertension (24). However, overall to date, the literature demonstrated a lower incidence of deaths due to cardiovascular disease, cancer and cerebrovascular disease among caregivers compared to non-caregivers (25–27). There is a further need to evaluate the association of specific types of caregiving with cause-specific mortality, to identify whether there are interventional opportunities for risk factor modification, in situations where adverse effects on caregiver lifestyle might translate into higher risk of disease (i.e. scenarios where the stress process theory applies).

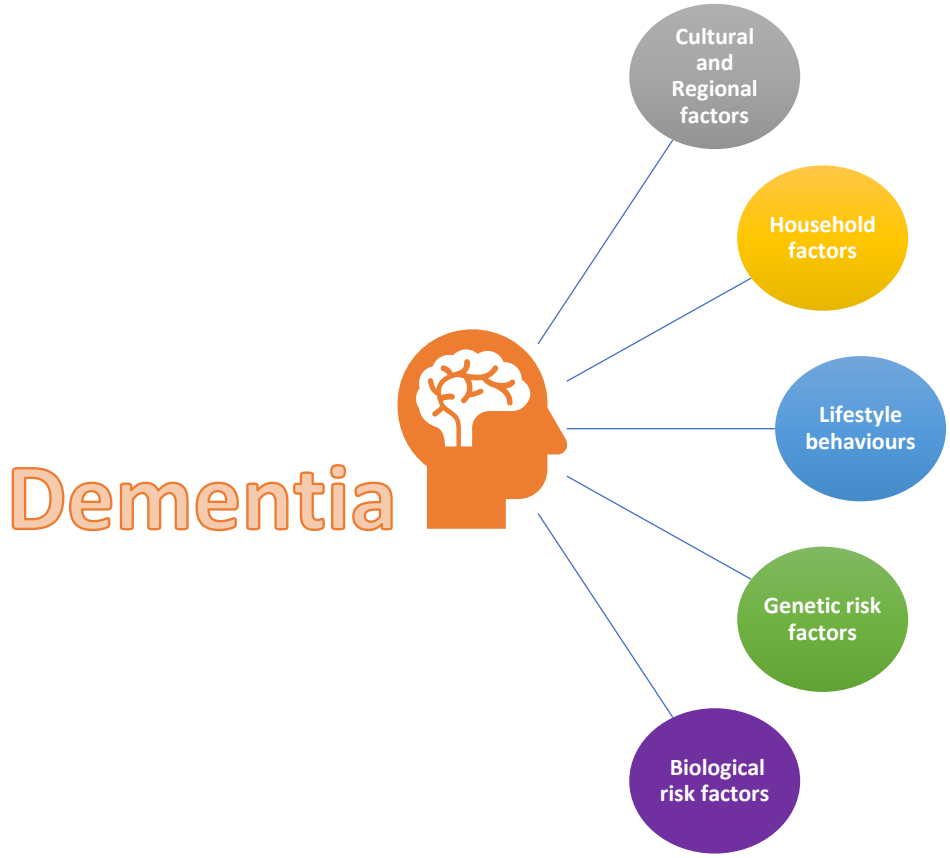
A recently published systematic review outlined the positive and negative impact of informally caring for persons with dementia (28). For some caregivers, they were glad to be able to provide dignity and care to their loved one with dementia, often feeling it is an

essential part of fulfilling their duty as spouse or child. Early diagnosis and early formal support initiation were found to contribute to this positive perspective on caregiving. For others, there was a negative impact including stress, social isolation, uncertainty for the future, financial strain and repercussions for their own personal lives and well-being. The imbalance towards negative impact of caregiving is one that is highlighted consistently throughout the literature. To address the true impact of this, further research is required to investigate how caregiving affects general health status and lifestyle habits and to quantify the possible adverse associations of caregiving on health outcomes. Better understanding this is not only of benefit to the well-being of the caregiver but also to the individual with dementia, to preserve the supports being provided to them.

1.4 Lifestyle Factors and Dementia

To better understand the full contribution of dementia multi-level measurements (Figure 1-2) are required to appropriately address its societal impact.

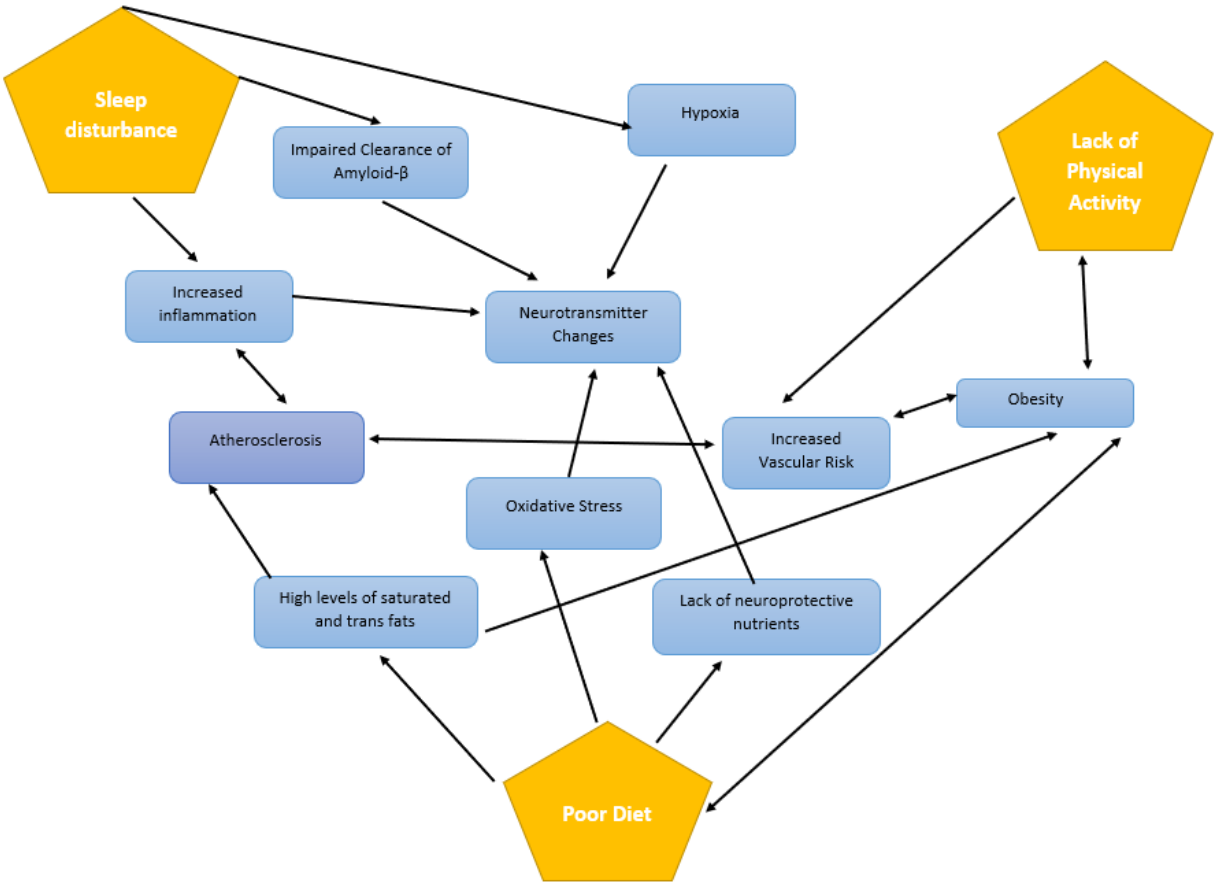
Figure 1-2 Multi-level risk factors for dementia



Modifiable risk factors for dementia have been identified as high-priority targets for prevention of cognitive impairment and decline (29,30) with evidence to support smoking cessation (31) and avoiding high alcohol consumption (32). There is conflicting evidence to support blood pressure lowering, with a recent meta-analysis suggesting treatment of hypertension may be associated with a lower risk of cognitive impairment (33) while a Cochrane review highlighted a lack of evidence to support blood pressure lowering in later life for dementia prevention (34) emphasising the need for dedicated studies to evaluate this further. Among lifestyle factors, diet and physical activity have been recommended as

targets for intervention, however there is less consensus on the optimal diet or exercise routine. Sleep is an additional lifestyle factor of which there is a growing body of evidence of its associated risk with dementia and is similar in complexity to diet and physical activity in terms of measurement, intervention and optimal dose. Each of these lifestyle habits impact cognition through multiple overlapping potential mechanisms (Figure 1-3). As part of this thesis, I have sought to consider these risk factors as potential targets not only for the individual with cognitive impairment but also their caregivers to determine if they would be suitable for household-level intervention. We will consider each of these targets from the perspective of dementia prevention and outline some of the challenges to date in developing appropriate precise guidance for each.

Figure 1-3 Potential mechanisms linking lifestyle habits and dementia in older adults



1.4.1 Diet and Cognitive Impairment

There has been a great interest in diet as a modifiable risk factor for dementia. This can be a challenging area to research with observational studies focusing on specific vitamin and mineral components. Until recently, there has been limited evidence to suggest any form of additional dietary supplements play a role in dementia prevention (35–38). However, the recently published LipiDiDiet clinical trial randomising participants with prodromal Alzheimer's Disease to Fortasyn Connect (Souvenaid) or placebo demonstrated promising improvements in cognition, functional outcomes and cerebral atrophy within the intervention group (39).Beyond this, there is a shift to explore whole dietary patterns. Dietary quality is important to consider as poor nutritional status among older adults has been associated with greater caregiver burden (40). The WHO recommend the Mediterranean diet for dementia prevention although the evidence remains limited with small effect sizes on cognitive performance demonstrated (41). The Mediterranean diet refers to a diet with high consumption of cereals, fruits, vegetables, legumes, tree nuts, seeds and olives, moderate consumption of fish, eggs, poultry, dairy and alcohol and low in consumption of red meat with olive oil as the main source of fat (42). It has been proposed that adhering to this diet may improve cognition through several biological mechanisms including reducing oxidative stress and neuroinflammation, improving metabolic control and minimising incidence of diabetes, hyperlipidaemia and coronary heart disease (43). Alongside the Mediterranean diet, dietary approaches to stop hypertension (DASH) has been identified as a dietary strategy of interest for prevention of cognitive decline, with the beneficial effects thought to be mediated through anti-inflammatory pathways (44). A recent systematic review identified that adherence to such diets in mid-life has promise for neuroprotection in later life (45). Additional dietary factors have shown promise through

antioxidant, and microbiome effects but quantitative assessment has been challenging due to heterogeneity among interventions and outcomes (46). The effect of gut microbiota alterations in particular on cognition is an emerging area of interest with promise shown in animal studies but with little data among human subjects, clinical recommendations at present are inconclusive (47). Buckinx et al. applied the GRADE approach (Grades of Recommendation, Assessment, Development, and Evaluation) to determine recommendations for the preferred diet to prevent or to treat cognitive impairment, and although diet was determined to have an important role, specific guidelines could not be determined from the evidence to date (48). Further randomised controlled trials targeting diet of at-risk populations with sufficient follow-up periods are necessary to truly determine impact on cognition.

There is a complex association between body mass index (BMI) and dementia with the relationship between weight and cognition changing throughout different life stages (49). Mid-life obesity has been associated with increased risk of dementia (50) with the mechanism underpinning this thought to be mediated through impaired vascular and metabolic pathways (51,52). Low BMI, however, may be a marker of neurodegeneration with some studies identifying weight loss as a preclinical marker of dementia (53,54) and suggesting higher BMI in older age may be protective.

BMI is the most commonly used anthropometric tool to estimate body weight and height. There are limitations to its interpretation, particularly among the older population, vulnerable to dementia, as it does not account for body composition (i.e. muscle Vs fat). BMI is not a reliable indicator of undernutrition, sarcopenia or altered distribution of body fat and the its clinical significance should be analysed in the context of functional ability and

co-morbidities in the frail older adult (55). Studies investigating lifestyle risk factors in this cohort should take caution in relying on BMI alone as a marker of optimal nutrition or dietary success.

1.4.2 Physical Activity and Cognitive Impairment

Physical activity has been identified as a key target for maintaining good cognitive function. There is still uncertainty around the optimal dose of physical activity for brain health with lack of clarity on how this is best measured (56). There are several factors to consider when investigating the effect of physical activity on long term cognition including stage of cognitive dysfunction, associated functional impairments, intensity of activity and type of exercise. Physical activity which improves cardiorespiratory fitness levels is thought to be potentially beneficial for prevention of cognitive decline among healthy older adults. This has been a challenging area for comparison given differences in cognitive testing used and there is uncertainty around which specific areas of cognitive function benefit the most (e.g. visuospatial skills, motor function, cognitive speed) (57). The cognitive benefit of physical activity in older adults has been reviewed extensively (58–60), but clear clinical consensus is difficult to determine as many trials are limited in size, have inappropriate control populations, have short follow-up periods and use cognitive measurement tools that may not reflect clinically meaningful change. In a systematic review of randomised clinical trials published in September 2021, Liu et al determined that older adults gain benefit from physical activity interventions in terms of mobility and physical functioning but overall there was no clear evidence of improvement in cognitive functioning (61). Another recent meta-analysis aiming to update the evidence on physical activity interventions and cognition had inconclusive findings with substantial heterogeneity (I^2 = 86%) and publication bias noted

among clinical trials (62). Further research is required not only to determine type and duration of physical activity but also if benefits vary by dementia type.

1.4.3 Sleep and Cognitive Impairment

Interrupted sleep and greater prevalence of sleep disorders are common features of dementia and there is growing evidence that poor sleep may be a risk factor for dementia. There is a U-shaped association with both sleep deprivation and excessive sleep associated with increased risk of mild cognitive impairment and dementia (29). The mechanism for this association remains unclear as it is uncertain if extremes in sleep duration are a risk factor or an early consequence of cognitive impairment. Biologically, shorter sleep durations have been associated with neuronal pathway disruption and amyloid-β accumulation (63) but there have been no similar causal mechanisms identified for longer sleep durations (64). New onset disturbed sleep in older age may be a very early feature of a dementia process and therefore may be a suitable time-point to intervene. Given the harm including increased risk of falls and hospitalisations associated with hypnotics and benzodiazepines often prescribed for sleep disturbance, greater emphasis should be placed on sleep hygiene practices and behavioural interventions. The mechanisms behind the association of sleep and poor cognition are complex and multifactorial. There are several proposed hypotheses. First, insomnia, a common condition among older adults, can cause short term and long term cognitive disruption through immediate impairment of several cognitive domains and having limited important periods of sleep to embed procedural memories (65). Second, the presence of obstructive sleep apnoea (OSA) leads to fragmented, poor quality sleep, chronic intermittent hypoxia and neuroinflammation which may be contributing factors in the neurodegenerative process underpinning many dementias (66). Finally, sleep duration is a target to be considered, with Wu et al demonstrating the lowest incidence of cognitive

disorders among individuals sleeping 7-8 hours a night compared to those reporting shorter or longer durations of sleep (67). Given the bidirectional relationship that exists between sleep and cognition, well designed clinical trials are needed to guide management of disordered sleep for both prevention of dementia and to prevent further decline among those with cognitive impairment.

1.5 Shared Behaviours in Households

Given the estimated contribution of lifestyle behaviours to the risk and progression of dementia, and the impact this condition has on household structures, a logical approach would be to target the household as the unit for intervention for some of the behaviours outlined above. Families shape health at an individual level by not only influencing wellbeing at a genetic level, but at an environmental level (68,69), with members often demonstrating shared behaviours including diet, physical activity and smoking. Despite this, there have been limited studies with households and families as the target unit of randomisation, with most household-level trials in the literature focusing on investigating behavioural change environments for children (70–72). By intervening at household level, it is hypothesised that lifestyle adaptations will be better sustained by changing the overall routine and habitual patterns of families. Although adults influence health behaviours of children, there is uncertainty if this would be reflected in other household types, in particular those who are older who may no longer have children living with them.

Observational studies have demonstrated where targeted health interventions (e.g. diet) for cardiovascular risk have been implemented, spouses of participants, who were not themselves enrolled in the study, changed their lifestyle behaviour suggesting indirect benefits to household members when such interventions are employed by one person

(73,74). Another population based study demonstrated family status had significant influence over self-reported physical and mental health, worse outcomes associated within families who were older, had lower income and lacked availability to insurance (75). Further investigation is needed to determine the feasibility and the effectiveness of lifestyle interventions targeting households with an older age range, where at least one individual has cognitive impairment.

1.6 Caregiver Factors and Care Recipient Mortality

Caregiver burden, with resultant inadequate care provision, has emerged as a significant factor which may mediate care recipient mortality (76–79). These studies have highlighted the complexity of the caregiver-care recipient relationship with caregiver burden potentially increasing as care recipient health declines beyond factors which could be adjusted for within study models. Lack of information on cultural perspectives on caregiving and differences in disease trajectories for the individuals receiving care were limitations to these studies, both important psychosocial factors which may affect self-reporting of burden. With a growing aging population worldwide, and the greater need to rely on informal care, inclusion of caregivers alongside care recipients within targeted research will better identify households most “at risk” and at greatest need of additional supportive structures.

1.7 Overall Objective

My thesis explores the diverse roles household members may play in developing preventative strategies for dementia.

In Chapter 2 and 3, I analyse the NIH-AARP Diet and Health Study (n=288,267 older adults) to explore the association of caregiving with frequency of lifestyle risk factors and mortality. In Chapter 2, I specifically explore whether caregivers have a higher burden of

cardiovascular risk factors, compared to non-caregivers, testing the hypothesis that caregiving might adversely affect lifestyle risk factors. My objective was to determine whether household-level interventions of lifestyle risk factors might be especially relevant to some caregivers, and to specifically identify which risk factors may be most important. In Chapter 3, I evaluate the association of caregiving and mortality within the same cohort and determine whether the association differs among different causes of death (including cardiovascular disease, cancer, and Alzheimer's disease). To date, studies have reported inconsistent findings, and the NIH dataset offers a uniquely large cohort of older adults that collected information on caregiving for adults and children, meaning that we can explore different types, and intensity (by duration), of caregiving on all-cause, and cause-specific mortality. In Chapter 4, I report on the role of proxy respondents in epidemiologic studies of neurological conditions that affect neurocognition, employing the example of stroke, which shares many of the same challenges as research in dementia. In this Chapter, I report on the implications of not using proxy respondents on external validity of research findings and on the regional variations in prevalence and determinants of proxy use. In Chapter 5, I report the results of a systematic review and meta-analysis evaluating household level behavioural interventions to modify lifestyle risk factors (diet, sleep and physical activity) for the prevention of cognitive decline. In Chapter 6, I detail the findings of semi-structured interviews performed among community level households affected by cognitive impairment to determine their beliefs, attitudes and preferences towards clinical trials evaluating interventions to modify lifestyle risk factors within households. In the final chapter, I further expand on the challenges and opportunities for designing household level trials of lifestyle interventions for the prevention of cognitive decline, specifically focusing on the role of adaptive design methods and trial feasibility.

The overarching theme of this work is to determine the role of household level interventions for the prevention of cognitive decline, the benefit that it may confer on household members providing care and to add to the evidence base for future trial methodologies.

Chapter 2

NIH-AARP: Association of Caregiving with Lifestyle Cardiovascular Disease Risk Factors

2.1 Introduction

Caregivers are individuals who provide regular assistance with personal and instrumental activities of daily living (ADLs) to those with functional or cognitive impairment (13). Previous observational studies have suggested that women caregiving for grandchildren and unwell spouses are at higher risk of cardiovascular disease (CVD) compared to non-caregivers (80,81), which may be mediated by an increase prevalence of cardiovascular risk factors, or lower frequency of screening and management of risk factors such as hypertension (82). There are reasons to suspect that caregiving may adversely affect lifestyle risk factors, whereby individuals may be at higher risk of sleep disruption and stress and are less likely to have opportunities for regular physical activity or healthy dietary choices. Higher caregiver strain is associated with increased risk of mortality (19,20,83), so identifying modifiable risk factors within high intensity long term caregivers is an important priority to consider in the overall wellbeing of households impacted by dementia.

The association of caregiving with cardiovascular risk factors has been evaluated in a number of studies of caregivers for individuals with dementia. A recent systematic review reported lower levels of physical activity and social support among caregivers (84). Other studies have reported an association between caregiving and hypertension, poor dietary quality, sleep impairment, smoking and physical inactivity (85–88). A key limitation of those studies is the small sample sizes included, meaning that studies were underpowered to detect association for many risk factors. These studies also included specific caregiver populations (usually high burden caregivers) rather than a population across the spectrum of caregiving. In addition, most studies have not evaluated multiple risk factors simultaneously, although studies have reported a higher mean Framingham score in caregivers of individuals with dementia, compared to non-caregivers (89) supporting an

overall increased in frequency of risk factors, but does not lend insights into the specific burden of individual risk factors, which may be the more relevant interventional targets.

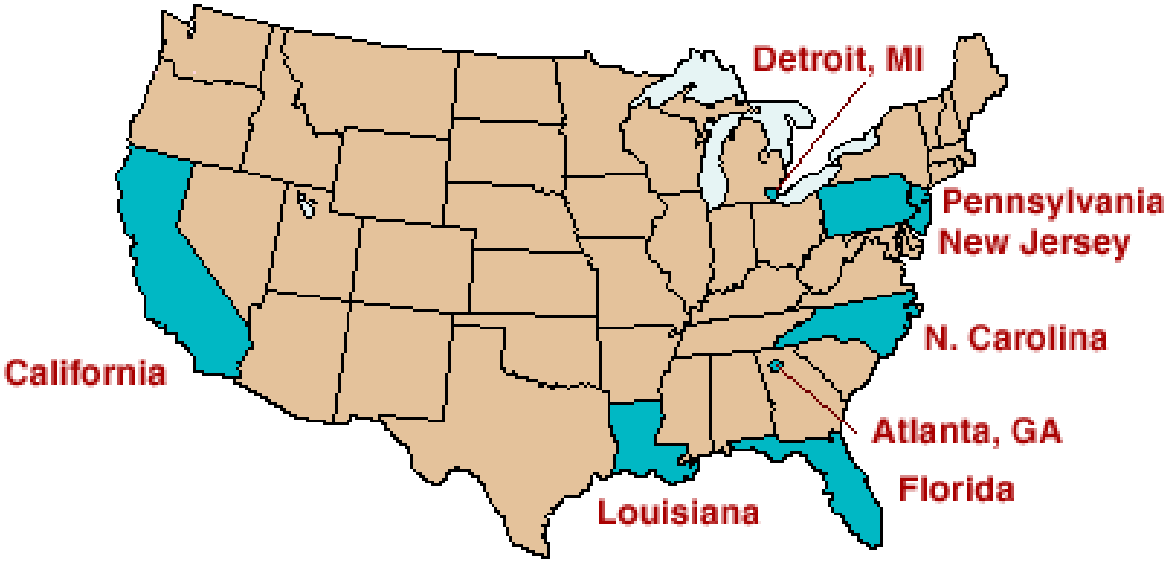
In this study, we evaluated the association of caregiving with prevalence of cardiovascular risk factors, with a particular focus on lifestyle risk factors including diet, physical activity, and sleep. As a large prospective cohort study, the National Institutes of Health American Association of Retired Persons (NIH-AARP) Diet and Health Study provides a unique opportunity to explore lifestyle risk factors and their association with caregiving to further identify new hypotheses for future research targeting caregiver health outcomes.

2.2 Methods

2.2.1 Study Population

This study analysed data from NIH-AARP (90), a prospective study, established primarily to understand the association between diet and cancer. Questionnaires were mailed to current members of the AARP aged 50-69 years, and who resided in one of six states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or in two metropolitan areas (Atlanta, Georgia and Detroit, Michigan) (Figure 2-1). If participants moved out of these states or cities, they were still eligible to participate in the study.

Figure 2-1: Regions included in the NIH-AARP Study



The NIH-AARP had three phases of data collection (Figure 2-2) a baseline questionnaire sent in 1995-1996 (Phase I; completed satisfactorily by 566,398 respondents), a supplementary survey sent in 1996 (Phase II) and a final questionnaire sent to all living participants in 2004 (Phase III). Eligible participants were those who completed information on caregiving of adults and/or children in the final questionnaire. The study was approved by the National Cancer Institute Special Studies Institutional Review Board. We submitted a formal request for data to the NIH-AARP publications committee, with a detailed statistical analysis plan, which was approved in April 2020.

Figure 2-2 Timeline of Data Collection for NIH-AARP Study

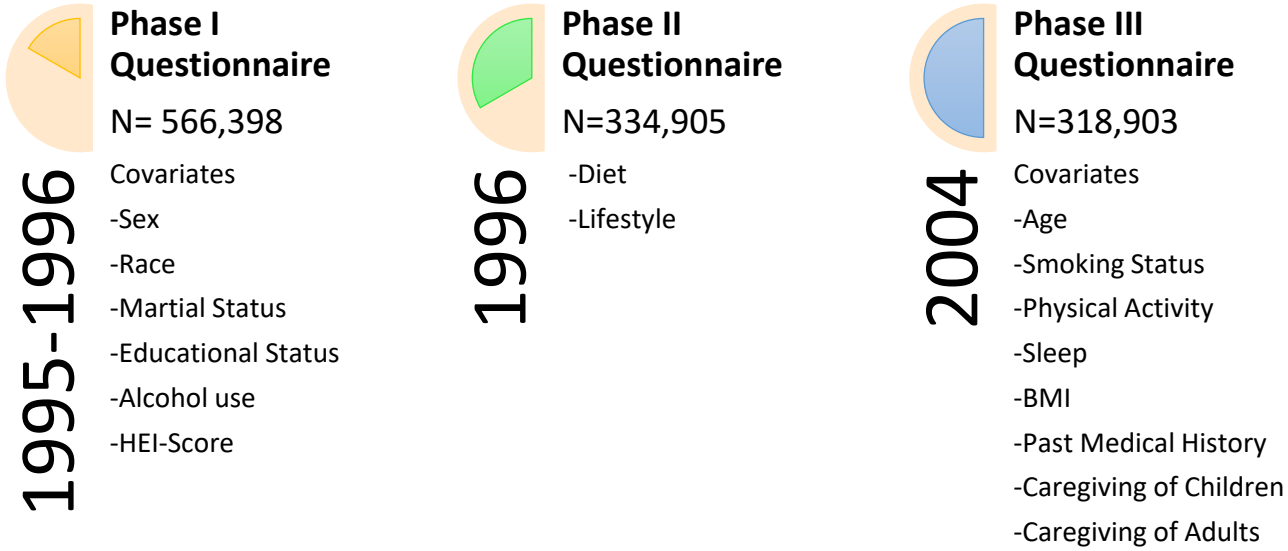


Figure 2-2 This figure represents the timeline of data collection for this prospective cohort study. The number of participants and the covariates collected used in this study are outlined below each questionnaire. The inception cohort for this study was obtained from the Phase III questionnaire in 2004 which collected information on caregiving.

2.2.2 Assessment of Caregiving

Caregiving of adults and children was captured at Phase III data collection and represents the inception cohort for the current analyses. Records were excluded if there was no information on caregiving of adults and/or children. After exclusions, 288,267 participants were included in this analysis.

Caregiving of adults was determined using a question in the Phase III questionnaire asking, “During the past 12 months, approximately how much time per week did you participate in caring for another adult (for example, lifting, pushing a wheelchair, etc.)”. Caregiving of children was determined using a question in the Phase III questionnaire asking, “During the past 12 months, approximately how much time per week did you participate in caring for children (for example, pushing a stroller, playing, lifting, etc.).” Each participant

selected average total time per week spent caregiving adults and children separately. Respondents were grouped into non-caregivers, caregivers of adults and caregivers of children.

2.2.3 Cardiovascular Risk Factor Assessment

The timeline of covariate collection is outlined in Figure 2-2. Along with caregiving status (self-reported), Phase III of data collection recorded information on smoking status, age, Body Mass Index (BMI), hours in a twenty-four-hour period spent sleeping at night or napping, and self-reported medical history including previous history of cardiovascular Disease (CVD), diabetes, hypertension, chronic obstructive pulmonary disease (COPD) and end stage kidney disease (ESKD). Phase III also measured if the participant had trouble with ADLs in the past year due to physical or emotional ill health. Previous history of CVD was defined as a participant ever receiving a diagnosis of myocardial infarction, angina, or coronary disease. Physical Activity was reported using the variable vigorous physical activity. Vigorous physical activity comprised of the sum of the following individual activities; jogging, tennis, swimming, cycling and aerobic exercise measured in hours per week. Participants could select from the following categories: none, 5 minutes, 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2-3 hours, 4-6 hours, 7-10 hours and greater than 10 hours. The World Health Organisation (WHO) and Physical Activity Guidelines for Americans recommend 75 minutes to 150 minutes a week of vigorous-intensity aerobic physical activity for adults (91). For the purpose of this analysis, physical activity was divided into two categories: less 75 minutes per week and greater than or equal to 75 minutes per week. Sleep was reported as time spent per day over past 12 months sleeping at night or napping during the day. Participants could select from the following categories: None, less than 3 hours, 3-4 hours, 5-6 hours, 7-8 hours, 9-10 hours, 11-12 hours and more than 12 hours.

BMI was calculated using height reported in Phase I data collection and the weight specified on Phase III of data collection using the formula weight in kilograms divided by height in meters squared. The smoking variable considered all questions asked about smoking during Phase III of data collection and categorised participants as never smoked, former smoker and current smoker.

Demographics and baseline frequency of risk factors including sex, race, marital status, educational status, alcohol use and diet were measured at Phase I of data collection. Alcohol use was reported as current use of alcohol in the past year, with respondents answering yes or no. A summary estimate of diet quality was reported using the Healthy Eating Index (HEI) score. The HEI score is a measure of adherence to federal diet recommendations, and the score in this study aligns with the 2010 Dietary guidelines for Americans (92). This score comprises of 12 components for a total of 100 points. Six components score up to five points (dark green vegetables, fruit, seafood and total protein and plant protein foods); 5 components score up to ten points (whole and refined grains, low-fat dairy, fatty acids and sodium) and 1 component can score up to twenty points (energy from solid fats, added sugars, and any alcohol in excess of 13 g/1000 kcal). An ideal overall HEI score of 100 reflects that the set of foods aligns with key dietary recommendations where a higher score reflects a healthier diet. For the purpose of this analysis, HEI score was divided into two categories; HEI score less than 50 (poor diet) or HEI score greater than or equal to 50 (good diet) following review on cublic spline. Within the adjustment models, diet was explored as a continuous variable.

2.2.4 Statistical Analyses

Descriptive statistics were used to present baseline demographics and risk factors for caregivers of adults, caregivers of children and non-caregivers. Continuous variables were reported as mean (SD) and compared using linear model Analysis of variance (ANOVA). Categorical variables were reported in proportions and compared using Pearson's Chi-squared test. Unconditional logistic regression analyses were performed to determine the univariate and multivariable association of caregiving with cardiovascular risk factors, generating individual models for each cardiovascular risk factor, including physical activity, smoking, alcohol use, diet and history of hypertension, diabetes, or CVD. For sleep and BMI, where a J-shaped association has been reported with cardiovascular risk, we used multinomial logistic regression to determine the association with caregiving. In each of these models, we estimated the odds ratios (OR) and 95% confidence intervals (95% CI). The fully adjusted model (aOR) adjusted for the following continuous variables; age, vigorous physical activity, diet (HEI score) and body mass index (BMI) and the following categorical variables; race (non-Hispanic white [reference], African American, Hispanic, Asian), sex, smoking (never/former [reference] or current smoker), current alcohol use (within last 12 months), average hours of sleep (≤6 hrs, 7-8 hrs [reference] or ≥9 hours), self-reported history of depression; trouble with activities of daily living (none/slight trouble, significant trouble); quality of life since retirement (better/same, worse); self-reported general health (good/excellent, fair/poor) and self-reported history of diabetes, hypertension, CVD, COPD and ESKD. We completed subgroup analyses by age (< 65 years or ≥65 years), sex, formal education level achieved (educated 0-12 years; those educated between 12 years of age and completing high school; those educated post high school, to college or postgraduate level),

ethnicity (Non-Hispanic white, African American, Hispanic, Asian), among those with and without trouble with ADLs, participants self-reporting history of CVD and stroke and those with no reported history of CVD or stroke. The Wald test was used to test for interaction. All statistical analysis was performed using R version 3.6.3.

2.3 Results

The total cohort (n=288,267) had a mean age of 70.0 (5.4) years, 41.5% (n=119,659) were female, 70% (n=201,913) were married and 92.6% (n=267,040) were non-Hispanic white. Further details of the characteristics of the study population are outlined in Table 2-1. Among the total cohort, 12.2 % (n=35,262) reported being a caregiver of adults, 18.1% (n=52,063) being a caregiver of children, 4.0% (n=11,595) reported being caregiver for both and 69.7% (n=200,942) were non-caregivers. Table 2-2 reports number of participants endorsing caregiving by amount of time spent caregiving per week.

Within the caregiving population, caregivers were more likely to be female, married, black and have completed high school (p-value=<0.001). Figure 2-3 illustrates the proportion of respondents within each group (caregiver of adults, caregiver of children and non-caregivers) by sex, marital status, and race.

2.3.1 Association of Caregiving with Cardiovascular Risk Factors

2.3.1.1 Vigorous Physical Activity

On multivariable analyses, caregiving of adults (aOR 1.30; 95% CI 1.27-1.34) and of children (aOR 1.20; 95% CI 1.17-1.23) were associated with a significantly increased odds of regular vigorous physical activity, compared to no caregiving (Table 2-3). In the analysis by duration of caregiving, any caregiving over 30 minutes per week was associated with a significantly higher odds of vigorous physical activity (Table 2-4, Table 2-5), while caregiving of children

for less than 30 minutes per week was associated with a significantly lower odds of participating in vigorous physical activity (aOR 0.91; 95% CI 0.87-0.95) (Table 2-5).

2.3.1.2 Diet

On multivariable analyses, caregiving of adults was associated with a significantly lower odds of poor diet (HEI score <50, aOR 0.92; 95% CI 0.86-0.99), while caregiving of children was not significantly associated with diet (aOR 0.99, 95% CI 0.93-1.05), compared to non-caregivers (Table 2-3). In an analysis by duration of caregiving, we observed that lower intensity caregiving was significantly associated with a lower odds of unhealthier diets (aOR 0.79; 95% CI 0.67-0.92 for adults and, aOR 0.85; 95% CI 0.76-0.95 for children less than 30 minutes per week) while caregiving for 7 hours or more per week was associated with a higher risk of poor diet among caregivers of adults (aOR 1.16; 95% CI 1.01-1.33) or children (aOR 1.30; 95% CI 1.15-1.46) (Table 2-4, Table 2-5).

2.3.1.3 Sleep Duration

On multivariable analysis, any caregiving was associated with a significantly lower odds of longer sleep duration (≥9 hours per night) (aOR 0.92; 95% CI 0.88-0.96 for adults and aOR 0.91; 95% CI 0.88-0.95 for children) compared to reference of 7-8 hours per night (Table 2-3). Caregiving of adults was associated with a significantly increased odds of short sleep duration (≤6 hours per night) (aOR 1.10; 95% CI 1.07-1.14), with a graded increase in odds by increasing duration of caregiving (aOR 1.41; 95% CI 1.33-1.51 for 7 hours or more caregiving) (Table 2-4). Caregiving of children was associated with a significantly increased odds of short sleep duration for caregiving over 7 hours per week only (aOR 1.08; 95% CI 1.02-1.14) (Table 2-5).

2.3.1.4 Body Mass Index

On multivariable analysis (reference BMI 18.5-24.9), caregiving for adults (aOR 1.09; 95% CI 1.06-1.12) and children (aOR 1.07; 95% CI 1.04-1.10) were associated with a significantly increased odds of being overweight/obese (BMI ≥ 25) (Table 2-3), with a graded increase in odds ratio for increasing duration of caregiving. Caregiving of children was associated with lower odds of being underweight (aOR 0.89; 95% CI 0.80-0.99) (BMI <18.5), while longer duration caregiving of adults (≥ 7 hours per week) was associated with a significantly increased odds of being overweight (aOR 1.17; 95% CI 1.09-1.24) (Table 2-4).

2.3.1.5 Smoking

On multivariable analysis, caregiving of adults (aOR 0.90; 95% CI 0.85-0.96) and caregiving of children (aOR 0.80; 95% CI 0.76-0.84) were associated with a significantly lower overall odds of being a current smoker compared to non-caregivers (Table 2-3). However, longer duration caregiving of adults (≥ 7 hours per week) was significantly associated with higher odds of current smoking (aOR 1.14; 95% CI 1.02-1.28) (Table 2-4).

2.3.1.6 Alcohol Intake

On multivariable analysis, caregiving of adults (aOR 0.86; 95% CI 0.83-0.89) and of children (aOR 0.96; 95% CI 0.94-0.99) compared to no caregiving was less likely to be associated with alcohol use in the past year (Table 2-3) Caregiving of children for seven hours or more per week was associated with a significantly lower odds of alcohol consumption in the past year (aOR 0.79, 95% CI 0.75-0.84), but this association was not maintained among shorter durations of caregiving of children (Table 2-5).

2.3.1.7 Self-reported History of Diabetes

On multivariable analysis, caregiving of adults (aOR 0.93; 95% CI 0.89-0.97) was associated with a significantly lower likelihood of diabetes than no caregiving (Table 2-3).

2.3.1.8 Self-reported History of Hypertension

On multivariable analysis, caregiving of adults (aOR 0.96; 95% CI 0.93-0.99) was associated with a significantly lower likelihood of history of hypertension compared to non-caregivers (Table 2-3).

2.3.1.9 Self-reported History of Cardiovascular Disease

On multivariable analysis, caregiving of adults (aOR 0.95; 95% CI 0.91-0.99) was associated with a lower likelihood of history of cardiovascular disease compared to non-caregivers (Table 2-3). Caregiving of children (aOR 1.05; 95% CI 1.02-1.09) was associated with a greater likelihood of cardiovascular disease compared to non-caregivers (Table 2-3). On analyses based on duration of caregiving, caregiving of children for 2-6 hours per week (aOR 1.08, 95% CI 1.02-1.15) and 7 hours or more per week was associated with a greater likelihood of cardiovascular disease (aOR 1.12, 95% CI 1.04-1.21) (Table 2-5).

2.3.2 Subgroup Analyses

Subgroup analyses were performed based on sleep for six hours or less, overall caregiving and association with demographic factors (Table 2-6). P for interaction were non-significant for sex, age, race and educational status.

Subgroup analyses were performed based on sex, overall caregiving and association with behavioural risk factors (Table 2-7, Table 2-8). Caregiving of adults was associated with increased odds of increased vigorous physical activity and abnormal BMI, while caregiving of

children was associated with increased odds of increased vigorous physical activity (P for interaction <0.05). P for interaction were non-significant for poor diet, sleep, alcohol consumption, smoking and history of hypertension, diabetes and CVD.

2.4 Discussion

In this large US-based cohort of older adults, we report a complex association of caregiving with prevalence of cardiovascular risk factors. While the overall association of self-reported caregiving with vascular risk factors suggested a mostly positive relationship with many healthy lifestyle traits (with the exception of sleep), our findings also revealed that higher duration caregiving of adults was associated with an increased frequency of unhealthy cardiovascular behavioural risk factors. This study adds to the findings of Xu et al (84), which identified that duration of caregiving was a risk factor for CVD, supporting the need to develop and evaluate interventions to optimise cardiovascular risk factors in higher intensity caregivers.

We report a difference in association of caregiving with short sleep duration, among caregiver type and intensity. Short sleep duration, which has been associated with increased cardiovascular risk and mortality (93,94), was not associated with short-duration caregiving. In fact, caregiving of children (<30 minutes per week) was associated with a reduced odds of short sleep duration (Table 2-5). In contrast, longer duration caregiving of both adults (> 2 hours per week) and children (>7 hours per week) was associated with an increased odds of shorter sleep duration, with a graded increased in magnitude of odds ratio with increasing duration of adult caregiving. Reduced sleep duration may be a direct implication of the practical need to provide caregiving at night or in the early morning. An association of shorter sleep duration and caregiving has been reported for caregivers of individuals with

dementia, cancer and patients on dialysis (95–98), and bidirectionally associated with increased stress and mood impairment. A systematic review of previous studies that evaluated the association of caregiving and sleep impairment, reported that sleep impairment affected 50-70% of caregivers of family members with dementia (87) with many reporting adverse effects on sleep quality (e.g. falling asleep, sleep interruption). In some of those studies, sleep impairments were more common in women than men, (96,99–101) which we do not report in our study (P for interaction non-significant, Table 2-6). Our analysis suggests that the association of caregiving and short sleep duration may emerge primarily as an outcome of duration of caregiving and supports the opportunity of further interventional research to improve sleep patterns among caregivers.

The association of caregiving with diet quality also illustrates the contextually dependent association of caregiving with behavioural risk factors, in that lower intensity caregiving was associated with a healthier dietary quality (i.e. higher HEI score), but higher intensity (≥7 hours per week) was associated with a lower diet quality. While these findings support a potentially beneficial aspect of lower intensity caregiving, it identifies dietary quality as a potentially important target for intervention in higher burden caregivers, a finding that is also consistent with previous research studies. In a cross-sectional study by Tana et al, they reported a significant association between poor nutritional status and caregiver burden among 406 caregivers in Italy (40). An analysis of the Caregiving in the Healthy Aging in Neighbourhoods of Diversity across Life Span (HANDLS) study (n=1,945) reported on the cross-sectional and prospective association of diet quality (also measured using the HEI) (86). This study reported improvements in diet quality over time with caregiving for children, but a reduction in diet quality over time for older adult caregiving. Adverse effects on diet may manifest as increases or reductions in BMI, depending on type

of adverse changes of dietary patterns, and we observed an increase in both lower and higher BMI among those with higher intensity caregiving.

Regular physical activity is an important determinant of cardiovascular health, and physical and cognitive functioning. Moreover, it has been identified as potentially important target for caregiver dyads (102). In our study, we observed an overall increase in levels of regular physical activity among caregivers, and suggestion of a graded increase in magnitude of association by duration of time spent caregiving. However, our findings contrast those of longitudinal studies of caregivers with dementia, which report a reduction in physical activity with increased longitudinal exposure to caregiving for a spouse with dementia (103,104). Most likely, the inconsistency in findings, between our study and others, relates to our inability to subclassify caregivers into a specific category of caregivers to individuals with dementia. Taken together, the collective findings suggest a transition in levels of physical activity among caregivers, with initial higher levels (compared to general older adult population), then gradual reduction over time, and as caregiver burden increases there is reduction in regular physical activity.

Within our analyses, we observe that adverse behavioural risk factors may emerge at different stages of increased caregiver exposure and burden, for example we observe the emergence of adverse patterns in diet and sleep behaviours, but not in physical inactivity for caregiving over 7 hours. The mechanisms underpinning these varying associations may differ by risk factors. Increased time spent on caregiving may simply limit the amount of time required to maintain healthy approaches to some behaviours (e.g. physical activity, shopping for healthy foods), while increased caregiver stress might mediate impairments in sleep, dietary patterns, and other behaviours. An example in our analysis of stress-related

behaviours may be smoking, where we observe a 14% increase in odds of current smoking for adult caregivers of 7 hours or more, but a reduced odds among low duration caregiving. Caregiving smoking carries the additional consequence of environmental tobacco smoke exposure to the individual requiring caregiving. The increase may reflect an impaired ability to quit smoking, or re-uptake of prior habit in a stressful situation (88). We did not find an association of caregiving and current alcohol consumption, although increase in problem-drinking behaviours have been reported in studies of high-burden caregivers (105–107), again supporting the contention that the emergence of adverse behaviours may be different for different risk factors.

Consistent with our finding for cardiovascular risk factors, the current literature would suggest that caregiver health outcomes are dependent on caregiver intensity, with caregivers who are emotionally distressed more likely to report negative health outcomes. Accordingly, different definition of 'caregiving' among studies, either by level of care delivered or time spent caregiving, may translate into differing association with adverse health outcomes (108). In this study, caregivers did not self-select to enrol, instead participants were targeted as they were members of the active retirement association. As caregivers were not the primary inception cohort, our findings may be more representative of a broader spectrum of older adult caregiver, albeit poorly classified.

Caregiving of adults overall had a lower association with reported history of hypertension or CVD, but those who participated in higher intensity caregiving duties of children had higher odds of having a history of CVD. This is in contrast to previous findings with in the Nurses' Health Study which identified higher risk of cardiovascular disease among women caregiving for disabled or ill spouse for ≥9 hours per week (81), however,

their study was a prospective cohort study, rather than a cross-sectional study, which may account for the difference in findings.

2.5 Limitations

There are several limitations to this study. First within this study, caregiving was determined using a single question for adults and children rather than using a validated tool. Therefore, we did not have detail on type of caregiving, level of dependence of care recipient and if there were other supports in place to assist the carer. This would provide greater insight into variation in lifestyle behaviours based on intensity of care provided. In addition, we were unable to categorise the burden of exposure of caregiving beyond 10 hours per week and the intensity of care provided across the duration of time spent delivering assistance to the care recipient. Moreover, we are unable to quantify the level of caregiver strain or burn-out. Second, the overall population included in this study were mainly Non-Hispanic white, highly educated, married individuals reflecting the population that may join an active retired association. As a result, the impact of socioeconomic status on lifestyle health behaviours could not be adequately explored and we may not have captured individuals most likely to culturally enter into caregiving roles. As this study required participants to complete and return questionnaires, the population were able and inclined to participate, but as previously mentioned it was not a self-selected caregiving population. Third, it must be noted that many of the variables included may be subject to social desirability bias as the study was dependent on participants self-reporting on behaviours including smoking, alcohol use, diet and physical activity. As this study was questionnaire based, variables such as blood pressure and diabetes were based on history rather than objective ambulatory measurements. Fourth, the recording of BMI was a limitation, given that it was calculated

using height recorded during Phase I and weight recorded during Phase III, and given that this was an older cohort, height may have changed within this time period e.g. in the setting of vertebral fractures. Fifth, some behaviours were measured at different time points to the caregiving variable so it is possible that these behaviours may have undergone change during this time which we did not capture. In particular, diet and alcohol use were recorded in Phase I of the study and were not measured prospectively meaning these behaviours may have changed by Phase III, where caregiving was reported. Many of the behavioural variables were measured 17 years ago (2004), which means our results should be interpreted with caution given lifestyle recommendations and public health initiatives which may have emerged in the interim may have since influenced risk factor prevalence within this cohort.

2.6 Conclusions

Our study reports that low-moderate duration caregiving (less than 30 minutes, 30 minutes-1.5 hours and 2-6 hours) is associated with healthier lifestyle behaviours, compared to non-caregivers. However, our findings also revealed that higher duration caregiving of adults was associated with an increased frequency of unhealthy cardiovascular behavioural risk factors, namely shorter sleep durations, poor diet, increased BMI and smoking. Strategies targeting improved nutrition, weight loss, better sleep and engagement in preventative health screening should be considered for 'at risk' caregiver populations.

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2.8 Sources of Funding

None

2.9 Disclosure of Conflict of Interest

None

Figure 2-3 Breakdown of Sex, Race, Marital Status and Level of Education by Caregiving Type

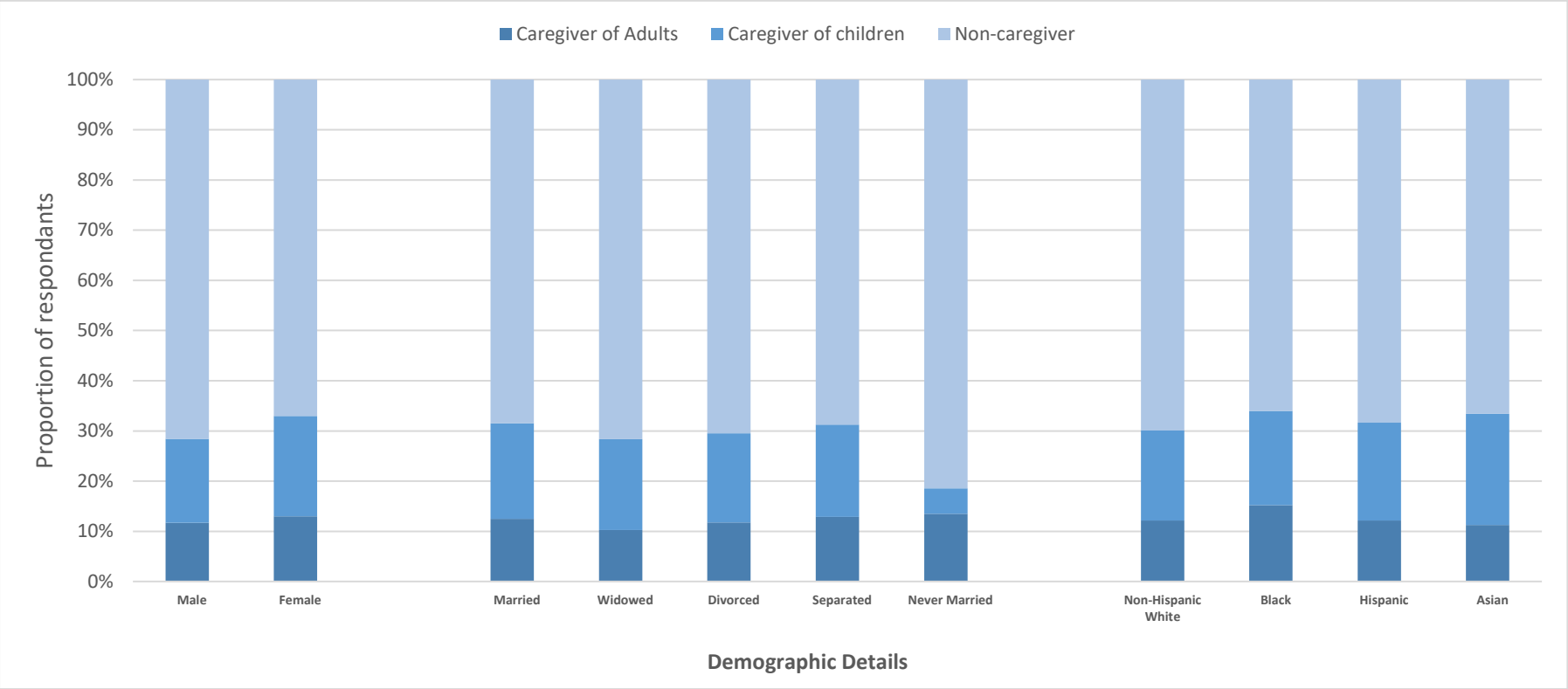

Figure 2-3 reports a stacked column chart of caregiving use by sex, marital status, and race. The dark blue represents use of caregiver of adults, while medium blue represents caregivers of children and the light blue represents non-caregivers. The stacked columns represent proportion of respondents in each category.

Table 2-1 Baseline characteristics in the NIH-AARP Diet and Health study population by caregiving

	Caregiver of Adults (N=35262)	Caregiver of children (N=52063)	Non-caregiver (N=200942)	Total (N=288267)	P value
Age					< 0.001
Mean (SD)	69.6 (5.5)	68.6 (5.1)	70.5 (5.3)	70.0 (5.4)	
Sex					< 0.001
Female	15564 (44.1%)	23884 (45.9%)	80211 (39.9%)	119659 (41.5%)	
Marital Status					< 0.001
Married	25222 (71.5%)	38458 (73.9%)	138233 (68.8%)	201913 (70.0%)	
Widowed	2998 (8.5%)	5278 (10.1%)	20894 (10.4%)	29170 (10.1%)	
Separated/Divorced	4870 (13.8%)	7303 (14.0%)	28876 (14.4%)	41059 (14.3%)	
Never Married	1942 (5.5%)	730 (1.4%)	11708 (5.8%)	14380 (5.0%)	
Race					< 0.001
Non-Hispanic White	32401 (91.9%)	47936 (92.1%)	186703 (92.9%)	267040 (92.6%)	
Black	1433 (4.1%)	1771 (3.4%)	6218 (3.1%)	9422 (3.3%)	
Hispanic	560 (1.6%)	895 (1.7%)	3144 (1.6%)	4599 (1.6%)	
Asian	481 (1.4%)	947 (1.8%)	2845 (1.4%)	4273 (1.5%)	
Educational Status					< 0.001

Less than 8 years	1344 (3.8%)	1857 (3.6%)	8930 (4.4%)	12131 (4.2%)	
8-11 years	5787 (16.4%)	9016 (17.3%)	35488 (17.7%)	50291 (17.4%)	
12 years or completed high school	3713 (10.5%)	4800 (9.2%)	18648 (9.3%)	27161 (9.4%)	
Post-high school, College and postgraduate	23574 (66.9%)	35313 (67.8%)	133294 (66.4%)	192181 (66.7%)	
Smoking Status					< 0.001
Never	13839 (39.2%)	21203 (40.7%)	71197 (35.4%)	106239 (36.9%)	
Former	16339 (46.3%)	23743 (45.6%)	99136 (49.3%)	139218 (48.3%)	
Current	1930 (5.5%)	2725 (5.2%)	11745 (5.8%)	16400 (5.7%)	
Use of alcohol in last year (measured at Phase I)					< 0.001
Yes	26824 (76.4%)	40671 (78.4%)	157510 (78.7%)	225005 (78.4%)	
BMI					< 0.001
Underweight	442 (1.4%)	578 (1.3%)	2914 (1.7%)	3934 (1.6%)	
Healthy Weight	10126 (32.8%)	14827 (33.0%)	60813 (34.7%)	85766 (34.1%)	
Overweight	12711 (41.2%)	18714 (41.6%)	71486 (40.8%)	102911 (41.0%)	
Obese	7560 (24.5%)	10842 (24.2%)	40143 (22.9%)	58545(23.4%)	
HEI 2010 Score					< 0.001
HEI <40	105 (0.3%)	201 (0.4%)	720 (0.4%)	1026 (0.4%)	

HEI 40-59	6535 (18.5%)	9844 (18.9%)	37889 (18.9%)	54268 (18.8%)	
HEI 60-79	25491 (72.3%)	37582 (72.2%)	143635 (71.5%)	206708 (71.7%)	
HEI ≥80	3131 (8.9%)	4436 (8.5%)	18698 (9.3%)	26265 (9.1%)	
Vigorous Physical activity					< 0.001
<75mins per week	18208 (51.7%)	27437 (52.7%)	116437 (58.0%)	162082 (56.2%)	
≥75 mins per week	17032 (48.3%)	24619 (47.3%)	84481 (42.0%)	126132 (43.8%)	
Sleep*					< 0.001
≤ 6 hours	9884 (30.8%)	13352 (28.5%)	51648 (28.2%)	74884 (28.6%)	
7-8 hours	18325 (57.1%)	28073 (60.0%)	106518 (58.1%)	152916 (58.4%)	
≥ 9 hours	3874 (12.1%)	5371 (11.5%)	25021 (13.7%)	34266 (13.1%)	
History of Diabetes					< 0.001
Yes	5291 (15.0%)	7648 (14.7%)	32528 (16.2%)	45467 (15.8%)	
History of CVD					< 0.001
Yes	6050 (17.2%)	8660 (16.6%)	38374 (19.1%)	53084 (18.4%)	
History of Hypertension					< 0.001
Yes	18709 (53.1%)	27293 (52.4%)	109651 (54.6%)	155653 (54.0%)	
History of COPD					< 0.001
Yes	2857 (8.1%)	3876 (7.4%)	16670 (8.3%)	23403 (8.1%)	

History of ESKD					< 0.001
Yes	122 (0.3%)	217 (0.4%)	939 (0.5%)	1278 (0.4%)	
History of Depression					< 0.001
Yes	5431 (15.4%)	6849 (13.2%)	26145 (13.0%)	38425 (13.3%)	
Trouble with ADLS					< 0.001
None/Slight amount	24293 (68.9%)	37298 (71.6%)	138213 (68.8%)	199804 (69.3%)	
Moderate amount	5601 (15.9%)	6948 (13.3%)	28813 (14.3%)	41362 (14.3%)	
Quite a bit/Enormous amount	3088 (8.8%)	4058 (7.8%)	21111 (10.5%)	28257 (9.8%)	

Data are n (%) or mean (SD).
BMI= Body Mass Index; CVD= Cardiovascular disease; ADL = Activities of Daily Living, HEI: Healthy Eating Index; COPD = Chronic Obstructive Pulmonary Disease; ESKD= End Stage Kidney Disease
*Reported time spent sleeping or napping in a 24 hour period
Data were missing in 1745 for marital status; 2933 for race; 6503 for educational status; 26410 for smoking status; 1256 for alcohol use; 37111 for BMI; 53 for vigorous physical activity; 26201 for Sleep; 24302 for diabetes; 18999 for history of CVD; 12086 for hypertension; 23495 for ESKD, 24003 for COPD, 23565 for depression; 18844 for Trouble with ADLs.

Table 2-2 Caregiving of adults and children by time spent each week

	Number of participants endorsing caregiving of adults by time per week										
	HRS/WEEK	**0 hrs**	**5mins**	**15mins**	**30mins**	**1hr**	**1.5hrs**	**2-3hrs**	**4-6hrs**	**7-10hrs**	**More than 10hrs**
Number of participants endorsing caregiving of Children by time per week	**0hrs**	200942 (69.71%)	3799 (1.32%)	6795 (2.36%)	8795 (3.05%)	9469 (3.28%)	3689 (1.28%)	7420 (2.57%)	4282 (1.49%)	2493 (0.86%)	5321 (1.85%)
	5mins	1750 (0.61%)	493 (0.17%)	343 (0.12%)	237 (0.08%)	144 (0.05%)	39 (0.01%)	74 (0.03%)	42 (0.01%)	15 (0.01%)	38 (0.01%)
	15mins	3113 (1.08%)	216 (0.07%)	488 (0.17%)	380 (0.13%)	260 (0.09%)	92 (0.03%)	140 (0.05%)	67 (0.02%)	30 (0.01%)	79 (0.03%)
	30mins	3674 (1.27%)	127 (0.04%)	264 (0.09%)	490 (0.17%)	389 (0.13%)	155 (0.05%)	198 (0.07%)	118 (0.04%)	57 (0.02%)	106 (0.04%)
	1hr	3880 (1.35%)	74 (0.03%)	162 (0.06%)	283 (0.10%)	478 (0.17%)	155 (0.05%)	260 (0.09%)	135 (0.05%)	74 (0.03%)	170 (0.06%)
	1.5hrs	1627 (0.56%)	36 (0.01%)	75 (0.03%)	127 (0.04%)	152 (0.05%)	108 (0.04%)	121 (0.04%)	54 (0.02%)	39 (0.01%)	56 (0.02%)
	2-3hrs	2908 (1.01%)	52 (0.02%)	115 (0.04%)	164 (0.06%)	260 (0.09%)	124 (0.04%)	266 (0.09%)	127 (0.04%)	66 (0.02%)	123 (0.04%)
	4-6hrs	1792 (0.62%)	20 (0.01%)	51 (0.02%)	91 (0.03%)	115 (0.04%)	47 (0.02%)	142 (0.05%)	96 (0.03%)	51 (0.02%)	109 (0.04%)
	7-10hrs	1126 (0.39%)	14 (0.004%)	35 (0.01%)	46 (0.02%)	73 (0.03%)	36 (0.01%)	74 (0.03%)	51 (0.02%)	55 (0.02%)	86 (0.03%)
	More than 10hrs	3797 (1.32%)	40 (0.01%)	93 (0.03%)	132 (0.05%)	219 (0.08%)	91 (0.03%)	210 (0.07%)	134 (0.05%)	102 (0.04%)	445 (0.15%)

Table 2-3 Overall caregiving and association with behavioural risk factors

Type of Caregiving	N	Vigorous physical Activity	Poor Diet (HEI Score <50)	Sleep [c]		BMI [d]:		Current Smoker	Alcohol (Current)*	History of Diabetes	History of Hypertension	History of Cardiovascular Disease
				≤6hrs	≥9hrs	<18.5 kg/m2	≥25 kg/m2[f]					
Model 1												
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Non-caregiving	154,503	1	1	1	1	1	1	1	1	1	1	1
Caregiving Adults	27,471	**1.28 (1.25-1.32)**	0.94 (0.88-1.01)	**1.12 (1.09-1.16)**	**0.89 (0.85-0.93)**	0.93 (0.83-1.05)	**1.08 (1.05-1.11)**	**0.93 (0.88-0.98)**	**0.87 (0.84-0.90)**	**0.90 (0.87-0.94)**	**0.94 (0.92-0.97)**	**0.88 (0.85-0.91)**
Caregiving Children	41,061	**1.22 (1.20-1.25)**	0.99 (0.94-1.05)	0.99 (0.97-1.02)	**0.82 (0.79-0.85)**	**0.84 (0.76-0.93)**	**1.07 (1.04-1.10)**	**0.88 (0.84-0.92)**	0.97 (0.95-1.00)	**0.89 (0.86-0.92)**	**0.91 (0.89-0.93)**	**0.84 (0.81-0.86)**
Model 2												
Non-caregivers	154,503	1	1	1	1	1	1	1	1	1	1	1
Caregiving Adults	27,471	**1.30 (1.27-1.34)**	**0.92 (0.86-0.99)**	**1.10 (1.07-1.14)**	**0.92 (0.88-0.96)**	0.94 (0.83-1.06)	**1.09 (1.06-1.12)**	**0.90 (0.85-0.96)**	**0.86 (0.83-0.89)**	**0.93 (0.89-0.97)**	**0.96 (0.93-0.99)**	**0.95 (0.91-0.99)**
Caregiving Children	41,061	**1.20 (1.17-1.23)**	0.99 (0.93-1.05)	0.98 (0.96-1.02)	**0.91 (0.88-0.95)**	**0.89 (0.80-0.99)**	**1.07 (1.04-1.10)**	**0.80 (0.76-0.84)**	**0.96 (0.94-0.99)**	0.97 (0.93-1.00)	0.99 (0.96-1.01)	**1.05 (1.02-1.09)**

[a] Model 1 Univariate
[b] Model 2 adjusting for age, race, sex, diet, smoking, alcohol, sleep, BMI, physical activity; history of Diabetes, Hypertension, Cardiovascular disease, Chronic obstructive pulmonary disease, End stage renal disease, , depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health
[c] Reference category 7-8 hours of sleep; [d] Reference category 18.5 - 24.9 kg/m2
[e] Underweight = BMI <18.5 kg/m2
[f] Overweight = BMI ≥25 kg/m2
*Current defined as use in the past year.
BMI= Body Mass Index; HEI= Healthy Eating Index; OR = odds ratio, CI = Confidence Interval

Table 2-4 Association between time spent caregiving of adults and lifestyle behavioural risk factors

Time caregiving for Adults per week	N	Vigorous physical Activity	Poor Diet (HEI Score <50)	Sleep [b]		BMI [c]		Current Smoker	Alcohol (Current)*	History of Diabetes	History of Hypertension	History of CVD
				≤6hrs	≥9hrs	Underweight [d]	Overweight-Obese [e]					
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
0 hrs	195564	1	1	1	1	1	1	1	1	1	1	1
Less than 30mins	6359	0.97 (0.92-1.03)	**0.79 (0.67-0.92)**	0.97 (0.91-1.04)	0.98 (0.90-1.07)	0.96 (0.76-1.23)	0.98 (0.93-1.05)	**0.69 (0.60-0.79)**	0.99 (0.92-1.06)	0.96 (0.89-1.04)	**0.93 (0.88-0.99)**	0.95 (0.88-1.03)
30mins-1.5hrs	10625	**1.35 (1.29-1.41)**	**0.86 (0.77-0.97)**	1.04 (0.99-1.09)	**0.93 (0.87-0.99)**	0.91 (0.76-1.10)	**1.08 (1.03-1.13)**	0.98 (0.90-1.07)	**0.87 (0.83-0.91)**	**0.89 (0.83-0.95)**	0.98 (0.94-1.03)	**0.93 (0.87-0.98)**
2-6hrs	5179	**1.40 (1.32-1.49)**	0.97 (0.83-1.13)	**1.11 (1.03-1.18)**	**0.84 (0.76-0.93)**	**0.76 (0.74-0.79)**	**1.11 (1.03-1.18)**	0.99 (0.87-1.12)	**0.86 (0.81-0.93)**	1.02 (0.94-1.11)	0.96 (0.90-1.02)	0.96 (0.88-1.04)
≥7 hrs	5308	**1.31 (1.24-1.40)**	**1.16 (1.01-1.33)**	**1.41 (1.33-1.51)**	1.02 (0.92-1.11)	1.23 (0.99-1.54)	**1.17 (1.09-1.24)**	**1.14 (1.02-1.28)**	**0.77 (0.72-0.82)**	0.92 (0.85-1.01)	0.98 (0.92-1.04)	0.92 (0.85-1.01)

[a] Multivariable Model adjusting for age, race, sex, diet, smoking, alcohol, sleep, BMI, physical activity; history of Diabetes, Hypertension, Cardiovascular disease, Chronic obstructive pulmonary disease, End stage renal disease, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health

[b] Reference category 7-8 hours of sleep

[c] Reference category 18.5 - 24.9 kg/m2

[d] Underweight = BMI <18.5 kg/m2

[e] Overweight = BMI ≥25 kg/m2

*Current defined as use in the past year.

BMI= Body Mass Index; HEI= Healthy Eating Index; OR = odds ratio; CI = Confidence Interval; hrs= hours; CVD= Cardiovascular Disease

Table 2-5 Association between time spent caregiving of children and lifestyle behavioural risk factors

Time caregiving for Children per week	N	Vigorous physical Activity	Poor Diet (HEI Score <50)	Sleep [b]		BMI [c]		Current Smoker	Alcohol (Current)*	History of Diabetes	History of Hypertension	History of CVD
				≤6hrs	≥9hrs	Underweight [d]	Overweight-Obese [e]					
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
0 hrs	172961	1	1	1	1	1	1	1	1	1	1	1
Less than 30mins	10471	**0.91 (0.87-0.95)**	**0.85 (0.76-0.95)**	**0.92 (0.87-0.96)**	1.01 (0.94-1.07)	0.85 (0.69-1.04)	0.98 (0.93-1.02)	**0.63 (0.56-0.70)**	1.01 (0.96-1.07)	**0.88 (0.82-0.94)**	**0.95 (0.90-0.99)**	1.00 (0.94-1.06)
30mins-1.5hrs	21123	**1.33 (1.28-1.37)**	0.98 (0.91-1.07)	1.00 (0.97-1.04)	**0.88 (0.85-0.94)**	**0.81 (0.70-0.94)**	**1.07 (1.04-1.11)**	**0.86 (0.80-0.91)**	0.99 (0.95-1.03)	1.00 (0.96-1.05)	0.97 (0.94-1.00)	1.03 (0.99-1.08)
2-6hrs	11031	**1.48 (1.41-1.54)**	1.07 (0.96-1.18)	1.02 (0.97-1.07)	**0.89 (0.83-0.95)**	0.95 (0.79-1.13)	**1.09 (1.04-1.14)**	**0.80 (0.73-0.88)**	0.96 (0.91-1.01)	0.96 (0.90-1.02)	1.00 (0.96-1.05)	**1.08 (1.02-1.15)**
≥7 hrs	7449	**1.47 (1.40-1.55)**	**1.30 (1.15-1.46)**	**1.08 (1.02-1.14)**	1.04 (0.95-1.13)	0.86 (0.69-1.07)	**1.21 (1.14-1.28)**	0.90 (0.81-1.00)	**0.79 (0.75-0.84)**	1.01 (0.93-1.09)	1.01 (0.95-1.06)	**1.12 (1.04-1.21)**

[a] Multivariable Model adjusting for age, race, sex, diet, smoking, alcohol, sleep, BMI, physical activity; history of Diabetes, Hypertension, Cardiovascular disease, Chronic obstructive pulmonary disease, End stage renal disease, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health

[b] Reference category 7-8 hours of sleep

[c] Reference category 18.5 - 24.9 kg/m2

[d] Underweight = BMI <18.5 kg/m2

[e] Overweight = BMI ≥25 kg/m2

*Current defined as use in the past year.

BMI= Body Mass Index; HEI= Healthy Eating Index; OR = odds ratio; CI = Confidence Interval; hrs= hours; CVD= Cardiovascular Disease

Table 2-6 Sub analysis of sleep less than six hours among different demographic populations of caregivers

Sub-Population Reporting sleeping six hours or less	Analytic Model	Non-Caregivers (Reference)	Participants Reporting Caregiving of Adults OR (95% CI)	P for Interaction
Male	Model 1	1.0	1.10 (1.05-1.15)	0.23
	Model 2	1.0	1.10 (1.05-1.15)	0.34
Female	Model 1	1.0	1.13 (1.08-1.18)	0.23
	Model 2	1.0	1.13 (1.08-1.18)	0.36
<65yrs of age	Model 1	1.0	1.15 (1.08-1.22)	0.96
	Model 2	1.0	1.13 (1.05-1.20)	0.74
≥65yrs of age	Model 1	1.0	1.11 (1.07-1.15)	0.96
	Model 2	1.0	1.10 (1.06-1.14)	0.74
Level of Education confined to age of 0-12 years	Model 1	1.0	1.08 (1.01-1.15)	0.49
	Model 2	1.0	1.08 (1.01-1.15)	0.42
Secondary Level Education	Model 1	1.0	1.11 (1.01-1.21)	0.49
	Model 2	1.0	1.08 (0.98-1.19)	0.42
Post high school education	Model 1	1.0	1.16 (1.10-1.21)	0.49
	Model 2	1.0	1.13 (1.08-1.19)	0.42
Non-Hispanic White	Model 1	1.0	1.12 (1.08-1.15)	0.49
	Model 2	1.0	1.10 (1.07-1.14)	0.43
Black	Model 1	1.0	1.11 (0.95-1.29)	0.49
	Model 2	1.0	1.15 (0.98-1.35)	0.43
Hispanic	Model 1	1.0	1.14 (0.90-1.43)	0.49
	Model 2	1.0	1.18 (0.92-1.51)	0.43

Asian	Model 1	1.0	1.40 (1.10-1.79)	0.49
	Model 2	1.0	1.33 (1.03-1.72)	0.43
Participants with trouble with ADLS	Model 1	1.0	1.08 (1.02-1.15)	0.99
	Model 2	1.0	1.07 (1.00-1.13)	0.99
Participants with history of CVD	Model 1	1.0	1.11 (1.03-1.19)	0.61
	Model 2	1.0	1.11 (1.03-1.20)	0.71
Participants with history of Stroke	Model 1	1.0	1.18 (0.99-1.40)	0.23
	Model 2	1.0	1.20 (1.00-1.43)	0.92

Model 1 Univariate
Model 2 Adjusting for age, race, sex, diet, smoking, alcohol, sleep, BMI, physical activity; history of Diabetes, Hypertension, Cardiovascular disease, Chronic obstructive pulmonary disease, End stage renal disease, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health
ADL = Activities of Daily living; CVD = Cardiovascular Disease; BMI = Body Mass Index; OR = odds ratio; CI = Confidence Interval

Table 2-7 Sex difference, adult caregiving and association with behavioural risk factors

Outcome	Model	Non-caregivers (Reference)	Caregiver (Men)	Caregiver (Women)	P For interaction
		Male N=93006 Female N=61497	N=15305	N=12166	
			OR (95% CI)	OR (95% CI)	
Vigorous physical Activity	Model 1	1.0	1.34 (1.30-1.39)	1.26 (1.21-1.31)	0.004
	Model 2	1.0	1.36 (1.31-1.41)	1.23 (1.17-1.28)	<0.001
Diet	Model 1	1.0	1.01 (0.93-1.09)	0.87 (0.77-0.97)	0.35
	Model 2	1.0	0.97 (0.88-1.06)	0.86 (0.75-0.97)	0.11
Sleep ≤6hrs	Model 1	1.0	1.10 (1.05-1.15)	1.13 (1.08-1.18)	0.98
	Model 2	1.0	1.09 (1.05-1.15)	1.13 (1.08-1.18)	0.53
Sleep ≥9hrs	Model 1	1.0	0.93 (0.89-0.99)	0.84 (0.78-0.90)	0.98
	Model 2	1.0	0.95 (0.90-1.00)	0.87 (0.80-0.93)	0.53
BMI: Underweight	Model 1	1.0	0.91 (0.75-1.10)	0.91 (0.78-1.05)	0.003
	Model 2	1.0	0.96 (0.79-1.16)	0.94 (0.81-1.09)	0.05
BMI: Overweight-Obese	Model 1	1.0	1.07 (1.02-1.11)	1.14 (1.09-1.19)	0.003
	Model 2	1.0	1.07 (1.03-1.12)	1.15 (1.09-1.20)	0.05
Current smoker	Model 1	1.0	0.87 (0.80-0.94)	0.95 (0.88-1.02)	0.23
	Model 2	1.0	0.88 (0.81-0.96)	0.93 (0.85-1.01)	0.01
Alcohol use in the past year	Model 1	1.0	0.84 (0.80-0.87)	0.94 (0.90-0.99)	0.16
	Model 2	1.0	0.83 (0.79-0.87)	0.88 (0.84-0.93)	0.73
History of Diabetes	Model 1	1.0	0.96 (0.92-1.00)	0.85 (0.80-0.90)	0.32
	Model 2	1.0	0.95 (0.90-1.00)	0.91 (0.85-0.97)	0.89
History of Hypertension	Model 1	1.0	0.97 (0.93-1.00)	0.93 (0.89-0.96)	0.06
	Model 2	1.0	0.97 (0.93-1.01)	0.97 (0.93-1.01)	0.19
History of Cardiovascular Disease	Model 1	1.0	0.93 (0.89-0.96)	0.87 (0.82-0.93)	0.09
	Model 2	1.0	0.92 (0.88-0.97)	1.03 (0.96-1.11)	0.46

Model 1 Univariate
Model 2 adjusting for age, race, sex, diet, smoking, alcohol, sleep, BMI, physical activity; history of Diabetes, Hypertension, Cardiovascular disease, Chronic obstructive pulmonary disease, End stage renal disease, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health
BMI = Body Mass Index; Underweight = BMI <18.5 kg/m2; Overweight = BMI ≥25 kg/m2
OR = Odds Ratio; CI = Confidence Interval

Table 2-8: Sex difference, child caregiving and association with behavioural risk factors

Outcome	Model	Non-caregivers (Reference)	Caregiver (Men)	Caregiver (Women)	P For interaction
		Male N=93006 Female N=61497	N=22165	N=18896	
			OR (95% CI)	OR (95% CI)	
Vigorous physical Activity	Model 1	1.0	1.32 (1.28-1.36)	1.18 (1.14-1.22)	<0.001
	Model 2	1.0	1.26 (1.22-1.30)	1.12 (1.08-1.16)	<0.001
Diet	Model 1	1.0	1.02 (0.95-1.10)	0.99 (0.90-1.09)	0.30
	Model 2	1.0	0.98 (0.91-1.06)	1.00 (0.90-1.10)	0.09
Sleep ≤6hrs	Model 1	1.0	1.00 (0.96-1.04)	0.96 (0.92-1.00)	0.07
	Model 2	1.0	0.99 (0.96-1.03)	0.99 (0.95-1.03)	0.13
Sleep ≥9hrs	Model 1	1.0	0.83 (0.80-0.88)	0.81 (0.77-0.86)	0.07
	Model 2	1.0	0.94 (0.89-0.99)	0.87 (0.83-0.93)	0.13
BMI: Underweight	Model 1	1.0	0.92 (0.78-1.09)	0.75 (0.65-0.85)	0.31
	Model 2	1.0	1.01 (0.86-1.19)	0.82 (0.72-0.94)	0.09
BMI: Overweight-Obese	Model 1	1.0	1.11 (1.07-1.15)	1.09 (1.05-1.13)	0.31
	Model 2	1.0	1.06 (1.02-1.10)	1.09 (1.05-1.13)	0.09
Current smoker	Model 1	1.0	0.85 (0.79-0.91)	0.86 (0.81-0.92)	0.59
	Model 2	1.0	0.79 (0.73-0.85)	0.81 (0.76-0.87)	0.34
Alcohol use in the past year	Model 1	1.0	0.99 (0.95-1.03)	1.02 (0.98-1.05)	0.69
	Model 2	1.0	0.97 (0.93-1.01)	0.96 (0.92-1.00)	0.58
History of Diabetes	Model 1	1.0	0.91 (0.87-0.94)	0.91 (0.87-0.96)	0.99
	Model 2	1.0	0.96 (0.92-1.00)	0.98 (0.92-1.04)	0.48
History of Hypertension	Model 1	1.0	0.92 (0.89-0.95)	0.91 (0.88-0.94)	0.71
	Model 2	1.0	0.99 (0.95-1.02)	0.99 (0.95-1.03)	0.02
History of Cardiovascular Disease	Model 1	1.0	0.87 (0.84-0.90)	0.91 (0.86-0.96)	0.50
	Model 2	1.0	1.02 (0.98-1.06)	1.13 (1.06-1.20)	0.87

Model 1 Univariate
Model 2 adjusting for age, race, sex, diet, smoking, alcohol, sleep, BMI, physical activity; history of Diabetes, Hypertension, Cardiovascular disease, Chronic obstructive pulmonary disease, End stage renal disease, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health
BMI = Body Mass Index; Underweight = BMI <18.5 kg/m2; Overweight = BMI ≥25 kg/m2
OR = Odds Ratio; CI = Confidence Interval

Chapter 3

Caregiving, All-Cause Mortality and Cause Specific Mortality:

Findings From the NIH-AARP Diet and Health Study

3.1 Introduction

The relationship between caregiving and caregiver mortality appears complex (13), with some prospective cohort studies reporting an increased risk of mortality in caregivers (compared to non-caregivers), most notably when caregiving for persons with significant functional and behavioural issues (19,20), while others reporting no association (83), or a lower risk of mortality among people providing informal caregiving (109–111). Caregiving is a diverse activity, and the association of caregiving and mortality may relate to the type of caregiving (adult or child), intensity of caregiving (duration and workload) and whether caregiving is chosen or imposed.

In evolving our understanding of the association of caregiving and mortality, a key consideration is cause-specific mortality. Many studies have focused on the association of caregiving with all-cause mortality rather than cause-specific mortality (20,22). One observational study from Northern Ireland explored cause-specific mortality and found the most common cause of mortality among caregivers was cancer followed by cardiovascular causes. In that study, caregiving was associated with a lower risk of death on follow-up, compared to non-caregivers, however, analysis focusing on young caregivers (aged 5-24 years) determined they were at higher risk of mortality than non-caregiving peers with risk increasing as caregiving intensity increased (25,112). Two more recent studies have also demonstrated a consistent lower risk of mortality among caregivers when cause-specific mortality was explored, particularly for mortality from cardiovascular, cerebrovascular and cancer causes (26,27). As detailed in our previous analysis (Chapter 2), the association of caregiving and cardiovascular risk factors is complex. Caregiving was associated with increased odds of poor sleep patterns and obesity in caregivers of adults but higher odds of

regular vigorous physical activity. Of further complexity, some associations with risk factors vary by type and intensity of caregiving.

The NIH-AARP study provides an opportunity to determine the association of caregiving with all-cause mortality and cause-specific mortality, and to explore factors that may mediate an association.

3.2 Methods

3.2.1 Study Population

To evaluate the association of caregiving and mortality, we analysed data from U.S. National Institutes of Health American Association of Retired Persons (NIH-AARP) Diet and Health Study (90). The NIH-AARP is a prospective cohort study, established primarily to understand the association between diet and cancer. From 1995 through 1996, 3.5 million baseline questionnaires (Phase I questionnaire) were mailed to current members of the AARP (formally the American Association of Retired Persons), aged 50-69 years, and who resided in one of six states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or in two metropolitan areas (Atlanta, Georgia and Detroit, Michigan). The questionnaire included a dietary section as well as some lifestyle questions. The initial survey was satisfactorily completed by 566,398 respondents. In late 1996, a supplementary survey (Phase II questionnaire) was mailed to those participants who had successfully completed the baseline survey (and did not have prostate, breast, or colon cancer at baseline), was completed by 334,905 respondents. A follow-up questionnaire (Phase III questionnaire) was sent to all living participants in the baseline cohort beginning in 2004. This questionnaire asked questions about time spent caregiving weekly for adults and children and serves as our inception cohort for the current study and was returned by

318,903 participants. The timeline of data collection is outlined in Figure 2-2 in Chapter 2. Eligible participants were those who completed information on caregiving of adults and/or children in the final questionnaire. The study was approved by the National Cancer Institute Special Studies Institutional Review Board. We submitted a formal request for data to the NIH-AARP publications committee, with a detailed statistical analysis plan, which was approved in April 2020.

3.2.2 Assessment of Exposure

Caregiving of adults was self-reported, and based on question included the Phase III questionnaire asking, *"During the past 12 months, approximately how much time per week did you participate in caring for another adult (for example, lifting, pushing a wheelchair, etc.)".* Caregiving of children was determined using a question in the Phase III questionnaire asking, "*During the past 12 months, approximately how much time per week did you participate in caring for children (for example, pushing a stroller, playing, lifting, etc.).***"** Respondents to these questions were categorised into non-caregivers, caregivers of adults and caregivers of children.

3.2.3 Cohort Follow up

Mortality was recorded by annually linking the cohort to the Social Security Administration Death Master File. To verify the participant was deceased, the National Death Index Plus (NDI) was searched and was used to obtain the cause of death. A previous study reported that 95% of deaths can be identified using this method (113). Follow-up time for all-cause mortality was from Aug 1, 2004 (time of questionnaire administration) to December 31, 2019. Annual linkage to the U.S. Postal Service's National Change of Address database was used to follow up on participants, through processing undeliverable mail, using address

change services, as well as participant notifications. This was to ensure all participant addresses were kept accurate and up to date.

3.2.4 Causes of Death

Causes of death were categorised using the National Centre for Health Statistics for vital status reporting (114) based on the causes of death provided by the NDI. Causes of death were categorised using the Surveillance, Epidemiology and End Results (SEER) database (115) which uses the International Classification of Diseases (ICD) classification. We investigated deaths from all causes, deaths due to cardiovascular disease and non-cardiovascular causes of death (inclusive of cancer, respiratory Disease, Alzheimer's disease, accident, suicide, homicide, diabetes, infectious causes, nephritis, nephrotic syndrome and nephrosis, chronic liver disease, congenital/perinatal and other/unknown cause of death).

3.2.5 Covariates

Several covariates were self-reported in questionnaires. These were categorised into demographic factors (age, race, sex, marital status, educational status), perception of health and well-being (depression, quality of life since retirement, self-reported general health status and trouble with activities of daily living), lifestyle cardiovascular risk factors (smoking, alcohol, body mass index, sleep duration, diet and physical activity) and co-morbidities (previous history of cardiovascular disease, diabetes, hypertension, stroke, transient ischaemic attack (TIA), chronic obstructive pulmonary disease (COPD) and end stage kidney disease (ESKD)). Educational status was estimated from the highest level of education reported by participants.

A summary diet score was estimated using the HEI (Healthy Eating Index). The HEI score is a measure of adherence to federal diet recommendations (range from 0-100), aligned

with the 2010 Dietary guidelines for Americans (92). The composition of this score is previously described in Chapter 2. A maximum HEI score of 100 reflects the 'healthiest diet', in that the set of food items aligns with key dietary recommendations with a higher score reflecting a better diet. Physical activity was measured in Phase III of data collection and self-reported using the variable vigorous physical activity. Vigorous physical activity comprises of the sum of the following individual activities; jogging, tennis, swimming, cycling, and aerobic exercise measured in hours per week. Alcohol use was reported during Phase I of data collection and was categorised as current use of alcohol in the past year, with respondents answering yes or no. The smoking variable considered all questions asked about smoking during Phase III of data collection and categorised participants as never smoked, former smoker and current smoker. Sleep was reported as time spent per day over past 12 months sleeping at night or napping during the day. Participants could select from the following categories: None, less than 3 hours, 3-4 hours, 5-6 hours, 7-8 hours, 9-10 hours, 11-12 hours and more than 12 hours.

3.2.6 Statistical Analyses

Descriptive statistics were used to report the covariates included in the adjusted models (Table 3-1) and to present underlying causes of death for caregivers of adults, caregivers of children and non-caregivers (Table 3-2, Table 3-3).

All-cause mortality was the primary outcome measure. Cause-specific mortality were secondary outcome measures. Hazard ratios (HR) and 95% confidence intervals (CI) for mortality associated with caregiving of adults and of children were estimated with the use of Cox proportional-hazards regression models. Non-caregivers were the reference category. We tested the proportional-hazards assumption by modelling the interaction of

caregiving by time to follow up. The underlying time variable was calculated from the scan date on the Phase III questionnaire which measured caregiving, until death from any cause, or the end of the follow-up on December 31, 2019.

Model 1 was univariate analysis of the association of caregiving with mortality. Model 2 adjusted for age (at time of follow up questionnaire); sex (male, female), race (Non-Hispanic White, Black, Hispanic, and Asian), marital status (married, widowed, separated, divorced, never married) and highest level of schooling completed (<8 years of age, 8-11 years of age, 12 years or completed high school, post high-school or some college, college and post-graduate). Model 3 adjusted for self-reported history of depression; trouble with activities of daily living (none/slight trouble, significant trouble); quality of life since retirement (better/same, worse); self-reported general health (good/excellent, fair/poor) and the variables included in model 2. Model 4 adjusted for co-morbidities including previous history of cardiovascular disease, diabetes, hypertension, stroke, TIA, COPD, ESKD and behavioural risk factors; smoking (never/former or current smoker); alcohol (reported alcohol use in the past 12 months versus none); body mass index (continuous variable); sleep (≤6 hrs, 7-8 hrs or ≥9 hours); vigorous physical activity (continuous variable) and diet (continuous variable) and the variables included in model 2. Model 5 adjusted for variables included in model 3 and 4.

In secondary analyses, we determined risk estimates for categories of caregiving within the caregiving cohort by increment of time spent caregiving each week. Categories included 1) caregiving of adults for less than 30 minutes, 30 minutes-1.5 hours, 2-6 hours, and 7 hours or more; 2) caregiving of children for less than 30 minutes, caregiving of children 30 minutes-1.5 hours, 2-6 hours, and 7 hours or more. Caregiving of children for

less than 30 minutes was the reference category for these analyses, as it was the lowest grouped duration of caregiving and given the age profile of participants felt to be representative of the least intensity caregiving category within the caregiver cohort. For cause-specific mortality, we collapsed duration of caregiving into increments of weekly time of <2 hours per week, 2-6 hours per week and 7 hours or more per week, with non-caregivers as the reference category. Analyses based on these categories was explored for the association between caregiving and all-cause mortality, CVD-mortality, cancer-related mortality, mortality due to Alzheimer's disease and mortality due to accident, suicide, or homicide. Kaplan-Meier curves were generated based on the univariate model to visually represent time from study entry to death displaying the probability of survival at time of study follow up (December 21st, 2019). Two sets of Kaplan-Meier curves were generated; first for caregivers of adults, caregivers of children and non-caregivers for all-cause, cardiovascular and non-cardiovascular mortality; second for caregivers of adults by duration of time (<2 hours, 2-6 hours, ≥7 hours) and non-caregivers for all-cause, cardiovascular mortality and cancer related mortality. The association between caregiving and all-cause mortality among subgroups by sex (male and female), self-perceived health (good/excellent or fair or poor) and history of cardiovascular disease (yes or no) and diabetes (yes or no) was performed and P for interaction calculated.

Two approaches were used to test the proportional-hazards assumption. First, using the Cox-proportional Hazards assumption to model the interaction of caregiving by time to follow-up. As this was statistically significant (p-value= <0.05) we proceeded to perform a milestone survival analysis. This was a cross-sectional assessment of the survival data at the prespecified time point (2 years) using Kaplan-Meier survival probabilities. This cut off was chosen following visual assessment of the Kaplan-Meier curve. This was to explore if there

was a reverse causal relationship (i.e. if some non-caregivers were vulnerable to attrition) to explain our proportional-hazards assumption findings.

In a sensitivity analysis, we matched for propensity scores (116) that reflected associations of caregiving of adults and of children with the other variables in the multivariate-adjusted models. Participants were matched based on age, race, sex, educational status and self-reported health status.

The NIH-ARRP dataset did not collect information on caregiver strain, which has been shown to be an important determinant of the association of caregiving and mortality. However, information on self-perceived quality of life and depression were recorded, and we used these variables as adjacent surrogate domains, in an analysis that categorised caregiving by quality of life (respondents rated quality of retired life compared to working life by the following categories: much better, somewhat better, about the same, somewhat worse and much worse) and formally diagnosed depression (yes or no). To test the hypothesis that lower mortality among caregivers may relate to enhanced resilience, we conducted an exploratory analysis which analysed the association of impairment in activities of daily living (ADLs) with mortality among caregivers and non-caregivers, to determine whether the magnitude of association differed (i.e. expect lower magnitude of association in caregivers if the resilience hypothesis held).

Finally, we report an updated meta-analysis of longitudinal prospective cohort studies of the association of informal caregiving of adults with mortality, updating the findings previously published by Mehri et al (117). This updated meta-analysis was done using the inclusion and exclusion criteria, search strategy and analytic approach reported by this group. In addition to the twelve studies previously identified

(21,22,22,25,26,83,110,111,118–121), our updated search identified an additional study by Mikkola et al published outside of the duration of the original search strategy (27). As Mikkola et al did not report the total effect of caregiving on mortality, rather they reported the effect by sex, we performed a fixed-effect meta-analysis model to generate an overall estimate. We completed a random-effect meta-analysis model to determine the total effect across all fourteen studies. This was completed using the Cochrane review manager 5.3.

All remaining statistical analysis was performed using R version 3.6.3 and statistical significance was set at $p<0.05$. As the analysis was exploratory in nature, we did not adjust p value for significance for multiple testing.

3.3 Results

Our analytic cohort consisted of 148,792 eligible participants (inception cohort for current analysis was participants who completed the Phase III questionnaire in 2004 and on whom vital status was confirmed through annual linkage with the Social Security Administration Death Master File). Among this cohort, 59,046 deaths were recorded between 1st of August 2004 and 31st of December 2019. Of the total population included, 12.16% (n=18,101) reported being an adult caregiver at the time of survey, 17.41% (n=25,907) reported being a caregiver of children and the remaining 70.42% (n=104,784) were non-caregivers. The mean age was 70.5 (5.1) years in those reporting caregiving for adults, 69.4 (4.8) years in those reporting caregiving for children and 71.1 (4.9) years in non-caregivers. Male respondents accounted for 60.2% (n=10,893) of caregivers of adults, 56.4% of caregivers of children (n=14,611) and 61.7% of non-caregivers (n=64,636). The majority of the analytic cohort were non-Hispanic white (94%). Most participants reported having good or excellent overall health status (90.1%, n=136,903), with 9.3% (n=1,717) of caregivers of adults, 8.8% of

caregivers of children (n=2,312) and 10.3% (n=11,052) of non-caregivers reporting their health as being fair or poor. Overall, caregivers were more likely to be female, black and to self-report health as being very good (p-value=<0.001) (Figure 3-1, Figure 3-2, Figure 3-3). Characteristics of the analytic population are outlined in Table 3-1.

Cardiovascular disease was the most common cause of death, attributed to 32.3% (n=19,101) of deaths in the cohort, followed by cancer (28.1%, n=16,608) respiratory disease (8.5%, n=5,005) and Alzheimer's disease (3.8%, n=2,249). Accident, suicide, or homicide was the underlying cause of death in 3.2% (n=1,871) of the cohort. A breakdown of underlying cause of death by caregiving population is outlined in Table 3-2 with breakdown of cause of death by time spent caregiving outlined in Table 3-3. In 16.9% (n=9,956) of participants who died, the cause of death was unknown.

3.3.1 Association of Caregiving with All-Cause Mortality

During follow up, mortality was 36.5% (n=6,614) among adult caregivers, 32.5% (n=8,420) among child caregivers and 42.0% (n=44,012) among non-caregivers. On multivariable analysis, self-reported caregiving for adults (HR 0.90; 95% CI 0.88-0.93) and children (HR 0.90; 95% CI 0.87-0.92) was associated with a reduced risk of all-cause mortality, compared to non-caregivers (Table 3-4, Figure 3-4). In an analysis by duration of caregiving, there was a diminution of the magnitude of association for adult caregiving with increasing duration (HR 0.88; 95%CI 0.85-0.91 for <2 hours per week, HR 0.94; 95%CI 0.88-0.99 for 2-6 hours per week and HR 0.95; 95%CI 0.89-1.01 for 7 hours or more per week). A gradient was not evident for child caregiving (HR 0.90; 95%CI 0.88-0.93 for <2 hours per week, HR 0.87: 95%CI 0.83-0.92 for 2-6 hours per week and HR 0.89; 95%CI 0.84-0.94 for 7 hours or more per week).

3.3.2 Association of Caregiving with Cause-Specific Mortality

During follow-up, 12.1% (n=2186) of adult caregivers, 10.2% (n=2637) of child caregivers and 13.6% (n=14,278) of non-caregivers had died from a reported cardiovascular cause. On multivariable analysis, caregiving for adults (HR 0.90; 95% CI 0.86-0.95) and children (HR 0.88; 95% CI 0.84-0.92) was associated with a reduced risk of cardiovascular mortality, compared to non-caregivers Table 3-4, Figure 3-4.

Mortality from non-cardiovascular causes was 24.5% (n=4428) in adult caregivers, 22.3% (n=5783) in child caregivers, and 28.4% (n=29,734) in non-caregivers. On multivariable analysis, caregiving for adults (HR 0.89; 95% CI 0.86-0.92) and children (HR 0.88; 95% CI 0.86-0.91) was associated with a reduced risk of mortality from non-cardiovascular causes, compared to non-caregivers (Table 3-4, Figure 3-4).

On multivariable analysis, compared to non-caregivers, any form of caregiving was associated with lower mortality from cancer (HR 0.90; 95% CI 0.87-0.93), Alzheimer's Disease (HR 0.84; 95% CI 0.77-0.92) and accidents, suicide, or homicide (HR 0.77; 95% CI 0.71-0.86). This lower risk of mortality extended to any duration of caregiving of adults or of children (Table 3-5).

Figure 3-5 represents univariate survival analysis of caregivers of adults by increasing intensity compared to non-caregivers for all-cause, cardiovascular and cancer mortality.

On analysis based on duration of caregiving, the pattern of diminishing magnitude of HR by increasing duration of caregiving was present for cardiovascular mortality and cancer mortality, but did not extend to Alzheimer's disease, where an opposing gradient was suggested by our analysis, with the lowest magnitude of association reported for highest intensity (≥7 hours) duration of mortality from Alzheimer's Disease compared to non-caregivers (HR 0.65; 95% CI 0.47-0.89) (Table 3-5).

3.3.3 Association of Caregiving with Mortality in Key Subgroups

On subgroup analysis by gender, self-reported health status, history of cardiovascular disease and history of diabetes, on multivariable analysis, caregiving for adults and children in all subgroups was associated with a reduced risk of mortality, compared to non-caregivers. P for interaction was not significant suggesting that the reduced risk of mortality was not explained by subgroup differences (Table 3-6).

3.3.4 Milestone Analysis

The Cox-proportional Hazards assumption was tested for all-cause mortality and was statistically significant (p-value= <0.05). On exploring the Kaplan-Meir curves, we elected to conduct a milestone analysis by duration of follow-up. We performed an analysis of all-cause mortality for participants whose follow up period terminated within the first two years of follow-up and those that were followed up from two years to end of follow-up. Overall, the association of caregiving and mortality among adult caregivers (HR 0.97; 95% CI 0.86-1.09) and child caregivers was not significant within short-term follow-up (HR 1.02; 95% CI 0.92-1.14) but was statistically significant after two years follow-up for both caregivers of adults (HR 0.90; 95% CI 0.88-0.93) and caregivers of children (HR 0.89; 95% CI 0.87-0.91) (Table 3-7).

3.3.5 Subgroup analysis of Caregiving Population Alone

In our analysis confined to caregivers (reference category was child caregiving < 30 minutes per week), we observed a graded reduction in all-cause mortality for increased duration of child caregiving but a graded increase in all-cause mortality with increased duration of adult caregiving, on univariate analysis. However, following multivariable adjustment, there was no significant association, suggesting that the association observed on univariate analysis

was explained by mediating and/or confounding variables (Figure 3-6). This finding was similar when explored for cardiovascular and non-cardiovascular mortality (Table 3-8).

3.3.6 Propensity Score-based Matching

We performed propensity score-based matching to explore the reflected associations of caregiving of adults and caregiving of children with variables in the adjusted models. Populations were matched based on age, sex, level of education and self-perceived health. Among the analytic population 18,285 caregivers of adults (Figure 3-7) were matched with 18,285 non-caregivers and 32,442 caregivers of children (Figure 3-8) were matched with 32,442 non-caregivers. Results obtained with the use of propensity-score based matched analysis were consistent with multivariable-adjusted Cox models and did not materially alter findings or conclusions (Table 3-9, Table 3-10).

Association of Caregiver Depression and Poor Quality of Life with Mortality

Caregiving, in the setting of history of depression or poor quality of life, was not associated with a stronger magnitude of association with mortality, compared to caregiving without these factors (Table 3-11).

3.3.7 Association of Impairment in ADL/Self-perceived Health with Mortality (Caregivers and Non-caregivers)

Self-reported ‘significant trouble’ with ADLs was associated with an increased mortality, which was significantly greater in caregivers compared to non-caregivers (p-interaction= 0.004), although the magnitude of difference in HR diminished with successive multivariable adjustment (Table 3-12). Self-perceived poor health was associated with increased

mortality, which was consistent in caregivers and non-caregivers (p-interaction=0.27) (Table 3-13).

3.3.8 Effect of caregiving of Adults on All-Cause Mortality: An Updated Meta-Analysis

An updated meta-analysis was performed. Among the fourteen studies included (n=449,047 caregivers of adults and n=2,277,524 non-caregivers) the pooled effect of informal caregiving demonstrated a statistically significant overall lower all-cause mortality associated with caregiving of adults (HR = 0.84; 95% CI = 0.78-0.90) compared to non-caregivers (Figure 3-9). This estimate was unchanged from that reported by Mehri et al (117). However, the I^2 was high (95%), which reflects high heterogeneity among the included studies.

3.4 Discussion

In this large prospective cohort study, we report that caregiving, for adults and children, is associated with overall lower risk of all cause-mortality and mortality from cardiovascular and non-cardiovascular causes. However, we observed an attenuation in magnitude of risk with increasing duration of caregiving, and among individuals providing adult caregiving for 7 hours per week or more, there was no significant association with risk of mortality, on multivariable analyses.

A recent meta-analysis of prospective cohort studies reported a lower risk of mortality in individual providing caregiving, based on an analysis of 12 prospective cohort studies (117). The summary estimate (HR 0.84, 95%CI 0.78-0.90) is similar to the estimate in our analysis for association of caregiving (HR 0.89; 95%CI 0.87-0.91 for adult caregiving). When we performed an updated meta-analysis with our findings and that of Mikkola et al (27), the overall summary estimate was unchanged. However, similar to Mehri at al we

report significant heterogeneity among studies (I^2=95%). Mehri et al explored potential sources of heterogeneity. In a subgroup analysis by region, they reported no significant association of caregiving and mortality in studies conducted in the US, and a lower mortality in studies from other regions. The investigators speculated that a difference may related to lesser community-level supports provided to caregivers in the US, compared to other regions. Our analysis, which includes a large US-based cohort of older adults, argues against a systematic difference in the association of caregiving and mortality in the US, and suggest that null findings from this subgroup analysis are more likely related to smaller sample size, and types of caregivers included (e.g. high-demand caregiving) in some studies.

In our analysis, both for cardiovascular risk factors and mortality, we observed evidence of a non-linear association by duration of caregiving. As such, our collective analysis provides support for both caregiver hypotheses. The overall lower risk of mortality observed is supportive of the healthy caregiver hypothesis, which may relate to an increased sense of purpose by providing care needs and the caregiver being more physically and cognitively engaged through this activity (122), with healthier individuals more likely to voluntarily take on caregiver duties. However, with increasing duration of caregiving, we observed an attenuation of risk, such that the significant association with lower mortality was lost with highest duration category (≥ 7 hours per week). We were unable to fully explore duration of caregiving (i.e. within ≥ 7 hours per week), or intensity (physical and psychological) of caregiving, which may have further altered the direction of association. However, our analysis of caregiving with poor self-perceived quality of life as a surrogate for caregiver strain, did not reveal a higher risk of mortality among caregivers reporting lower quality of life, but this variable did not directly link impaired quality of life with caregiving. In ways, this observation, of attenuation in association with lower mortality, parallels some of

our findings in Chapter 2, where we reported an association of lower duration caregiving with healthy lifestyle patterns, but among higher-duration adult caregiving (≥ 7 hours per week), we observed the emergence of unhealthy lifestyle and anthropometric risk factors. A major limitation in our study is the absence of information on the needs of the individual requiring caregiving, which appears to be an important determinant of the direction of association of caregiving with mortality. In the two studies reporting increased mortality with adult caregiving, caregivers were providing care to individuals with dementia or were defined as providing regular assistance in ADLs for disabled or sick adults (20,120). The presence of increased burden of care and level of disability of recipient has been shown to increase risk of mortality of caregivers of adults (19,20) and suggests there may be a sub-population of caregivers that may benefit from targeted intervention for lifestyle factors.

In our analysis of cause-specific mortality, we report an association of low-moderate duration caregiving with lower hazard of deaths due to CVD, cancer, Alzheimer's disease with the lowest risk associated with deaths due to accidents, suicide and homicide consistent with findings from some previous observational studies (26,27,110). However, in our analysis based on duration of caregiving, the lower hazard was lost for those caregiving for adults at highest intensities (≥7 hours) for specific causes of death, except for deaths due to Alzheimer's disease (HR 0.65; 95% CI 0.47-0.89) (Table 3-5). This finding supports that of Mikkola et al (27), and may be explained by two reasons; first, persons with dementia are unlikely to become caregivers of other adults and second it may be reflective of the healthy caregiver hypothesis that caregivers may remain more cognitively and physically engaged, protecting their own cognitive reserves.

It has been proposed that caregiving may enhance resilience in older adults, thereby mediating some of the observed association with lower mortality (13). Although a measure of resilience was not included our dataset, we explore it indirectly, by determining whether the association of impairment in ADL with mortality was modified by caregiver status. In that analysis, we report a lower hazard ratio among caregivers, compared to non-caregivers, for the association of impairment in ADL and mortality, with a significant p-interaction (Table 3-12). It is also notable that the reduced hazard of mortality among lower duration caregivers did not emerge until more than 2 years follow-up, which argues against a reverse causal relationship.

There is a clear role to identify certain cohorts of caregivers of adults, likely those delivering care for higher durations and intensities that may benefit from health interventions (i.e. those for whom the stress process model may have relevance). For example, those looking after more dependent co-morbid adults for durations of high intensity are often older, female, non-White, have lower income levels and more often live with their care recipient (123,124). Key additional factors to consider outside of these demographic findings include relationship to the care recipient, duration of daily care, functional status of the care recipient, tasks requiring assistance (i.e. personal or instrumental ADLs), provision of overnight care and professional home supports and therapies. Given the suggested protective benefit identified in this study, caregivers should be supported adequately and empowered within their roles, with healthcare providers mindful of those exposed to caregiving environments which are high demand, stressful and result in physical burden.

There were several limitations associated with this study. First, the cohort analysed were mainly white, well educated, married older adults in overall good health, limiting the generalisability to other socioeconomic populations. The design and sampling of the NIH-AARP study was intended to explore the relationship between diet and health which therefore may restrict the interpretation of our findings. Second, we did not have information on level of disability of care recipient, if they were living within the same household as the caregiver, their underlying diagnosis, the relationship between both parties and detail on caregiving duties provided. Third, as this study was questionnaire based, respondents self-reported key variables rather than objective measurements being obtained and therefore some covariates could be subject to self-reporting bias e.g. sleep and overall health status. Fourth, there was no clear measurement of caregiving strain in this study; in lieu of this we used history of depression and quality of life since retirement as surrogate markers. Finally, age was a significant confounder in this population. On adjustment for age alone there was no association with caregiving for adults and all-cause mortality which was unsurprising given the mean age of the analytic cohort was 70.8 years. However, on further adjustment for sex and race, caregiving for adults for higher periods of time (two hours or more) re-emerged as a risk factor for all-cause mortality suggesting the need for specific population selection.

Despite these limitations there were several strengths to this study. First was the large analytic population and follow-up period which allowed us to explore caregiving, lifestyle factors, all-cause and cause-specific mortality. In addition, this study uniquely captured time spent caregiving for adults and time spent caregiving for children allowing for a robust exploration of mortality across the spectrum of caregiving which older adults provide.

3.5 Conclusions

Caregiving of adults and children overall reduces mortality risk compared to non-caregivers, however within the caregiving cohort there may be individuals at higher risk which warrants further exploration, particularly those delivering high intensity care to other adults. Caregivers should be supported to maintain their roles, with encouragement of the benefits including sense of purpose and increased activity. Consideration should be given to targeted interventions within the retired population for those devoting long periods of time in high stress environments to the care of other adults. Future targets to explore as possible interventions for these individuals include primary health prevention, stress management and targeting lifestyle factors such as sleep, diet, and body mass index.

3.6 Acknowledgements

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Tumor Registry, Louisiana State University Health Sciences Center School of Public Health, New Orleans, Louisiana. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, The Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry, Raleigh, North Carolina. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services, Phoenix, Arizona. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Division of Public and Behavioral Health, State of Nevada Department of Health and Human Services, Carson City, Nevada. We are indebted to the participants in the NIH-AARP Diet and Health Study for their outstanding cooperation. We also thank Sigurd Hermansen and Kerry Grace Morrissey from Westat for study outcomes ascertainment and management and Leslie Carroll at Information Management Services for data support and analysis.

Figure 3-1 Caregiving of adults and children among women and men

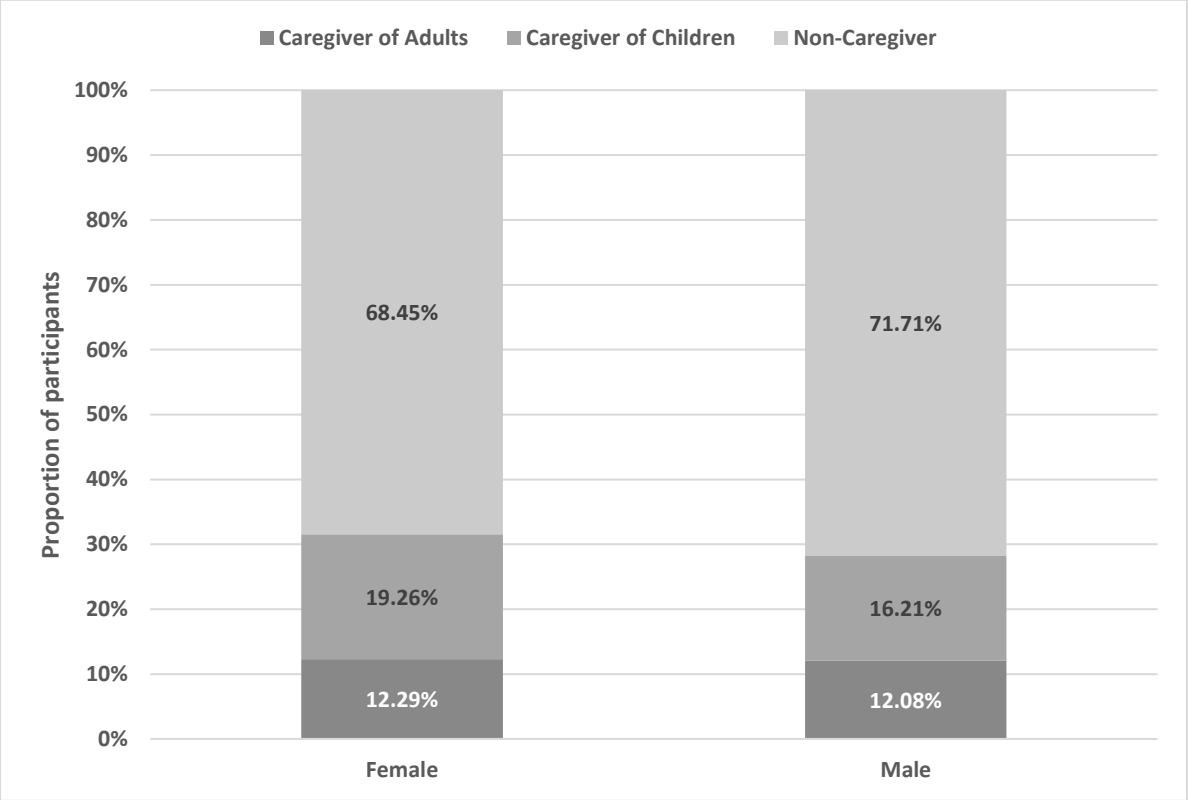


Figure 3-1 reports a stacked column chart of caregiving by gender. The dark grey represents proportion self-reporting caregiver of adults, while medium grey represents caregivers of children and the light grey represents non-caregivers. The stacked columns represent proportion of respondents in each category.

Figure 3-2 Caregiving of adults and children by Race

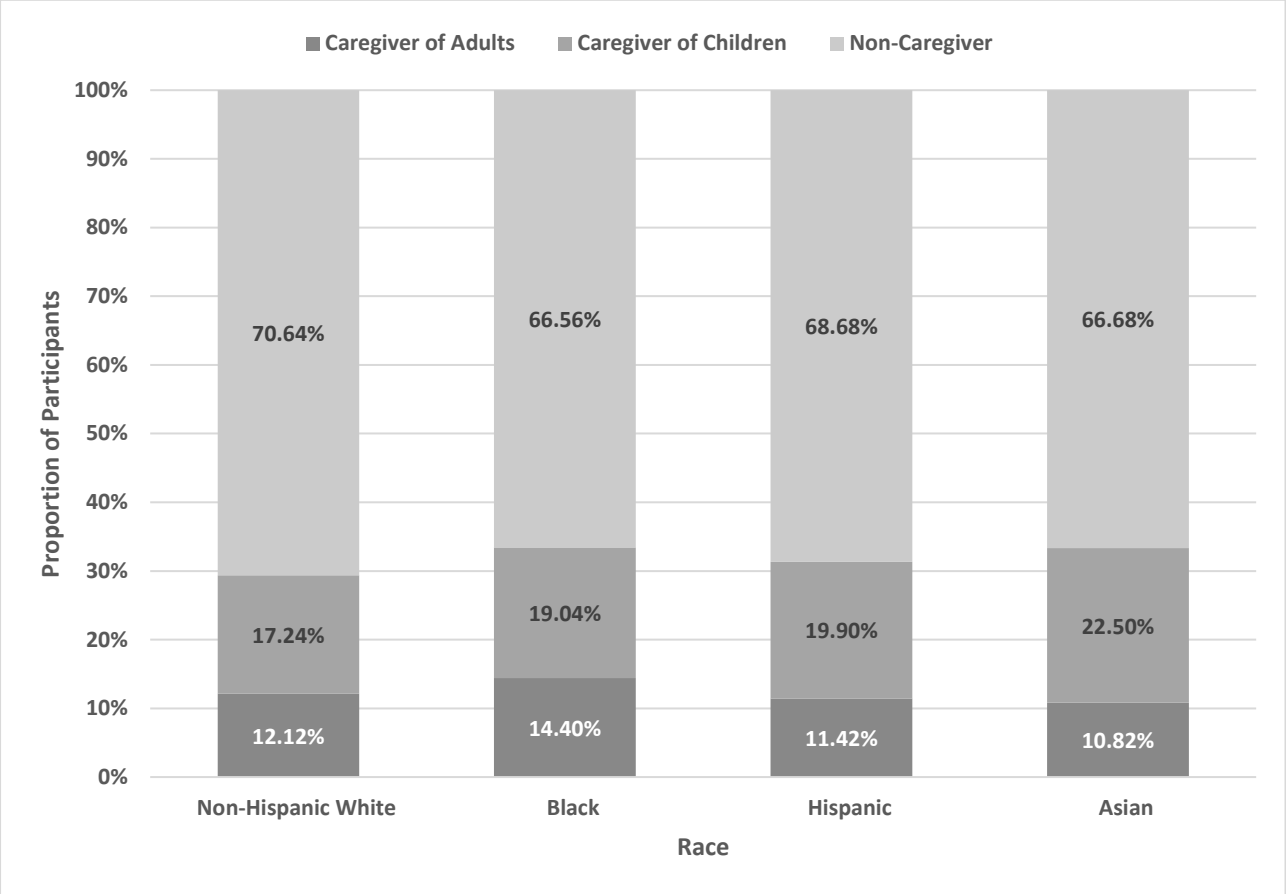


Figure 3-2 reports a stacked column chart of caregiving use by race. The dark grey represents use of caregiver of adults, while medium grey represents caregivers of children and the light grey represents non-caregivers. The stacked columns represent proportion of respondents in each category.

Figure 3-3 Self-Reported General Health Status Among Caregivers

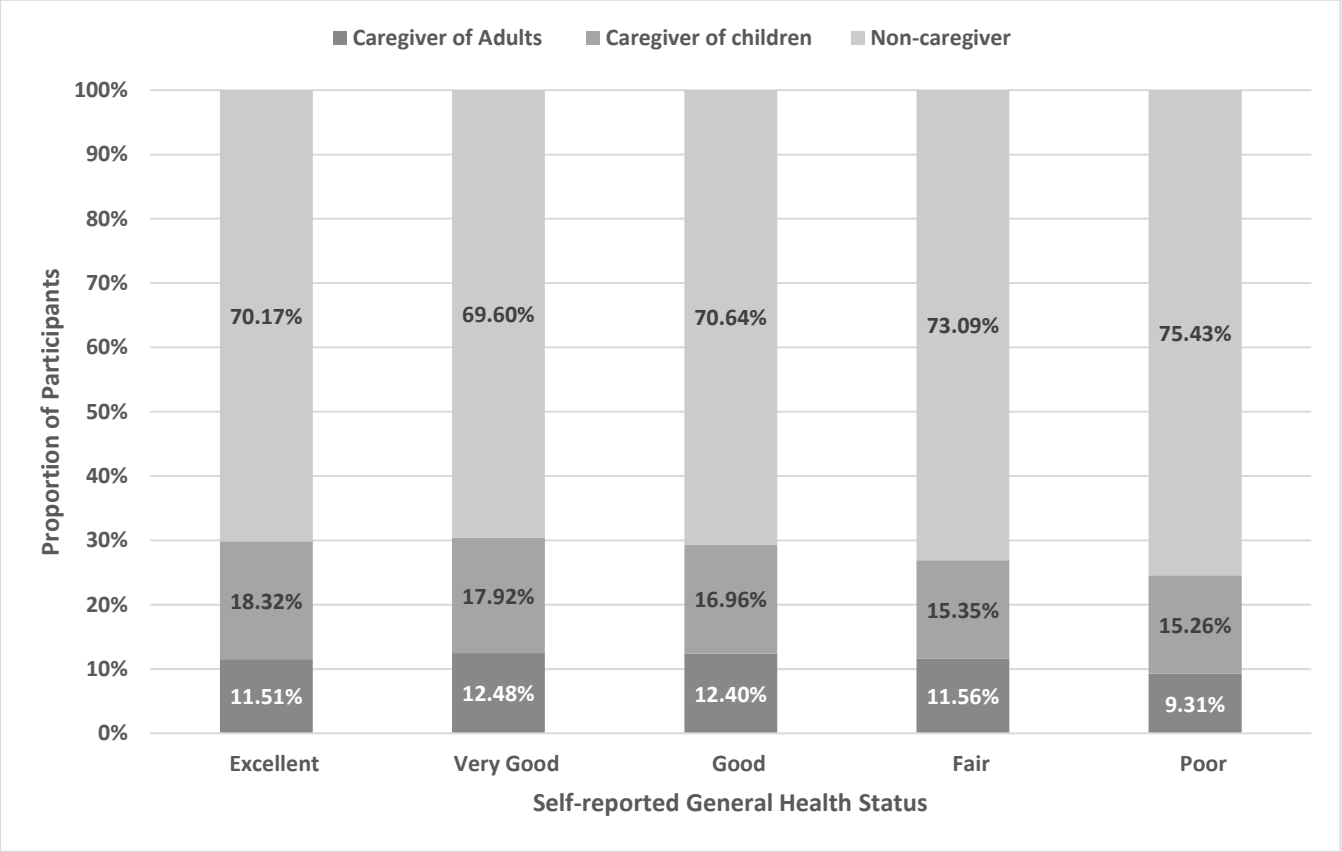


Figure 3-3 reports a stacked column chart of caregiving use by self-reported general health status. The dark grey represents use of caregiver of adults, while medium grey represents caregivers of children and the light grey represents non-caregivers. The stacked columns represent proportion of respondents in each category.

Table 3-1 Baseline participant characteristics

	Non-caregiver (N=104784)	Caregiver of Adults (N=18101)	Caregiver of children (N=25907)	Total (N=148792)	P value
Age					< 0.001
Mean (SD)	71.1 (4.9)	70.5(5.1)	69.4 (4.8)	70.8 (4.9)	
Sex					< 0.001
Female	40148 (38.3%)	7208 (39.8%)	11296 (43.6%)	58652 (39.4%)	
Race					< 0.001
Non-Hispanic White	98745 (94.2%)	16949 (93.6%)	24102 (93.0%)	139796 (94.0%)	
Black	3059 (2.9%)	662 (3.7%)	875 (3.4%)	4596 (3.1%)	
Hispanic	1581 (1.5%)	263 (1.5%)	458 (1.8%)	2302 (1.5%)	
Asian	1399 (1.3%)	227 (1.3%)	472 (1.8%)	2098 (1.4%)	
History of depression					< 0.001
Yes	13895 (13.3%)	2767 (15.3%)	3456 (13.3%)	20118 (13.5%)	
Quality of retired life (compared to working life)					< 0.001
Better/Same	92646 (88.4%)	15741 (87.0%)	23303 (89.9%)	131690 (88.5%)	
Worse	12138 (11.6%)	2360 (13.0%)	2604 (10.1%)	17102 (11.5%)	
Trouble with ADLs					< 0.001
None/Slight trouble	76359 (72.9%)	13313 (73.5%)	19853 (76.6%)	109525 (73.6%)	
Significant trouble	28425 (27.1%)	4788 (26.5%)	6054 (23.4%)	39267 (26.4%)	
Self-Reported General Health					< 0.001
Good/Excellent	94122 (89.8%)	16453 (90.9%)	23676 (91.4%)	134251 (90.2%)	
Fair/Poor	10662 (10.2%)	1648 (9.1%)	2231 (8.6%)	14541 (9.8%)	
BMI					< 0.001
Mean (SD)	27.1 (5.1)	27.3 (4.9)	27.2 (5.0)	27.1 (5.1)	
Sleep (hours/day) *					< 0.001
7-8hrs	60814 (59.3%)	10396 (58.6%)	15450 (60.9%)	86660 (59.5%)	
<6hrs	26393 (25.7%)	5023 (28.3%)	6576 (25.9%)	37992 (26.1%)	
≥9hrs	15415 (15.0%)	2326 (13.1%)	3324 (13.1%)	21065 (14.5%)	
Physical Activity**					< 0.001
<75 mins per week	59869 (57.1%)	9145 (50.5%)	13393 (51.7%)	82407 (55.4%)	
≥75 mins per week	44912 (42.9%)	8952 (49.5%)	12513 (48.3%)	66377 (44.6%)	
Smoking Status					< 0.001

Never/Former	98073 (93.6%)	17084 (94.4%)	24426 (94.3%)	139583 (93.8%)	
Current	6711 (6.4%)	1017 (5.6%)	1481 (5.7%)	9209 (6.2%)	
Use of alcohol in last year					
Yes	82488 (79.1%)	13919 (77.2%)	20219 (78.4%)	116626 (78.7%)	< 0.001
Total HEI-2015 Score					0.001
HEI <50	4126 (3.9%)	642 (3.5%)	1024 (4.0%)	5792 (3.9%)	
HEI 50-65	34964 (33.4%)	6084 (33.6%)	8824 (34.1%)	49872 (33.5%)	
HEI 66-80	55689 (53.1%)	9699 (53.6%)	13770 (53.2%)	79158 (53.2%)	
HEI ≥80	10005 (9.5%)	1676 (9.3%)	2289 (8.8%)	13970 (9.4%)	
History of CVD					
Yes	21269 (20.3%)	3374 (18.6%)	4678 (18.1%)	29321 (19.7%)	< 0.001
History of Diabetes					
Yes	18108 (17.3%)	2863 (15.8%)	4084 (15.8%)	25055 (16.8%)	< 0.001
History of Hypertension					
Yes	59222 (56.5%)	10016 (55.3%)	14040 (54.2%)	83278 (56.0%)	< 0.001
History of COPD					
Yes	4400 (4.2%)	616 (3.4%)	796 (3.1%)	5812 (3.9%)	< 0.001
History of ESKD					
Yes	492 (0.5%)	70 (0.4%)	127 (0.5%)	689 (0.5%)	0.247
History of Stroke					
Yes	4400 (4.2%)	616 (3.4%)	796 (3.1%)	5812 (3.9%)	< 0.001
History of TIA					
Yes	4703 (4.5%)	773 (4.3%)	965 (3.7%)	6441 (4.3%)	< 0.001

Table 3-1: Data are n (%) or mean (SD).
BMI= Body Mass Index; ADL = Activities of Daily Living; HEI= Healthy Eating Index; CVD = Cardiovascular Disease; COPD = Chronic Obstructive Pulmonary Disease; ESKD = End Stage Kidney Disease; TIA = Transient Ischaemic Attack
Data were missing in 7863 for BMI; 3075 for sleep; 8 for vigorous physical activity and 646 for alcohol use.
*Sleeping at night or napping during the day
**Sum duration (minutes/week) of vigorous intensity)

Table 3-2: Underlying cause of death by caregiving type

Underlying Cause of Death	Non-caregiver (N=44012)	Caregiver of Adults (N=6614)	Caregiver of children (N=8420)	Total (N=59046)
Cardiovascular Disease	14278 (32.4%)	2186 (33.1%)	2637 (31.3%)	19101 (32.3%)
Cancer (any)	12145 (27.6%)	1881 (28.4%)	2582 (30.7%)	16608 (28.1%)
Other/Unknown Cause of Death	7421 (16.9%)	1138 (17.2%)	1397 (16.6%)	9956 (16.9%)
Respiratory Disease	3873 (8.8%)	522 (7.9%)	610 (7.2%)	5005 (8.5%)
Alzheimer's disease	1695 (3.9%)	244 (3.7%)	310 (3.7%)	2249 (3.8%)
Accident, Suicide, or Homicide	1426 (3.2%)	189 (2.9%)	256 (3.0%)	1871 (3.2%)
Diabetes	1151 (2.6%)	149 (2.3%)	213 (2.5%)	1513 (2.6%)
Infectious Causes	918 (2.1%)	136 (2.1%)	195 (2.3%)	1249 (2.1%)
Nephritis, Nephrotic Syndrome and Nephrosis	802 (1.8%)	129 (2.0%)	154 (1.8%)	1085 (1.8%)
Chronic Liver Disease	275 (0.6%)	37 (0.6%)	59 (0.7%)	371 (0.6%)
Congenital/Perinatal	28 (0.1%)	3 (0.0%)	7 (0.1%)	38 (0.1%)

Table 3-3: Underlying cause of death by time spent caregiving

Underlying Cause of Death	Adults <30mins (N=977)	Adults 30mins-1.5hours (N=1844)	Adults 2-6 hours (N=999)	Adults ≥7 hours (N=1048)	Children <30mins (N=1788)	Children 30mins-1.5hrs (N=3624)	Children 2-6 hours (N=1839)	Children ≥7 hours (N=1169)	Total (N=13288)
Cardiovascular Disease	310 (31.7%)	626 (33.9%)	339 (33.9%)	345 (32.9%)	568 (31.8%)	1119 (30.9%)	590 (32.1%)	360 (30.8%)	4257 (32.0%)
Cancer (any)	259 (26.5%)	528 (28.6%)	279 (27.9%)	298 (28.4%)	536 (30.0%)	1103 (30.4%)	582 (31.6%)	361 (30.9%)	3946 (29.7%)
Other/Unknown Cause of Death	187 (19.1%)	301 (16.3%)	164 (16.4%)	172 (16.4%)	307 (17.2%)	600 (16.6%)	295 (16.0%)	195 (16.7%)	2221 (16.7%)
Respiratory Disease	80 (8.2%)	138 (7.5%)	94 (9.4%)	92 (8.8%)	128 (7.2%)	258 (7.1%)	130 (7.1%)	94 (8.0%)	1014 (7.6%)
Alzheimer's disease	39 (4.0%)	70 (3.8%)	30 (3.0%)	26 (2.5%)	60 (3.4%)	142 (3.9%)	68 (3.7%)	40 (3.4%)	475 (3.6%)
Accident, Suicide, or Homicide	38 (3.9%)	53 (2.9%)	24 (2.4%)	31 (3.0%)	66 (3.7%)	107 (3.0%)	51 (2.8%)	32 (2.7%)	402 (3.0%)
Diabetes	20 (2.0%)	48 (2.6%)	20 (2.0%)	27 (2.6%)	53 (3.0%)	82 (2.3%)	42 (2.3%)	36 (3.1%)	328 (2.5%)
Infectious Causes	20 (2.0%)	33 (1.8%)	18 (1.8%)	27 (2.6%)	32 (1.8%)	91 (2.5%)	45 (2.4%)	27 (2.3%)	293 (2.2%)
Nephritis, Nephrotic Syndrome and Nephrosis	18 (1.8%)	36 (2.0%)	24 (2.4%)	18 (1.7%)	29 (1.6%)	85 (2.3%)	24 (1.3%)	16 (1.4%)	250 (1.9%)
Chronic Liver Disease	5 (0.5%)	9 (0.5%)	7 (0.7%)	12 (1.1%)	8 (0.4%)	34 (0.9%)	11 (0.6%)	6 (0.5%)	92 (0.7%)
Congenital/Perinatal	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	3 (0.1%)	1 (0.1%)	2 (0.2%)	10 (0.1%)

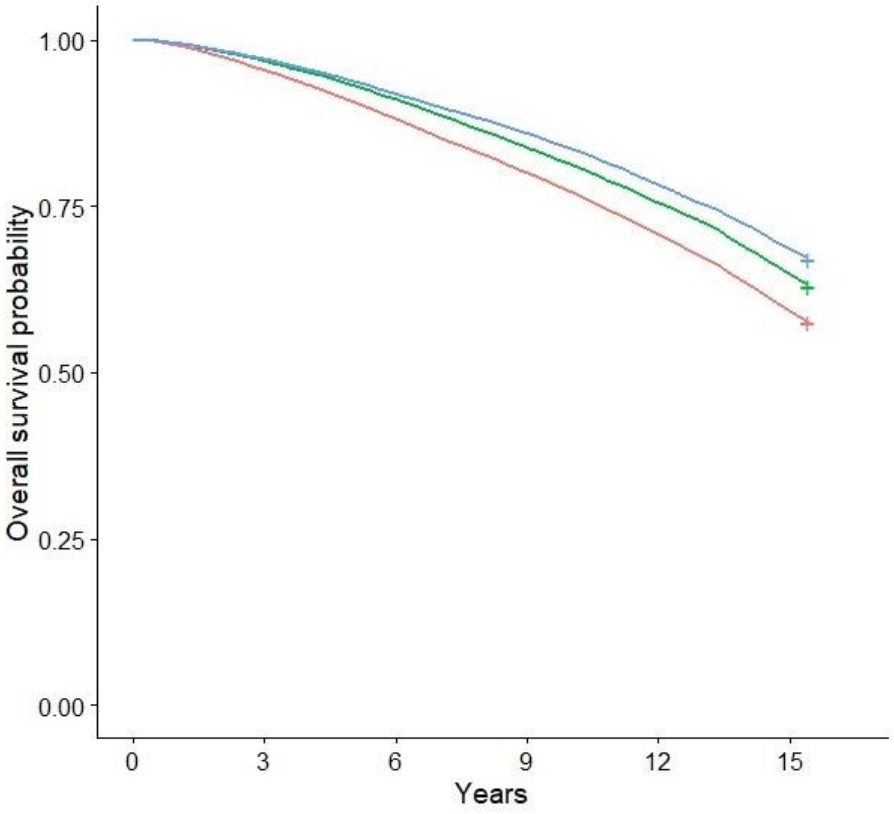
Table 3-4 Association between caregiving and all-cause, cardiovascular and non-cardiovascular mortality

	All-Cause Mortality	Cardiovascular Deaths	Non-Cardiovascular Deaths
Model 1 [a]	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Non-Caregivers	Ref	Ref	Ref
Caregiver of Adults	0.83 (0.81-0.85)	0.82 (0.78-0.86)	0.81 (0.79-0.84)
Caregiver of children	0.71 (0.70-0.73)	0.66 (0.64-0.69)	0.71 (0.69-0.73)
Model 2 [b]			
Non-Caregivers	Ref	Ref	Ref
Caregiver of Adults	0.88 (0.86-0.90)	0.88 (0.84-0.92)	0.86 (0.84-0.89)
Caregiver of children	0.86 (0.84-0.88)	0.85 (0.81-0.88)	0.85 (0.83-0.88)
Model 3 [c]			
Non-Caregivers	Ref	Ref	Ref
Caregiver of Adults	0.87 (0.85-0.90)	0.87 (0.83-0.91)	0.86 (0.83-0.89)
Caregiver of children	0.87 (0.85-0.89)	0.88 (0.83-0.90)	0.86 (0.84-0.89)
Model 4 [d]			
Non-Caregivers	Ref	Ref	Ref
Caregiver of Adults	0.91 (0.88-0.93)	0.91 (0.87-0.95)	0.89 (0.86-0.92)
Caregiver of children	0.89 (0.87-0.92)	0.87 (0.83-0.91)	0.87 (0.85-0.90)
Model 5 [e]			
Non-Caregivers	Ref	Ref	Ref
Caregiver of Adults	0.90 (0.88-0.93)	0.90 (0.86-0.95)	0.89 (0.86-0.92)
Caregiver of children	0.90 (0.87-0.92)	0.88 (0.84-0.92)	0.88 (0.86-0.91)

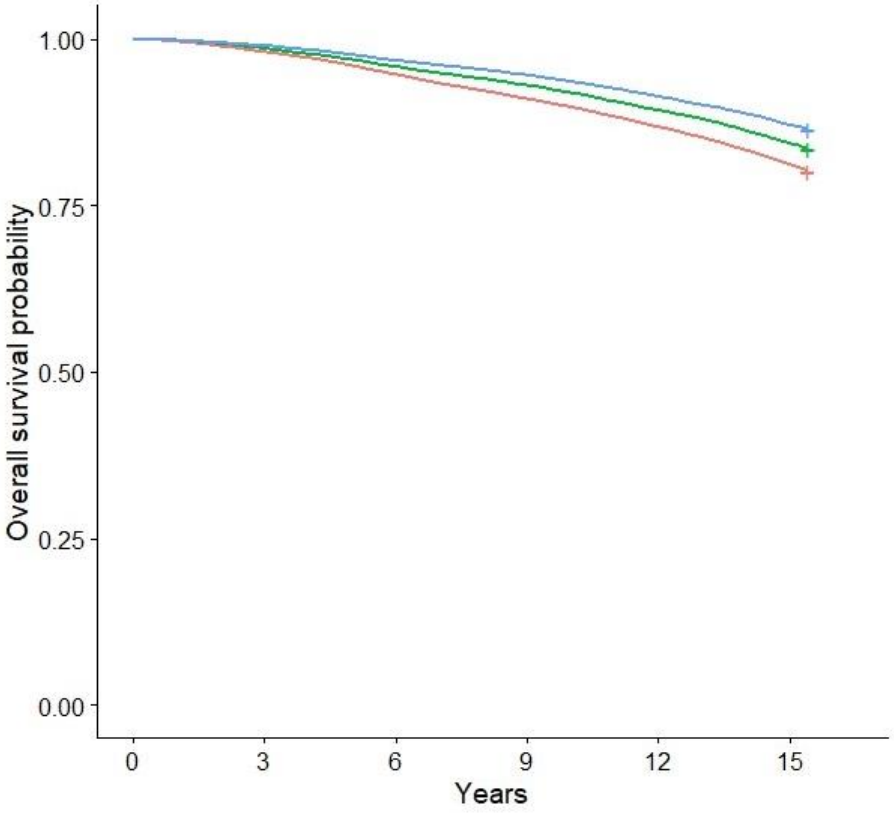
a =Univariate
b= Adjusted for age, race, sex marital status and education.
c= Adjusted for age, race, sex, marital status, education, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health
d= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index and sleep, history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, Transient ischaemic attack and chronic obstructive pulmonary disease
e= Adjusted for all variables included in models c and d.

Figure 3-4 Kaplan Meier curve all-cause mortality, CVD mortality, mortality from non- CVD causes

All-cause mortality



Cardiovascular mortality



Mortality from Non-Cardiovascular Causes

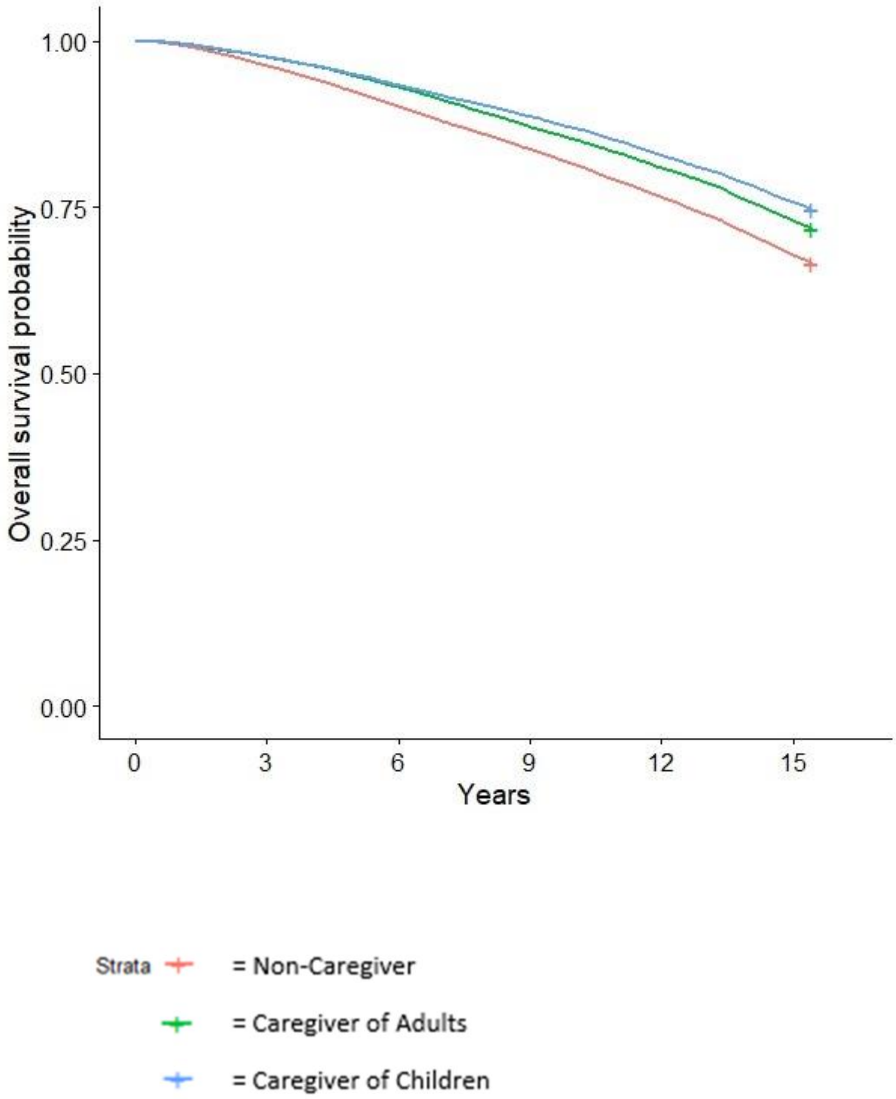


Figure 3-4 Univariate Survival curves for caregivers of adults (green line, n = 18,501), caregivers of children (blue line, n = 26,422) and non-caregivers (red line, n = 107,061), from the NIH-AARP Diet and Health Study over the 15 years of follow-up after enrolment, 2004–2019 for all causes of death, death from cardiovascular causes and death from non-cardiovascular causes.

Table 3-5 Association between caregiving and all-cause mortality, CVD mortality, cancer related mortality, mortality due to Alzheimer's disease and mortality due to accident, suicide, or homicide

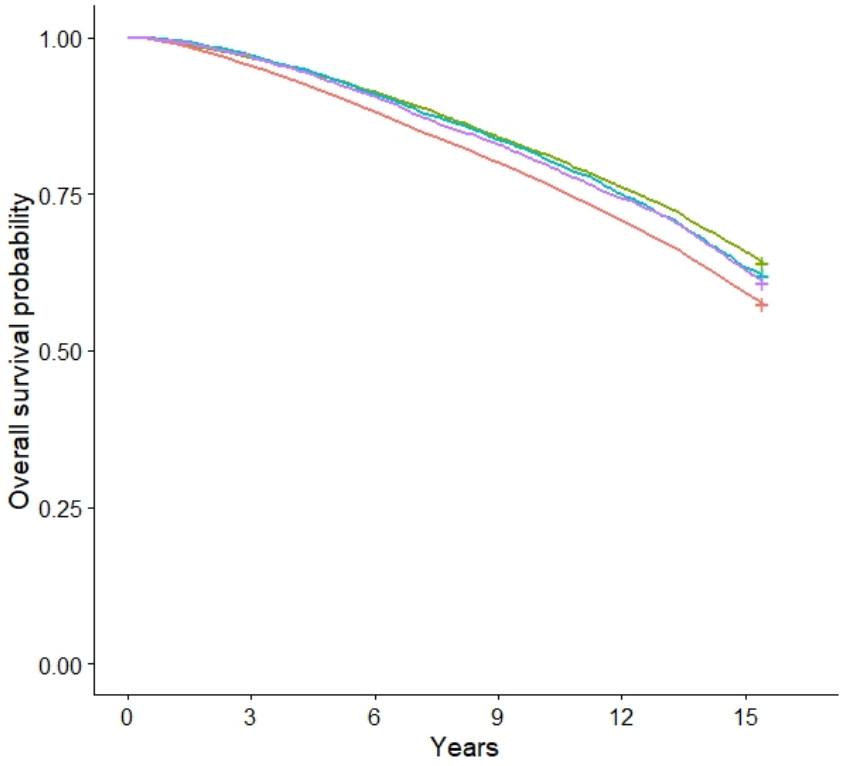
	All-Cause Mortality HR (95% CI)		Mortality due to Cardiovascular Disease HR (95% CI)		Cancer Mortality HR (95% CI)		Alzheimer's disease Mortality HR (95% CI)		Mortality due to Accident, Suicide, Homicide HR (95% CI)	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Any Caregiving	0.76 (0.75-0.78)	0.90 (0.88-0.92)	0.72 (0.70-0.75)	0.89 (0.86-0.92)	0.78 (0.75-0.80)	0.90 (0.87-0.93)	0.68 (0.63-0.72)	0.84 (0.77-0.92)	0.66 (0.60-0.72)	0.77 (0.71-0.86)
Any Adult	0.83 (0.81-0.85)	0.90 (0.88-0.93)	0.82 (0.78-0.86)	0.90 (0.86-0.95)	0.82 (0.78-0.86)	0.90 (0.86-0.95)	0.75 (0.67-0.84)	0.82 (0.73-0.93)	0.70 (0.62-0.80)	0.74 (0.65-0.85)
Any Child	0.71 (0.70-0.73)	0.90 (0.87-0.92)	0.66 (0.64-0.69)	0.88 (0.84-0.92)	0.75 (0.72-0.78)	0.91 (0.87-0.95)	0.64 (0.57-0.71)	0.86 (0.77-0.96)	0.63 (0.56-0.70)	0.80 (0.71-0.90)
Any Caregiving										
<2 hrs week	0.77 (0.75-0.79)	0.90 (0.88-0.92)	0.73 (0.70-0.76)	0.88 (0.84-0.92)	0.78 (0.75-0.81)	0.89 (0.86-0.93)	0.71 (0.64-0.78)	0.86 (0.78-0.96)	0.68 (0.61-0.76)	0.77 (0.62-0.86)
2-6 hrs week	0.73 (0.71-0.76)	0.90 (0.87-0.93)	0.72 (0.67-0.76)	0.92 (0.86-0.98)	0.78 (0.73-0.83)	0.92 (0.86-0.98)	0.68 (0.58-0.80)	0.86 (0.72-1.01)	0.63 (0.52-0.75)	0.77 (0.64-0.93)
≥7 hrs week	0.63 (0.52-0.78)	0.93 (0.76-1.15)	0.52 (0.36-0.76)	0.77 (0.52-1.15)	0.64 (0.45-0.92)	0.90 (0.61-1.33)	0.61 (0.25-1.46)	1.12 (0.46-2.70)	*Not sig (v large CI)*	*Not sig (v large CI*
Adult Caregiving										
<2 hrs week	0.80 (0.77-0.83)	0.88 (0.85-0.91)	0.79 (0.75-0.84)	0.89 (0.84-0.94)	0.78 (0.73-0.83)	0.86 (0.81-0.92)	0.74 (0.64-0.86)	0.85 (0.73-0.99)	0.68 (0.58-0.80)	0.74 (0.62-0.87)
2-6 hrs week	0.88 (0.83-0.93)	0.94 (0.88-0.99)	0.90 (0.81-0.99)	0.97 (0.87-1.07)	0.89 (0.80-0.99)	0.96 (0.86-1.07)	0.82 (0.63-1.07)	0.81 (0.61-1.08)	0.76 (0.57-1.02)	0.77 (0.56-1.05)
≥7 hrs week	0.92 (0.87-0.98)	0.95 (0.89-1.01)	0.92 (0.83-1.01)	0.91 (0.81-1.01)	0.94 (0.84-1.05)	0.96 (0.86-1.07)	0.68 (0.50-0.91)	0.65 (0.47-0.89)	0.77 (0.57-1.04)	0.73 (0.52-1.00)

Children Caregiving										
<2 hrs week	0.75 (0.73-0.77)	0.90 (0.88-0.93)	0.69 (0.66-0.73)	0.88 (0.83-0.92)	0.78 (0.74-0.82)	0.91 (0.87-0.96)	0.69 (0.61-0.78)	0.88 (0.77-0.99)	0.68 (0.60-0.78)	0.81 (0.71-0.94)
2-6 hrs week	0.67 (0.64-0.70)	0.87 (0.83-0.92)	0.63 (0.59-0.69)	0.88 (0.81-0.96)	0.73 (0.67-0.79)	0.90 (0.83-0.98)	0.62 (0.51-0.76)	0.88 (0.71-1.08)	0.57 (0.46-0.72)	0.77 (0.61-0.98)
≥7 hrs week	0.63 (0.60-0.67)	0.89 (0.84-0.94)	0.57 (0.51-0.63)	0.87 (0.78-0.97)	0.66 (0.59-0.73)	0.90 (0.80-0.99)	0.52 (0.39-0.68)	0.80 (0.60-1.06)	0.50 (0.37-0.67)	0.77 (0.56-1.05)

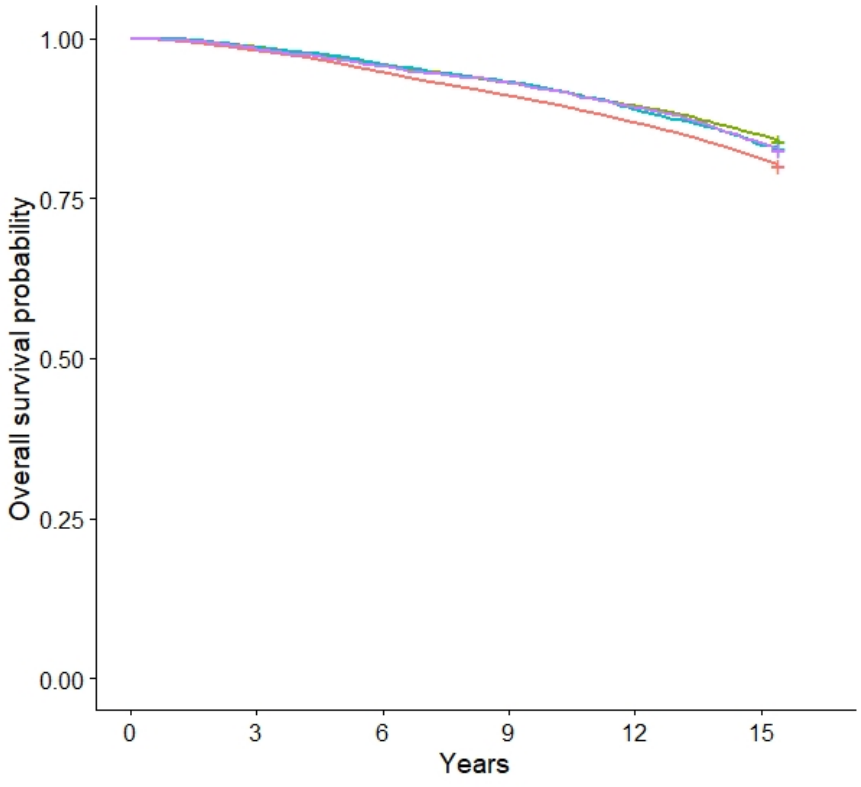
Model 1= Univariate,
Model 2= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index, sleep, , depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, transient ischaemic attack and chronic obstructive pulmonary disease
Hrs= Hours; HR= Hazard Ratio; CI = Confidence Interval

Figure 3-5 Kaplan Meier curve all-cause mortality, CVD mortality and cancer related mortality

All-Cause Mortality



CVD-Mortality



Cancer related Mortality

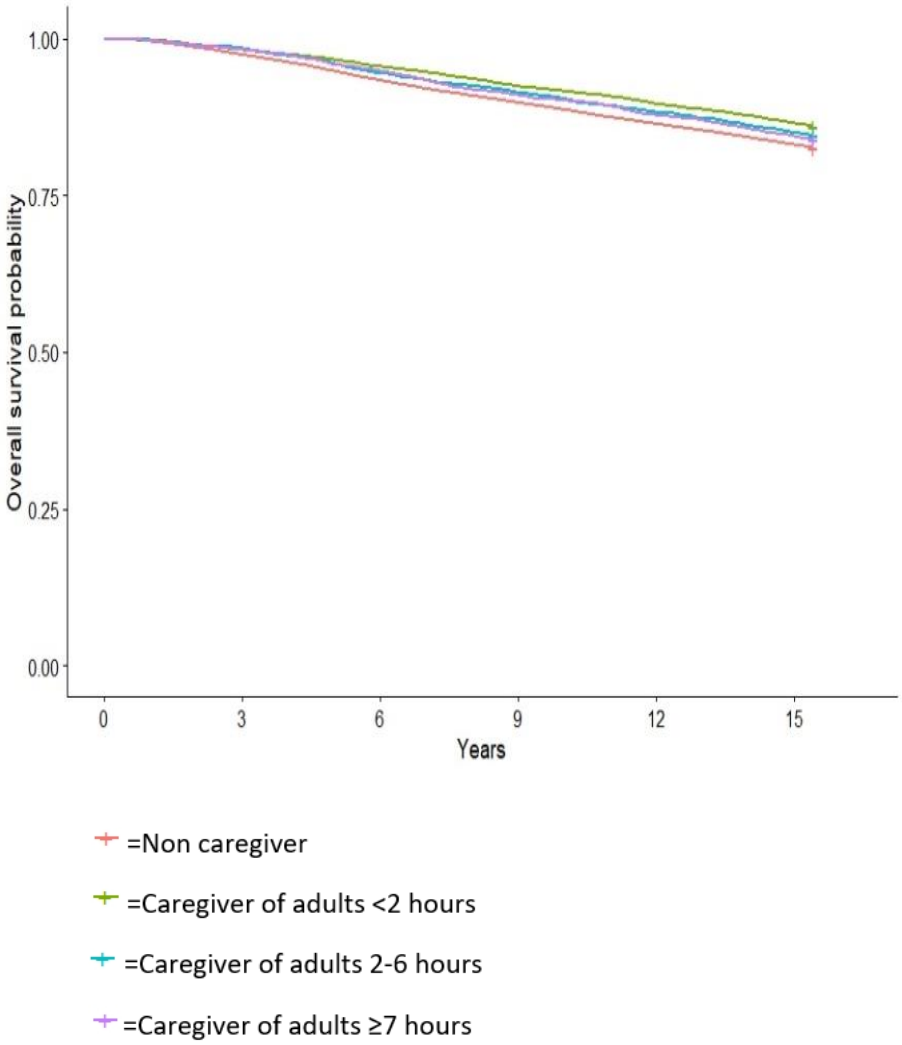


Figure 3-5 Univariate Survival curves for caregivers of adults by time spent caregiving from the NIH-AARP Diet and Health Study over the 15 years of follow-up after enrolment, 2004–2019 for all causes of death, death from cardiovascular causes and death from cancer.

Table 3-6: Association Between caregiving and all-cause mortality among subgroups by sex, self-perceived health and history of cardiovascular disease and diabetes

	Total Population	Male	Female	P-value*	Reporting health as Good or Excellent	Reporting health as Fair/Poor	P-value*	History of CVD	No History of CVD	P-value*	History of Diabetes	No History of Diabetes	P-value *
	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	
Model 1 [a]													
Non-Caregivers	Ref	Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref	
Caregiver of Adults	0.83 (0.81-0.85)	0.87 (0.84-0.90)	0.76 (0.73-0.80)	<0.001	0.84 (0.82-0.86)	0.77 (0.72-0.83)	0.015	0.85 (0.81-0.90)	0.83 (0.80-0.85)	0.42	0.82 (0.77-0.87)	0.83 (0.81-0.86)	0.072
Caregiver of children	0.71 (0.70-0.73)	0.74 (0.72-0.77)	0.70 (0.67-0.72)	<0.001	0.72 (0.70-0.73)	0.76 (0.71-0.81)	0.015	0.74 (0.71-0.78)	0.72 (0.70-0.74)	0.42	0.76 (0.72-0.80)	0.71 (0.69-0.73)	0.072
Model 2 [b]													
Non-Caregivers	Ref	Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref	
Caregiver of Adults	0.88 (0.86-0.90)	0.89 (0.87-0.92)	0.84 (0.81-0.88)	0.006	0.89 (0.87-0.92)	0.81 (0.75-0.87)	0.03	0.87 (0.83-0.92)	0.88 (0.86-0.91)	0.74	0.85 (0.80-0.90)	0.89 (0.87-0.92)	0.11
Caregiver of children	0.86 (0.84-0.88)	0.89 (0.86-0.91)	0.82 (0.78-0.85)	0.006	0.87 (0.85-0.89)	0.86 (0.81-0.92)	0.03	0.84 (0.81-0.88)	0.86 (0.84-0.89)	0.74	0.86 (0.82-0.91)	0.86 (0.84-0.89)	0.11
Model 3 [c]													
Non-Caregivers	Ref	Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref	
Caregiver of Adults	0.87 (0.85-0.90)	0.88 (0.85-0.91)	0.85 (0.81-0.89)	0.077	0.88 (0.86-0.91)	0.80 (0.74-0.86)	0.018	0.86 (0.82-0.91)	0.88 (0.85-0.91)	0.7	0.85 (0.80-0.89)	0.88 (0.86-0.91)	0.12
Caregiver of children	0.87 (0.85-0.89)	0.89 (0.87-0.92)	0.84 (0.81-0.87)	0.077	0.88 (0.85-0.90)	0.87 (0.82-0.93)	0.018	0.85 (0.82-0.89)	0.88 (0.85-0.90)	0.7	0.88 (0.84-0.93)	0.87 (0.85-0.90)	0.12
Model 4 [d]													
Non-Caregivers	Ref	Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref	
Caregiver of Adults	0.91 (0.89-0.93)	0.92 (0.89-0.95)	0.89 (0.85-0.93)	0.005	0.92 (0.89-0.95)	0.85 (0.79-0.91)	0.12	0.91 (0.87-0.96)	0.91 (0.88-0.94)	0.89	0.89 (0.84-0.94)	0.92 (0.89-0.94)	0.19
Caregiver of children	0.89 (0.87-0.91)	0.92 (0.89-0.95)	0.84 (0.81-0.88)	0.005	0.90 (0.87-0.92)	0.88 (0.82-0.94)	0.12	0.88 (0.84-0.92)	0.89 (0.87-0.92)	0.89	0.90 (0.85-0.94)	0.89 (0.86-0.91)	0.19

Model 5 [e]													
Non-Caregivers	Ref	Ref	Ref		Ref	Ref		Ref	Ref		Ref	Ref	
Caregiver of Adults	0.90 (0.88-0.93)	0.91 (0.88-0.94)	0.89 (0.85-0.94)	0.053	0.91 (0.89-0.94)	0.84 (0.78-0.91)	0.095	0.90 (0.86-0.95)	0.91 (0.88-0.93)	0.95	0.89 (0.84-0.94)	0.91 (0.88-0.94)	0.17
Caregiver of children	0.90 (0.87-0.92)	0.92 (0.89-0.95)	0.86 (0.83-0.90)	0.053	0.90 (0.88-0.92)	0.88 (0.83-0.94)	0.095	0.88 (0.84-0.93)	0.90 (0.88-0.93)	0.95	0.91 (0.86-0.95)	0.89 (0.87-0.92)	0.17

a =Univariate

b= Adjusted for age, race, sex marital status and education.

c= Adjusted for age, race, sex, marital status, education, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health

d= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index and sleep, history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, Transient ischaemic attack and chronic obstructive pulmonary disease; e= Adjusted for all variables included in models c and d. HR= Hazard Ratio; CI = Confidence Interval

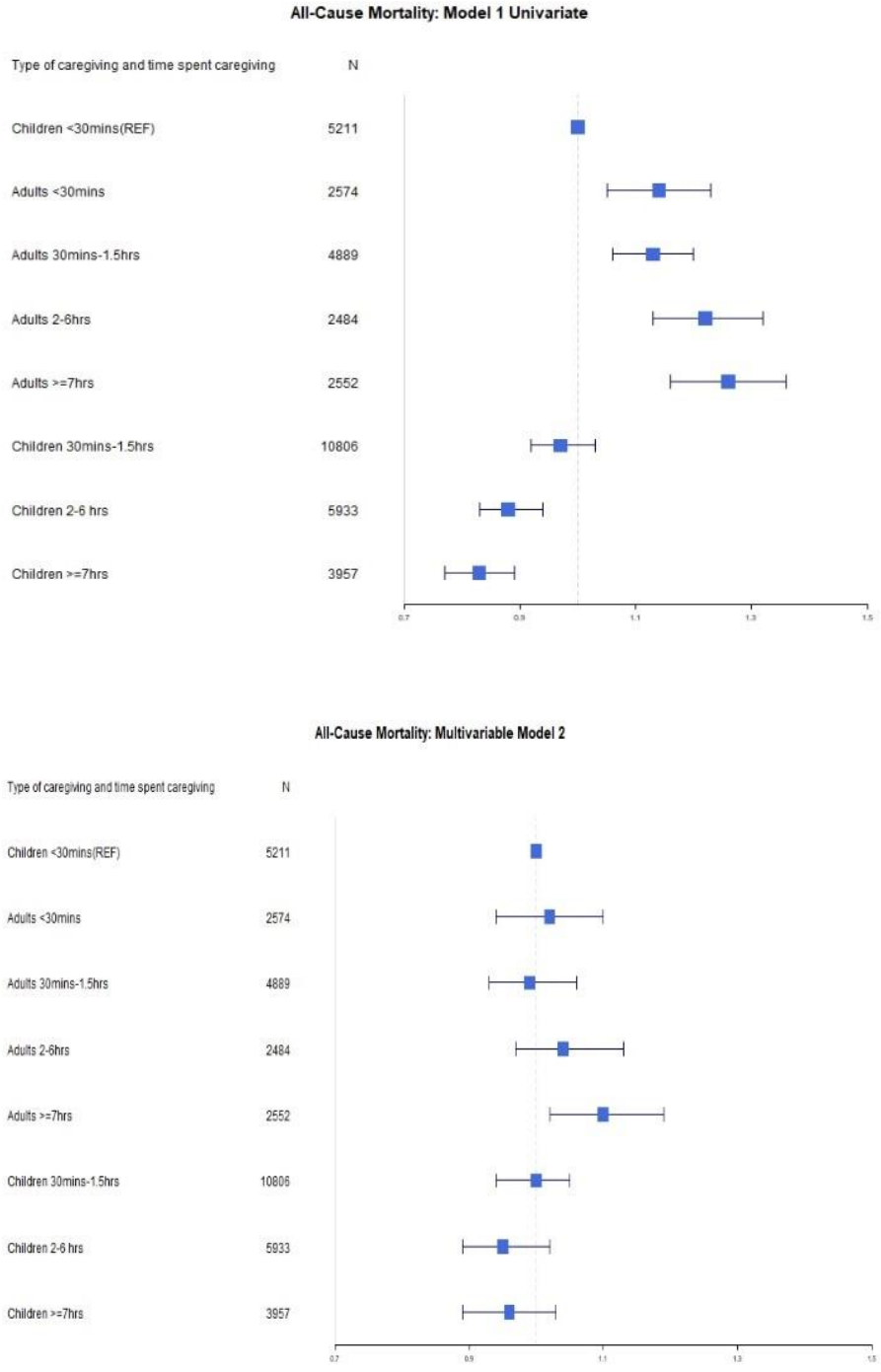
*= P for Interaction

Table 3-7: Caregiving and all-cause mortality by time to follow up

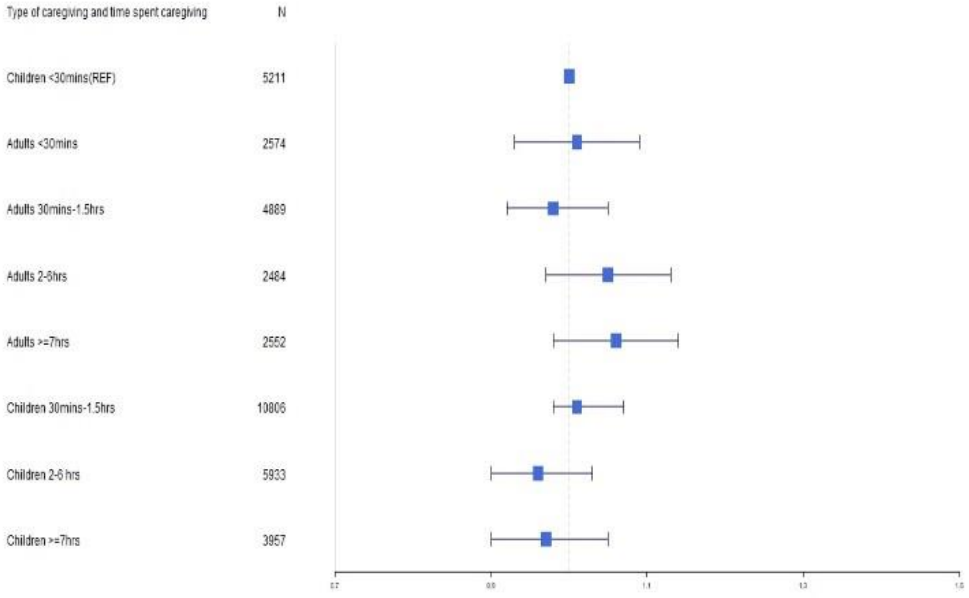
	Less than 2 years follow up Adults (n=331) Children(n=431) Non-caregiver (n=2666)	**2 years follow up or more Adults (n=17,770) Children(n=25,476) Non-caregiver (n=102,118)**
Model 1 [a]	HR (95% CI)	HR (95% CI)
Non-Caregivers	Ref	Ref
Caregiver of Adults	0.93 (0.83-1.00)	0.83 (0.81-0.86)
Caregiver of children	1.04 (0.94-1.10)	0.72 (0.70-0.74)
Model 2 [b]		
Non-Caregivers	Ref	Ref
Caregiver of Adults	0.93 (0.83-1.04)	0.89 (0.86-0.91)
Caregiver of children	1.03 (0.93-1.14)	0.87 (0.84-0.89)
Model 3 [c]		
Non-Caregivers	Ref	Ref
Caregiver of Adults	0.95 (0.85-1.07)	0.88 (0.86-0.90)
Caregiver of children	1.04 (0.94-1.16)	0.88 (0.86-0.90)
Model 4 [d]		
Non-Caregivers	Ref	Ref
Caregiver of Adults	0.95 (0.85-1.07)	0.90 (0.88-0.93)
Caregiver of children	1.01 (0.91-1.13)	0.88 (0.86-0.91)
Model 5 [e]		
Non-Caregivers	Ref	Ref
Caregiver of Adults	0.97 (0.86-1.09)	0.90 (0.88-0.93)
Caregiver of children	1.02 (0.92-1.14)	0.89 (0.87-0.91)

a =Univariate
b= Adjusted for age, race, sex marital status and education.
c= Adjusted for age, race, sex, marital status, education, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health
d= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index and sleep, history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, Transient ischaemic attack and chronic obstructive pulmonary disease
e= Adjusted for all variables included in models c and d. HR= Hazard Ratio; CI = Confidence Interval

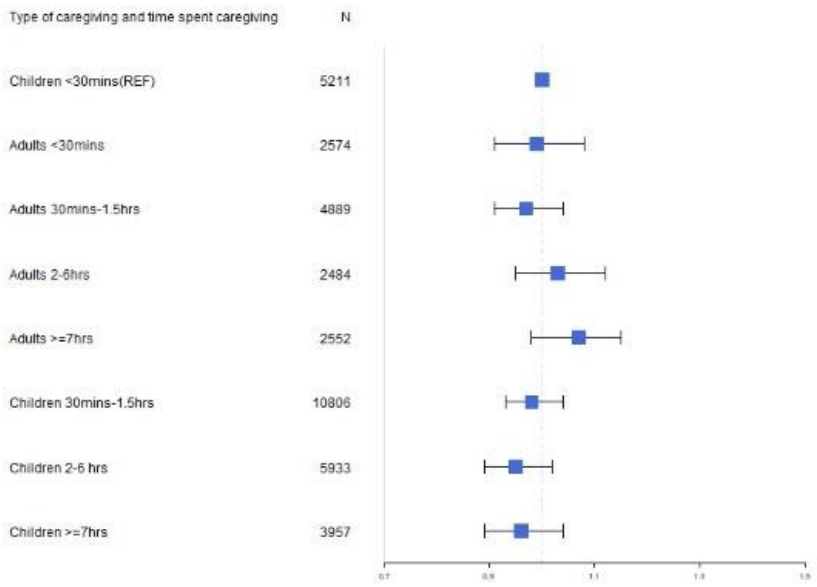
Figure 3-6 Association between caregiving and all-cause mortality among caregivers



All-Cause Mortality: Multivariable Model 3



All-Cause Mortality: Multivariable Model 4



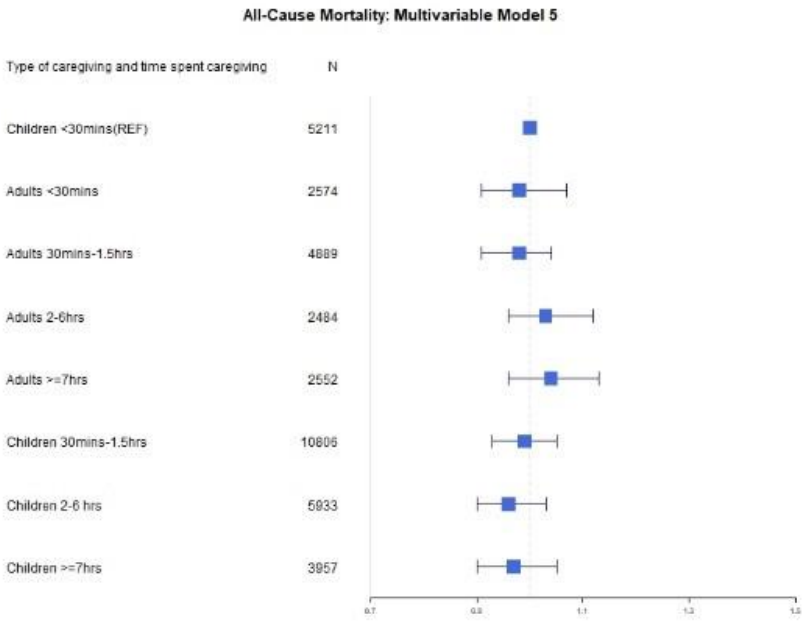


Figure 3-6: Hazard ratios for death from all causes and from specific causes are for the comparison of caregivers of children and of adults by time spent caregiving compared to caregivers of children for thirty minutes or less per week. Participants were classified by duration of caregiving; caregiving of adults for less than 30 mins, 30minutes-1.5 hours, 2-6 hours, and 7 hours or more, caregiving of children for less than 30 mins, caregiving of children 30minutes-1.5 hours, 2-6 hours and 7 hours or more. Risk estimates were adjusted as follows: Model 1 =Univariate; Model 2=Adjusted for age, race, sex marital status and education; Model 3=Adjusted for age, race, sex, marital status, education, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health; Model 4= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index and sleep, history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, Transient ischaemic attack and chronic obstructive pulmonary disease; Model 5=Adjusted for all variables included in models c and d. Horizontal lines represent 95% confidence intervals.

Table 3-8 Association Between caregiving and cardiovascular and non-cardiovascular mortality among caregivers

Duration of caregiving by time per week	Cardiovascular Deaths HR (95% CI)	Non-Cardiovascular Deaths HR (95% CI)
Model 1 [a]		
Children <30mins	Ref	Ref
Adults <30mins	1.16 (1.01-1.33)	1.14 (1.04-1.25)
Adults 30mins-1.5hrs	1.22 (1.09-1.36)	1.11 (1.02-1.20)
Adults 2-6 hrs	1.36 (1.19-1.55)	1.21 (1.10-1.33)
Adults ≥7hrs	1.35 (1.18-1.54)	1.26 (1.15-1.38)
Children 30mins-1.5hrs	0.94 (0.85-1.04)	0.98 (0.92-1.05)
Children 2-6 hrs	0.88 (0.79-0.99)	0.88 (0.81-0.95)
Children ≥7hrs	0.79 (0.69-0.90)	0.83 (0.76-0.91)
Model 2 [b]		
Children <30mins	Ref	Ref
Adults <30mins	0.99 (0.86-1.13)	1.02 (0.93-1.12)
Adults 30mins-1.5hrs	1.01 (0.90-1.13)	0.98 (0.90-1.06)
Adults 2-6 hrs	1.10 (0.96-1.25)	1.04 (0.95-1.14)
Adults ≥7hrs	1.11 (0.97-1.27)	1.10 (1.01-1.21)
Children 30mins-1.5hrs	0.97 (0.88-1.08)	1.00 (0.93-1.07)
Children 2-6 hrs	0.98 (0.87-1.10)	0.94 (0.86-1.01)
Children ≥7hrs	0.95 (0.84-1.09)	0.95 (0.87-1.04)
Model 3 [c]		
Children <30mins	Ref	Ref
Adults <30mins	0.98 (0.85-1.12)	1.01 (0.92-1.11)
Adults 30mins-1.5hrs	1.00 (0.85-1.12)	0.97 (0.90-1.05)
Adults 2-6 hrs	1.10 (0.96-1.26)	1.04 (0.95-1.14)
Adults ≥7hrs	1.04 (0.91-1.19)	1.07 (0.97-1.17)
Children 30mins-1.5hrs	0.99 (0.90-1.09)	1.01 (0.94-1.08)
Children 2-6 hrs	1.00 (0.89-1.12)	0.95 (0.88-1.02)
Children ≥7hrs	0.97 (0.88-1.11)	0.96 (0.88-1.05)
Model 4 [d]		
Children <30mins	Ref	Ref
Adults <30mins	0.98 (0.85-1.13)	1.13 (1.03-1.24)
Adults 30mins-1.5hrs	0.98 (0.87-1.10)	1.10 (1.02-1.19)
Adults 2-6 hrs	1.10 (0.96-1.27)	1.20 (1.10-1.32)
Adults ≥7hrs	1.05 (0.92-1.21)	1.24 (1.14-1.36)
Children 30mins-1.5hrs	0.96 (0.87-1.07)	0.98 (0.91-1.04)
Children 2-6 hrs	0.98 (0.87-1.10)	0.87 (0.80-0.94)
Children ≥7hrs	0.97 (0.84-1.10)	0.83 (0.76-0.90)
Model 5 [e]		
Children <30mins	1	1
Adults <30mins	0.97 (0.84-1.12)	0.99 (0.89-1.09)
Adults 30mins-1.5hrs	0.97 (0.87-1.10)	0.97 (0.90-1.06)
Adults 2-6 hrs	1.10 (0.96-1.27)	1.03 (0.94-1.14)
Adults ≥7hrs	1.02 (0.88-1.17)	1.07 (0.97-1.18)
Children 30mins-1.5hrs	0.97 (0.87-1.07)	0.98 (0.92-1.06)
Children 2-6 hrs	0.99 (0.88-1.11)	0.93 (0.86-1.01)
Children ≥7hrs	0.98 (0.85-1.12)	0.96 (0.87-1.06)

a =Univariate; b= Adjusted for age, race, sex marital status and education.
c= Adjusted for age, race, sex, marital status, education, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health

d= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index and sleep, history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, Transient ischaemic attack and chronic obstructive pulmonary disease
e= Adjusted for all variables included in models c and d. HR= Hazard Ratio; CI = Confidence Interval

Figure 3-7 Histogram of propensity score matched adult caregivers Vs non-caregivers

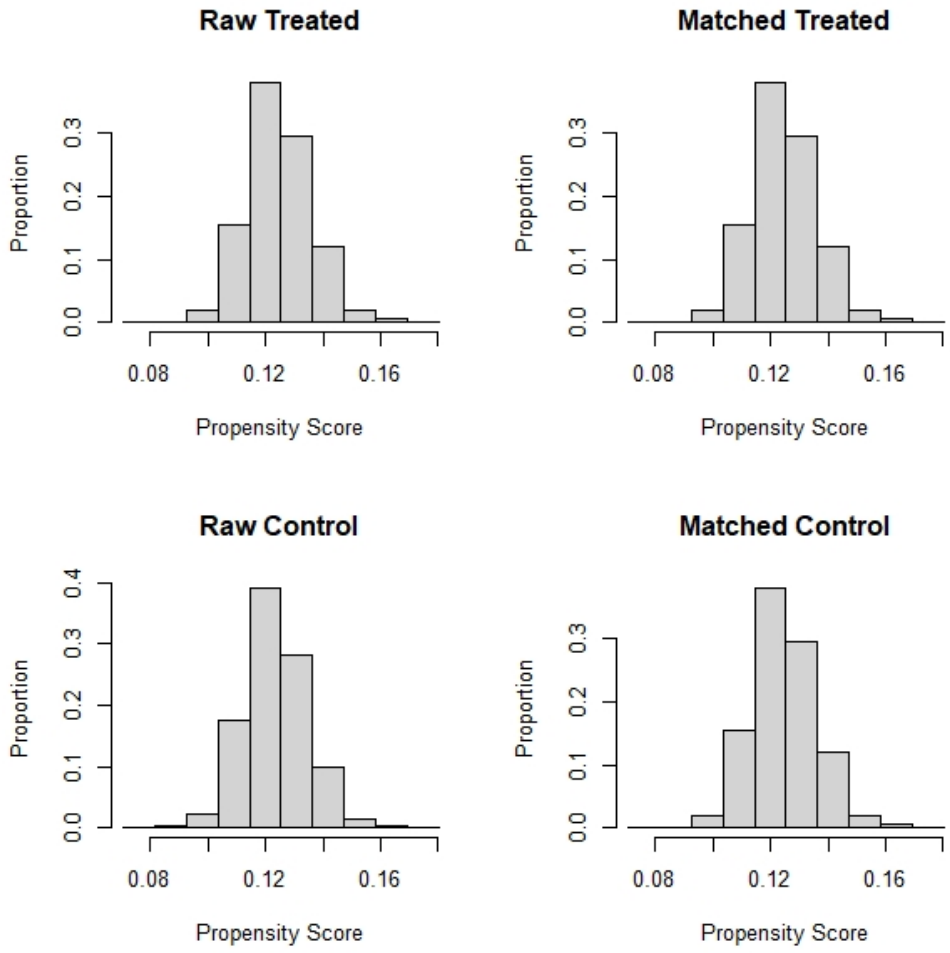


Figure 3-7 Histograms showing the density of propensity score distribution in the adult caregiver (treated population) and non-caregiver (control population) groups before and after matching.

Figure 3-8 Histogram of propensity score matched child caregivers Vs non-caregivers

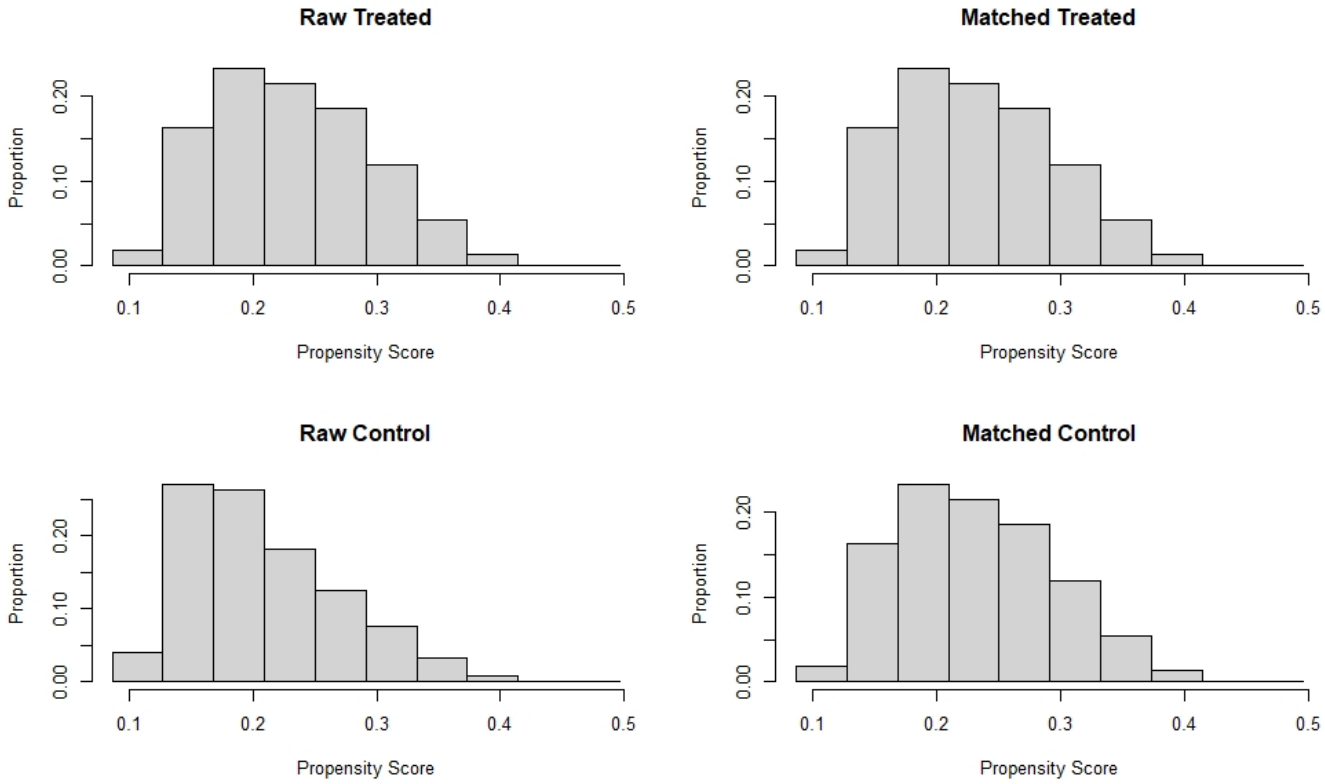


Figure 3-8 Histograms showing the density of propensity score distribution in the caregiver of children (treated population) and non-caregiver (control population) groups before and after matching.

Table 3-9 Association between caregiving of adults and all-cause mortality, among matched participants and total population

	All-Cause Mortality *MATCHED POPULATION	All-Cause Mortality *TOTAL POPULATION
Model 1 [a]	**HR (95% CI)**	**HR (95% CI)**
Non-Caregivers	Ref	Ref
Caregiver of Adults	0.94 (0.91-0.97)	0.83 (0.81-0.85)
Model 2 [b]		
Non-Caregivers	Ref	Ref
Caregiver of Adults	0.94 (0.91-0.97)	0.88 (0.86-0.90)
Model 3 [c]		
Non-Caregivers	Ref	Ref
Caregiver of Adults	0.92 (0.89-0.95)	0.87 (0.85-0.90)
Model 4 [d]		
Non-Caregivers	Ref	Ref
Caregiver of Adults	0.95 (0.92-0.99)	0.91 (0.88-0.93)
Model 5 [e]		
Non-Caregivers	Ref	Ref
Caregiver of Adults	0.94 (0.90-0.97)	0.90 (0.88-0.93)

a =Univariate
b= Adjusted for age, race, sex marital status and education.
c= Adjusted for age, race, sex, marital status, education, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health
d= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index and sleep, history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, Transient ischaemic attack and chronic obstructive pulmonary disease
e= Adjusted for all variables included in models c and d.

HR= Hazard Ratio; CI = Confidence Interval

Table 3-10 Association between caregiving of children and all-cause mortality, among matched participants and total population

	All-Cause Mortality *MATCHED POPULATION	All-Cause Mortality *TOTAL POPULATION
Model 1 [a]	**HR (95% CI)**	**HR (95% CI)**
Non-Caregivers	Ref	Ref
Caregiver of children	0.88 (0.85-0.90)	0.71 (0.70-0.73)
Model 2 [b]		
Non-Caregivers	Ref	Ref
Caregiver of children	0.89 (0.87-0.91)	0.86 (0.84-0.88)
Model 3 [c]		
Non-Caregivers	Ref	Ref
Caregiver of children	0.88 (0.86-0.91)	0.87 (0.85-0.89)
Model 4 [d]		
Non-Caregivers	Ref	Ref
Caregiver of children	0.91 (0.88-0.93)	0.89 (0.87-0.92)
Model 5 [e]		
Non-Caregivers	Ref	Ref
Caregiver of Children	0.90 (0.88-0.93)	0.90 (0.87-0.92)

a =Univariate
b= Adjusted for age, race, sex marital status and education.
c= Adjusted for age, race, sex, marital status, education, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health
d= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index and sleep, history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, Transient ischaemic attack and chronic obstructive pulmonary disease
e= Adjusted for all variables included in models c and d.

HR= Hazard Ratio; CI = Confidence Interval

Table 3-11 Association of caregiver depression and quality of life with all-cause mortality among adult caregivers

	All-Cause Mortality HR (95% CI)				
	Model 1 [a]	**Model 2 [b]**	**Model 3 [c]**	**Model 4 [d]**	**Model 5 [e]**
Adult Caregiving (with depression)					
<2 hrs week	0.76 (0.70-0.82)	0.81 (0.75-0.88)	0.82 (0.76-0.89)	0.86 (0.79-0.93)	0.86 (0.79-0.93)
2-6 hrs week	0.81 (0.71-0.92)	0.84 (0.74-0.96)	0.87 (0.76-1.00)	0.90 (0.78-1.03)	0.91 (0.80-1.05)
≥7 hrs week	0.82 (0.72-0.93)	0.86 (0.75-0.97)	0.81 (0.71-0.92)	0.93 (0.81-1.06)	0.89 (0.80-1.02)
Adult Caregiving (without depression)					
<2 hrs week	0.81 (0.78-0.83)	0.86 (0.83-0.89)	0.86 (0.83-0.89)	0.88 (0.85-0.91)	0.88 (0.85-0.91)
2-6 hrs week	0.86 (0.81-0.91)	0.90 (0.85-0.95)	0.90 (0.84-0.95)	0.94 (0.88-1.00)	0.93 (0.87-0.99)
≥7 hrs week	0.89 (0.84-0.95)	0.94 (0.89-1.00)	0.89 (0.84-0.95)	0.97 (0.91-1.03)	0.93 (0.87-0.99)
Adult Caregiving (poor QoL since retirement)					
<2 hrs week	0.78 (0.70-0.86)	0.80 (0.72-0.89)	0.78 (0.72-0.85)	0.85 (0.77-0.95)	0.83 (0.77-0.95)
2-6 hrs week	0.69 (0.59-0.82)	0.71 (0.60-0.83)	0.76 (0.67-0.87)	0.78 (0.66-0.92)	0.82 (0.71-0.94)
≥7 hrs week	0.70 (0.62-0.80)	0.75 (0.66-0.85)	0.78 (0.70-0.87)	0.85 (0.74-0.97)	0.86 (0.76-0.96)
Adult Caregiving (better/same QoL since retirement)					
<2 hrs week	0.81 (0.78-0.84)	0.87 (0.84-0.90)	0.87 (0.84-0.90)	0.89 (0.86-0.92)	0.89 (0.86-0.92)
2-6 hrs week	0.87 (0.82-0.93)	0.92 (0.87-0.98)	0.92 (0.87-0.98)	0.95 (0.90-1.01)	0.95 (0.90-1.01)
≥7 hrs week	0.89 (0.83-0.94)	0.94 (0.88-1.00)	0.91 (0.86-0.97)	0.96 (0.90-1.03)	0.94 (0.89-1.01)

a =Univariate
b= Adjusted for age, race, sex marital status and education.
c= Adjusted for age, race, sex, marital status, education, depression, Quality of life since retirement compared to working life, personal trouble with activities of daily living, self-reported overall health
d= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index and sleep, history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, Transient ischaemic attack and chronic obstructive pulmonary disease
e= Adjusted for all variables included in models c and d.
HR= Hazard Ratio; CI = Confidence Interval

Table 3-12 Association between trouble with activities of daily living and mortality, among caregivers and non-caregivers

Trouble with Activities of Daily living (ADL)	Non-caregivers	Caregivers (any)	P Interaction
	HR (95% CI)	**HR (95% CI)**	
Model 1 [a]			
None/Slight Trouble	Ref	Ref	
Significant Trouble	1.90 (1.87-1.95)	1.75 (1.70-1.82)	<0.001
Model 2 [b]			
None/Slight Trouble	Ref	Ref	
Significant Trouble	1.87 (1.83-1.90)	1.72 (1.66-1.78)	<0.001
Model 3 [c]			
None/Slight Trouble	Ref	Ref	
Significant Trouble	1.64 (1.60-1.67)	1.52 (1.47-1.58)	<0.001
Model 4 [d]			
None/Slight Trouble	Ref	Ref	
Significant Trouble	1.51 (1.48-1.55)	1.45 (1.39-1.50)	0.003
Model 5 [e]			
None/Slight Trouble	Ref	Ref	
Significant Trouble	1.43 (1.40-1.46)	1.37 (1.32-1.43)	0.004

a =Univariate
b= Adjusted for age, race, sex marital status and education.
c= Adjusted for age, race, sex, marital status, education, depression, Quality of life since retirement compared to working life, self-reported overall health
d= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index and sleep, history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, Transient ischaemic attack and chronic obstructive pulmonary disease
e= Adjusted for all variables included in models c and d.
HR= Hazard Ratio; CI = Confidence Interval

Table 3-13 Association between self-reported health and mortality, among caregivers and non-caregivers

Self-Reported Health	Non-caregivers	Caregivers (any)	P Interaction
	HR (95% CI)	**HR (95% CI)**	
Model 1 [a]			
Good/Excellent	Ref	Ref	
Fair/Poor	1.85 (1.80-1.90)	1.83 (1.74-1.92)	0.60
Model 2 [b]			
Good/Excellent	Ref	Ref	
Fair/Poor	1.89 (1.84-1.95)	1.88 (1.79-1.87)	0.46
Model 3 [c]			
Good/Excellent	Ref	Ref	
Fair/Poor	1.49 (1.45-1.54)	1.53 (1.46-1.61)	0.38
Model 4 [d]			
Good/Excellent	Ref	Ref	
Fair/Poor	1.38 (1.34-1.42)	1.37 (1.30-1.44)	0.27
Model 5 [e]			
Good/Excellent	Ref	Ref	
Fair/Poor	1.24 (1.20-1.27)	1.23 (1.17-1.30)	0.27

a =Univariate
b= Adjusted for age, race, sex marital status and education.
c= Adjusted for age, race, sex, marital status, education, depression, Quality of life since retirement compared to working life, trouble with activities of daily living
d= Adjusted for age, race, sex, marital status, education, vigorous physical activity, smoking, alcohol use, diet, body mass index and sleep, history of hypertension, diabetes, cardiovascular disease, end stage kidney disease, stroke, Transient ischaemic attack and chronic obstructive pulmonary disease
e= Adjusted for all variables included in models c and d.
HR= Hazard Ratio; CI = Confidence Interval

Figure 3-9 Forest plot of the effect of caregiving of adults on all-cause mortality (random-effects model)

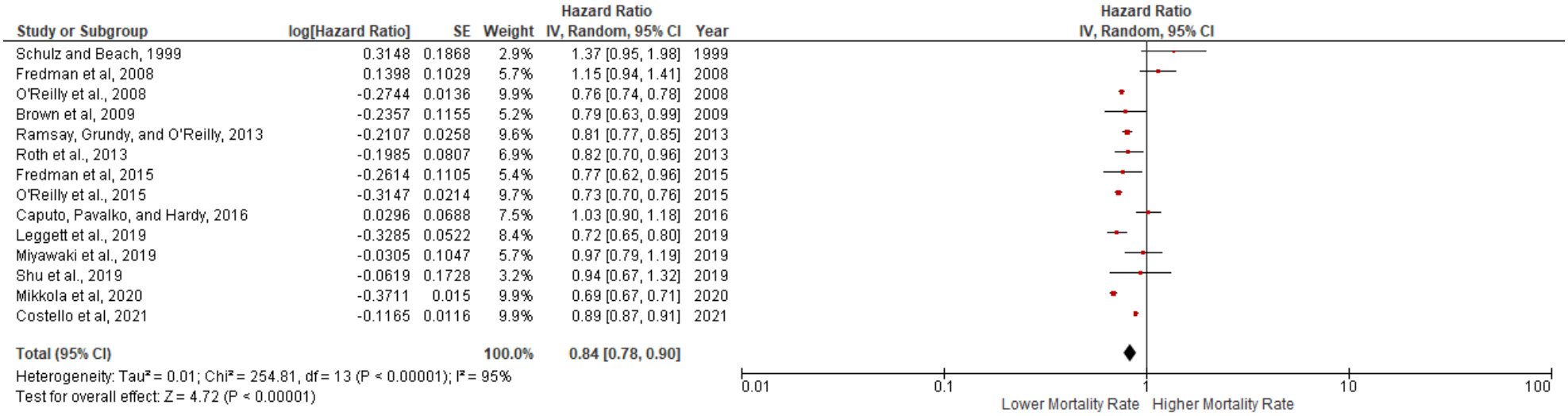


Figure 3-9: Forest plot showing the effect of caregiving of adults on mortality. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. A random-effects model was used to estimate the overall effect of informal caregiving on mortality across the 14 studies. The diamond at the bottom represents the combined effect across the studies and corresponding confidence interval.

Chapter 4

Role of Proxy Respondents in International Stroke Research: Experience of the INTERSTROKE Study

Maria Costello, Conor Judge, Martin J. O'Donnell, Michelle Canavan, Salim Yusuf on behalf of the INTERSTROKE investigators - Role of Proxy Respondents in International Stroke Research: Experience of the INTERSROKE Study; Awarded Michael J O Donnell award in recognition of outstanding research by a registrar in medicine Galway University Hospital Research Day June 2021

Introduction

Measuring patient-reported information in stroke (and neurovascular) research is challenging, due to the high proportion of patients with impairments in communication. At least one-half of hospitalised patients with acute stroke are aphasic (125,126), or cognitively impaired, limiting their ability to complete an inventory of questions (127). In some research studies, patients who are unable to complete questionnaires are excluded, leading to selection bias with disproportionate loss of patients with severe stroke which substantially impairs the external validity, particularly when the objective is to include a truly representative sample.

An alternate approach to exclusion of such patients is the use of a proxy respondent as their representative. The use of proxy respondents has been demonstrated to be reliable for recalling personal medical history of research participants and has been effective in populations unable to recall historical information (128–131), especially for directly observed variables (e.g. activities of daily living, smoking). For other more subjective measures (e.g. psychosocial stress, quality of life), use of proxy respondents may be less reliable (132,133), although a proxy respondent may sometimes provide more valid information for these factors (134,135).

Use of proxy respondents has led to an increase in the proportion of patients with severe stroke (and other conditions that impair communication) included in research studies, but research on the topic is limited to small studies in high-income settings (136,137). The role of proxy respondents in international studies, including low and middle-income regions has not been previously reported. Proxy respondents were utilised in the INTERSTROKE study to enhance the inclusion of a representative sample of patients with acute stroke (138). The primary INTERSTROKE analysis reported similar magnitudes of

association regarding stroke risk factors when information is derived from proxy respondents, or directly from patients.

This analysis aimed to evaluate the role of proxy respondents, by estimating the magnitude of avoidable selection bias incurred if proxy respondents were not utilised and to report regional variations in prevalence and determinants of proxy use.

4.1 Methods

4.1.1 Study Design and Participants

INTERSTROKE is a large, international case control study of risk factors for first stroke. 13,462 stroke patients and 13,483 matched controls were recruited between Jan 11, 2007 and Aug 8, 2015 from 142 centres in 32 countries (138). Cases were patients with first acute stroke and were enrolled to the study within five days of symptom onset and within 72 hours of hospital admission. Cases were defined using the WHO clinical criteria for stroke (139) and were confirmed using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) brain imaging. The study was approved by local ethics committees at all recruitment sites and written informed consent was obtained for all participants.

4.1.2 Definition of Proxy Respondent

Patients unable to communicate adequately could be enrolled if they had a valid proxy respondent. A valid proxy respondent was considered a spouse or first degree relative who was living in the same home or aware of the participant's previous medical history and current therapies. Participants were excluded from these analyses if there was no information on respondent type (n=144).

4.1.3 Measurement of Risk Factors and Stroke Severity

Standardized questionnaires were used to collect data on demographics, lifestyle risk factors and characteristics of acute stroke from participants. Pre-admission functional impairment was measured using pre-admission modified-Rankin scale (m-RS; Table 4-1), which was grouped as 0 (no disability), 1 (no significant disability despite symptoms) and >1 at least some disability). Stroke severity was measured using the m-RS at time of stroke, level of consciousness and disabling clinical features (aphasia and homonymous hemianopia). Modified-Rankin scale at time of stroke was grouped in the following categories 0,1,2,3,4,5 with each level representing increasing levels of disability. Level of consciousness refers to level of consciousness of stroke cases at time of presentation. Aphasia and homonymous hemianopia were required to be present for 24 hours or more before recruitment. History of cardiac risk factors was defined as any medical history of angina, myocardial infarction, transient ischemic attack (TIA) or peripheral arterial disease. Hypertension was defined as a history of self-reported hypertension or a blood pressure reading of greater than 140/90 mmHg at time of recruitment. Ischaemic strokes were further subclassed by Oxfordshire Community Stroke Project (OCSP) classification system (140). This classification categorises stroke by following clinical syndromes: total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), posterior circulation infarcts (POCI) and lacunar infarcts (LACI). Countries were grouped by income using the 2011 World Bank Country Income Categories: high income (Australia, Canada, Croatia, Denmark, Germany, Ireland, Poland, Sweden, United Arab Emirates, and the UK), middle income (Argentina, Brazil, Chile, China, Columbia, Ecuador, Malaysia, Peru, Russia, South Africa, Turkey, India, Nigeria, Pakistan, Philippines, and Sudan), and low income (Mozambique and Uganda). All data were transferred to the Population Health Research

Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada for quality-control checks and statistical analysis.

Table 4-1 Modified Rankin Scale

0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk and attend to bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

4.1.4 Statistical Analysis

Descriptive statistics were used to present baseline demographics and risk factors. Continuous variables were reported as mean (SD) and compared using linear model ANOVA. Categorical variables were reported in proportions and compared using Pearson's Chi-squared test.

Proportion of stroke cases within age, sex, and global region categories and by stroke severity (m-RS at time of stroke) requiring use of proxy or assistance of a proxy were represented on stacked column charts (Figure 4-1, Figure 4-2, Figure 4-3). A violin plot was used to visually demonstrate the distribution of data by stroke severity and proxy use (Figure 4-2).

Univariate (model 1) and multivariable (model 2 and model 3) logistic regression was completed to estimate the adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) for factors associated with use of proxy; demographic factors (age, sex, marital status,

education status, region, occupation), preadmission m-RS and m-RS at time of interview, aphasia, homonymous hemianopia and level of consciousness at time of stroke). Multivariable model 2 included age, sex and markers of stroke severity (m-RS on admission, aphasia, homonymous hemianopia and level of consciousness at time of stroke). The multivariable model 3 included age, sex, marital status, education status, region, occupation, preadmission MRS, MRS at time of stroke, aphasia, homonymous hemianopia and level of consciousness at time of stroke. All statistical analyses were performed using R version 3.6.3.

4.2 Results

4.2.1 INTERSTROKE Participants

Among 13,318 cases, questionnaires were completed by patient alone in 36.3% (n=4837), combination of patient and proxy in 21.9% (n=2,910) and proxy alone in 41.8% (n=5571). Table 4-2 shows demographic details and stroke characteristics, grouped by respondent type (no proxy, proxy or both).

Table 4-2 Demographic and clinical characteristics of cases

	Overall (N=13318)	Proxy (N=4837)	Both (N=2910)	No Proxy (N=5571)	P Value*
Age					< 0.001
Mean years (SD)	62.2 (13.6)	63.2 (13.6)	61.1 (13.2)	61.9 (13.7)	
Range (yrs)	17-99	18-98	17-94	18-99	
Female	5375/13318 (40.4%)	2154/4837 (44.5%)	1113/2910 (38.2%)	2108/5571 (37.8%)	< 0.001
Region					< 0.001
Western Europe/North America/Australia	1915/13318 (14.4%)	82/4837 (1.7%)	151/2910 (5.2%)	1682/5571 (30.2%)	
Eastern/central Europe/Middle East	1390/13318 (10.4%)	261/4837 (5.4%)	259/2910 (8.9%)	870/5571 (15.6%)	
Africa	948/13318 (7.1%)	478/4837 (9.9%)	254/2910 (8.7%)	216/5571 (3.9%)	
South Asia	2830/13318 (21.2%)	1639/4837 (33.9%)	694/2910 (23.8%)	497/5571 (8.9%)	
China	3916/13318 (29.4%)	1305/4837 (27.0%)	1150/2910 (39.5%)	1461/5571 (26.2%)	
South East Asia	851/13318 (6.4%)	456 /4837 (9.4%)	157/2910 (5.4%)	238/5571 (4.3%)	
South America	1468/13318 (11.0%)	616 /4837 (12.7%)	245/2910 (8.4%)	607/5571 (10.9%)	
Marital Status					< 0.001
Never married	540/13317 (4.1%)	140/4837 (2.9%)	85/2910 (2.9%)	315/5570 (5.7%)	
Married/Living with Partner	10091/13317 (75.8%)	3636/4837 (75.2%)	2322/2910 (79.8%)	4133/5570 (74.2%)	
Widowed	2123/13317 (15.9%)	922/4837 (19.1%)	427/2910 (14.7%)	774/5570 (13.9%)	
Separated/Divorced	563/13317 (4.2%)	139/4837 (2.9%)	76/2910 (2.6%)	348/5570 (6.2%)	
Educational Status					< 0.001
None	2129/13316 (16.0%)	1245/4837 (25.7%)	522/2910 (17.9%)	362/5569 (6.5%)	
1-8 years	4882/13316 (36.7%)	1829/4837 (37.8%)	1268/2910 (43.6%)	1785/5569 (32.1%)	
9-12 years	3496/13316 (26.3%)	1053/4837 (21.8%)	649/2910 (22.3%)	1794/5569 (32.2%)	
Trade School/College/University	2809/13316 (21.1%)	710/4837 (14.7%)	471/2910 (16.2%)	1628/5569 (29.2%)	
Occupation					< 0.001
Professional	1368/13312 (10.3%)	305/4836 (6.3%)	225/2910 (7.7%)	838/5566 (15.1%)	
Business/Clerical/Police	1492/13312 (11.2%)	531/4836 (11.0%)	304/2910 (10.4%)	657/5566 (11.8%)	
Farmer/General and Skilled Labour	6949/13312 (52.2%)	2399/4836 (49.6%)	1613/2910 (55.4%)	2937/5566(52.8%)	
Housewife	2332/13312 (17.5%)	1258/4836 (26.0%)	525/2910 (18.0%)	549/5566 (9.9%)	
Disability/Social Security	352/13312 (2.6%)	142/4836 (2.9%)	110/2910 (3.8%)	100/5566 (1.8%)	
Other	819/13312 (6.2%)	201/4836 (4.2%)	133/2910 (4.6%)	485/5566 (8.7%)	
Regional Income					< 0.001
HIC	3246/12871 (25.2%)	317/4564 (6.9%)	401/2828 (14.2%)	2528/5479 (46.1%)	
MIC	6235/12871 (48.4%)	2377/4564 (52.1%)	1552/2828 (54.9%)	2306/5479 (42.1%)	
LIC	3390/12871 (26.3%)	1870/4564 (41.0%)	875/2828 (30.9%)	645/5479 (11.8%)	
MRS Score >1 preadmission	575/13316 (4.3%)	227/4837 (4.7%)	91/2910 (3.1%)	257/5569 (4.6%)	0.213

History of Cardiac Risk Factors	1871/13318 (14.0%)	599/4837 (12.4%)	312/2910 (10.7%)	960/5571 (17.2%)	< 0.001
History of Hypertension	9665/13318 (72.6%)	3520/4837 (72.8%)	2046/2910 (70.3%)	4099/5571 (73.6%)	0.355
History of TIA	316/13315 (2.4%)	63/4835 (1.3%)	58/2910 (2.0%)	195/5570 (3.5%)	< 0.001
Alcohol History and Frequency					< 0.001
Never/former	9300/13298 (69.9%)	3878/4834 (80.2%)	2105/2908 (72.4%)	3317/5556 (59.7%)	
Low/moderate	3327/13298 (25.0%)	813/4834 (16.8%)	664/2908 (22.8%)	1850/5556 (33.3%)	
High intake/binge	671/13298 (5.0%)	143/4834 (3.0%)	139/2908 (4.8%)	389/5556 (7.0%)	
History of Diabetes	2407/13317 (18.1%)	799/4836 (16.5%)	522/2910 (17.9%)	1086/5571 (19.5%)	< 0.001
History of High Cholesterol	1950/13316 (14.6%)	369/4835 (7.6%)	317/2910 (10.9%)	1264/5571(22.7%)	< 0.001
Level of Physical Activity During Leisure Time					< 0.001
Mainly sedentary	6924/13310 (52.0%)	3103/4833 (64.2%)	1641/2910 (56.4%)	2180/5567 (39.2%)	
MRS Score at time of Stroke					< 0.001
0	451/13317 (3.4%)	21/4837 (0.4%)	45/2909 (1.5%)	385/5571 (6.9%)	
1	2120/13317 (15.9%)	174/4837 (3.6%)	418/2909 (14.4%)	1528/5571 (27.4%)	
2	2648/13317 (19.9%)	496/4837 (10.3%)	643/2909 (22.1%)	1509/5571 (27.1%)	
3	3387/13317 (25.4%)	1157/4837 (23.9%)	973/2909 (33.4%)	1257/5571 (22.6%)	
4	2998/13317 (22.5%)	1629/4837 (33.7%)	620/2909 (21.3%)	749/5571 (13.4%)	
5	1713/13317 (12.9%)	1360/4837 (28.1%)	210/2909 (7.2%)	143/5571 (2.6%)	
Level of Consciousness at time of stroke					< 0.001
Alert	9307 (69.9%)	1823/4832 (37.7%)	2373/2909 (81.6%)	5111/5568 (91.8%)	
Drowsy	3156 (23.7%)	2253/4832 (46.6%)	495/2909 (17.0%)	408/5568 (7.3%)	
Unconscious	846 (6.4%)	756/4832 (15.6%)	41/2909 (1.4%)	49/5568 (0.9%)	
Aphasia at time of stroke	4231/13314 (31.8%)	2350/4833 (48.6%)	820/2910 (28.2%)	1061/5571 (19.0%)	< 0.001
Homonymous Hemianopia at time of stroke	1082/13318 (8.1%)	505/4837 (10.4%)	164/2910 (5.6%)	413/5571 (7.4%)	< 0.001
Stroke Type					< 0.001
Ischemic	10311/13276 (77.7%)	3131/4821 (64.9%)	2248/2906 (77.4%)	4932/5549 (88.9%)	
ICH	2965/13276 (22.3%)	1690/4821 (35.1%)	658/2906 (22.6%)	617/5549 (11.1%)	
OCSP Classification					< 0.001
TACI	642/13279 (4.8%)	349/4822 (7.2%)	126/2906 (4.3%)	167/5551 (3.0%)	
PACI	4797/13279 (36.1%)	1487/4822 (30.8%)	1198/2906 (41.2%)	2112/5551 (38.0%)	
POCI	1484/13279 (11.2%)	377/4822 (7.8%)	298/2906 (10.3%)	809/5551 (14.6%)	
LACI	2739/13279 (20.6%)	669/4822 (13.9%)	484/2906 (16.7%)	1586/5551 (28.6%)	
Other	646/13279 (4.9%)	248/4822 (5.1%)	141/2906 (4.9%)	257/5551 (4.6%)	
Location at 1 month					< 0.001
In-Hospital	1368/13283 (10.3%)	941/4825 (19.5%)	193/2906 (6.6%)	234/5552 (4.2%)	
Home	11141/13283 (83.9%)	3704/4825 (76.8%)	2575/2906 (88.6%)	4862/5552 (87.6%)	

Rehab	541/13283 (4.1%)	82/4825 (1.7%)	91/2906 (3.1%)	368/5552 (6.6%)	
Institutional Care	115/13283 (0.9%)	58/4825 (1.2%)	22/2906 (0.8%)	35/5552 (0.6%)	
Other	118/13283 (0.9%)	40/4825 (0.8%)	25/2906 (0.9%)	53/5552 (1.0%)	

Data are n (%) or mean (SD).

*P value comparing use of proxy alone to complete questionnaire vs non-use of proxy.

Western Europe, North America, Australia includes Australia, Canada, Denmark, Germany, Sweden, UK, and Ireland. Eastern and central Europe, Middle East includes Croatia, Poland, Russia, Turkey, Iran, Saudi Arabia, Kuwait, and United Arab Emirates. South America includes Argentina, Brazil, Chile, Colombia, Ecuador, and Peru. South Asia includes India and Pakistan. Southeast Asia includes Philippines, Thailand, and Malaysia. Africa includes Mozambique, Nigeria, South Africa, Sudan, and Uganda.

OCSP=Oxfordshire Community Stroke Project. MRS= Modified Rankin Scale. HIC=High Income Country. MIC=Middle Income Country. LIC=Low Income Country.

Regional income: Countries were grouped by income using the 2011 World Bank Country Income Categories; high income (Australia, Canada, Croatia, Denmark, Germany, Ireland, Poland, Sweden, United Arab Emirates, and the UK) middle income (Argentina, Brazil, Chile, China, Columbia, Ecuador, Malaysia, Peru, Russia, South Africa, Turkey, India, Nigeria, Pakistan, Philippines and Sudan), and low income (Mozambique and Uganda).

Data were missing in 1 for marital status; 2 for educational status; 6 for occupation; 447 for regional income; 2 for preadmission MRS; 3 for history of previous TIA; 20 for alcohol history ; 1 for history of diabetes; 2 for history of high cholesterol ; 10 for physical activity levels; 1 for MRS at time of stroke; 9 for level of consciousness at time of stroke; 4 for aphasia; 42 for diagnosis of stroke at one month, 39 for OCSP classification ; 35 for location at 1 month.

4.2.2 Use of Proxy Respondents by Age and Sex

Questionnaires were completed by proxy respondents alone more often for women 40.7% (n=2213) than men 34.3% (n=2754) (Figure 4-1), (OR 1.32;95% CI 1.22-1.43; P-v <0.001), although the association was not significant on multivariable analysis (aOR 0.88; 95% CI, 0.76-1.02). We report a graded increase in proxy use by increasing age (Figure 4-1). On multivariable analysis proxy use was more common in patients aged over 60 years, compared to younger patient groups, (aOR 1.36; 95% CI, 1.03-1.78 for 60-79 years; OR 2.07; 95% CI, 1.48-2.89 for those ≥80 years versus those aged under 40 years of age) (Table 4-3).

Figure 4-1 Proxy use by (A) Sex (B) Age

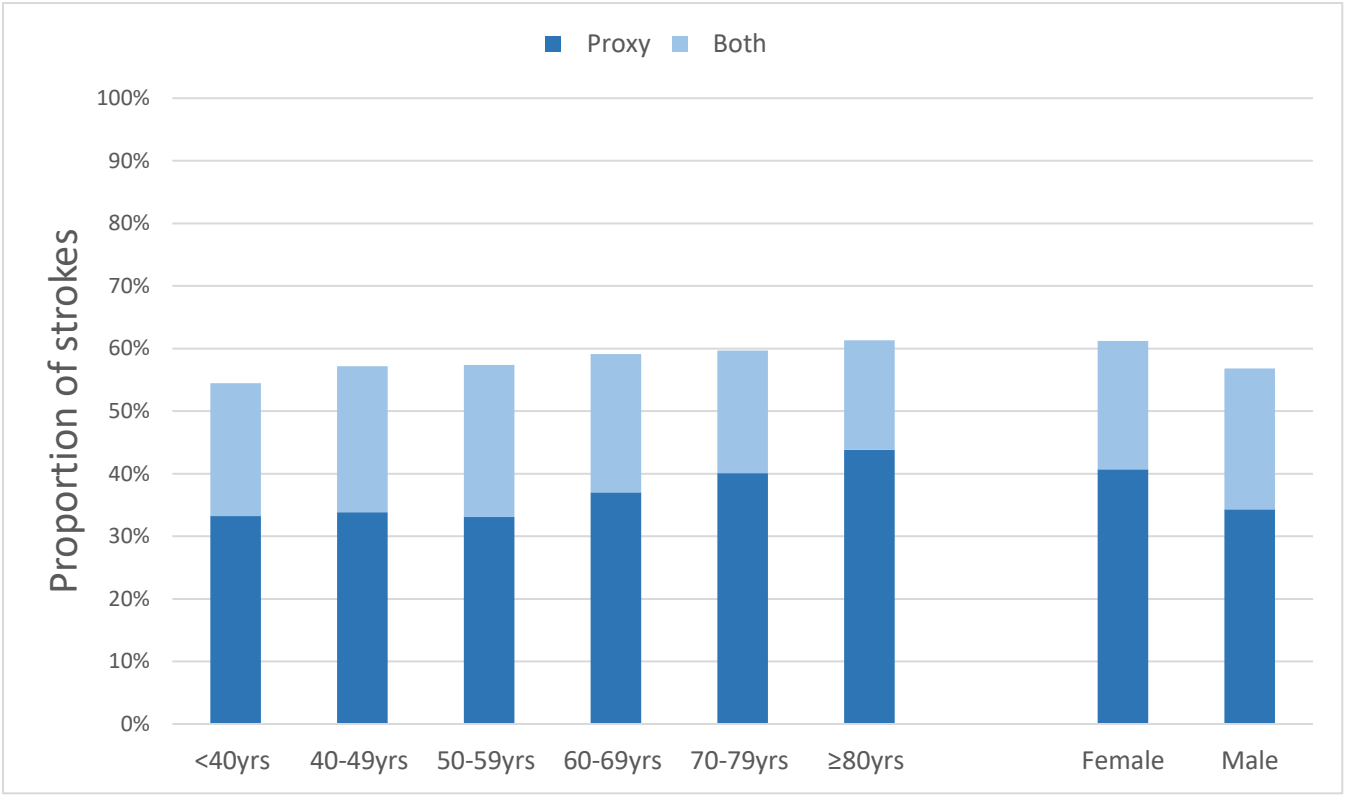


Figure 4-1 reports a stacked column chart of proxy use by age and gender. The dark blue represents use of proxy alone, while light blue represents assistance of a proxy. The stacked columns represent proportion of strokes in each category. This illustrates that proportion of cases reliant on proxy use compared to non-use of proxy increases with increasing age (p-value < 0.05). This figure also demonstrates that a higher proportion of cases in women compared to men are reliant on use of proxy (p-value < 0.05)

4.2.3 Proxy Respondent and Stroke Severity

Figure 4-2 demonstrates a graded increase in proxy respondent by increasing stroke severity. After adjustment for demographic factors and features associated with severe stroke, increasing disability at the time of stroke was associated with the need for proxy respondent to complete the questionnaire, m-RS of 1 (aOR 2.27; 95% CI, 1.41-3.82), m-RS of 2 (aOR 6.73; 95% CI, 4.24-11.21), m-RS of 3 (aOR 13.85; 95% CI, 8.77-22.98), m-RS of 4 (aOR 20.95; 95% CI, 13.21-34.9) and m-RS of 5 (aOR 39.2; 95% CI, 23.81-67.39). Proxy alone questionnaires were completed more often for patients with aphasia (48.6% versus 19%); (aOR 2.44; 95% CI, 2.15-2.78), reduced level of consciousness (aOR 5.88; 95% CI, 5.05-6.86) and who were unconscious (aOR 9.59; 95% CI, 6.85-13.69) at the time of presentation (Table 4-3). There was no association of pre-existing functional impairment with proxy use.

Figure 4-2 Stroke Severity (Modified Rankin Score) and Use of Proxy

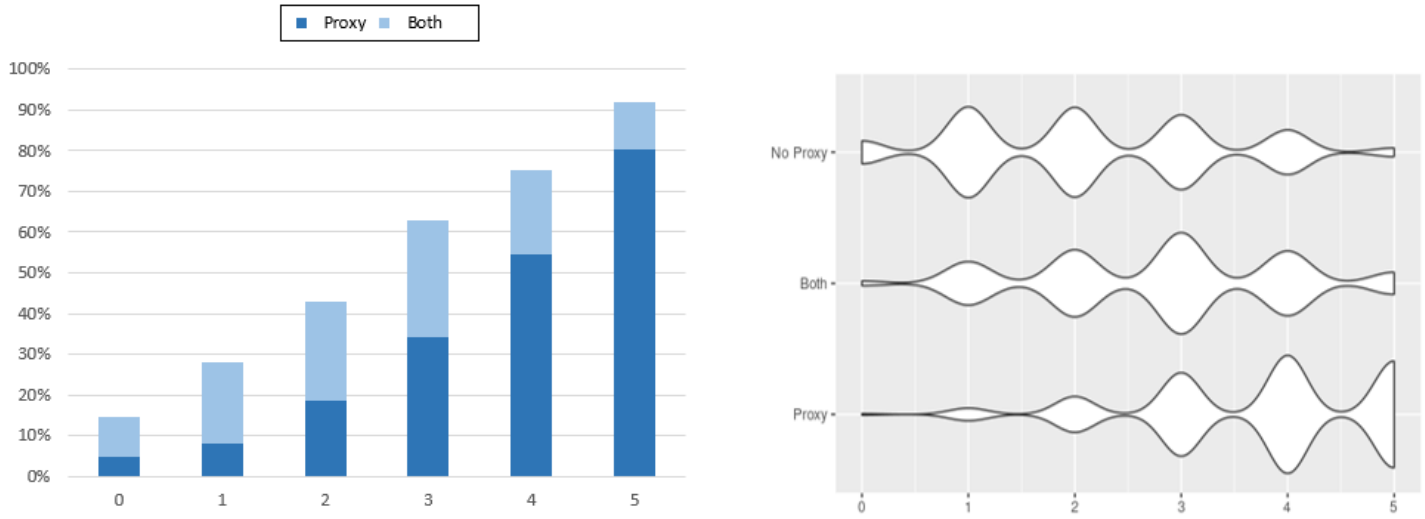
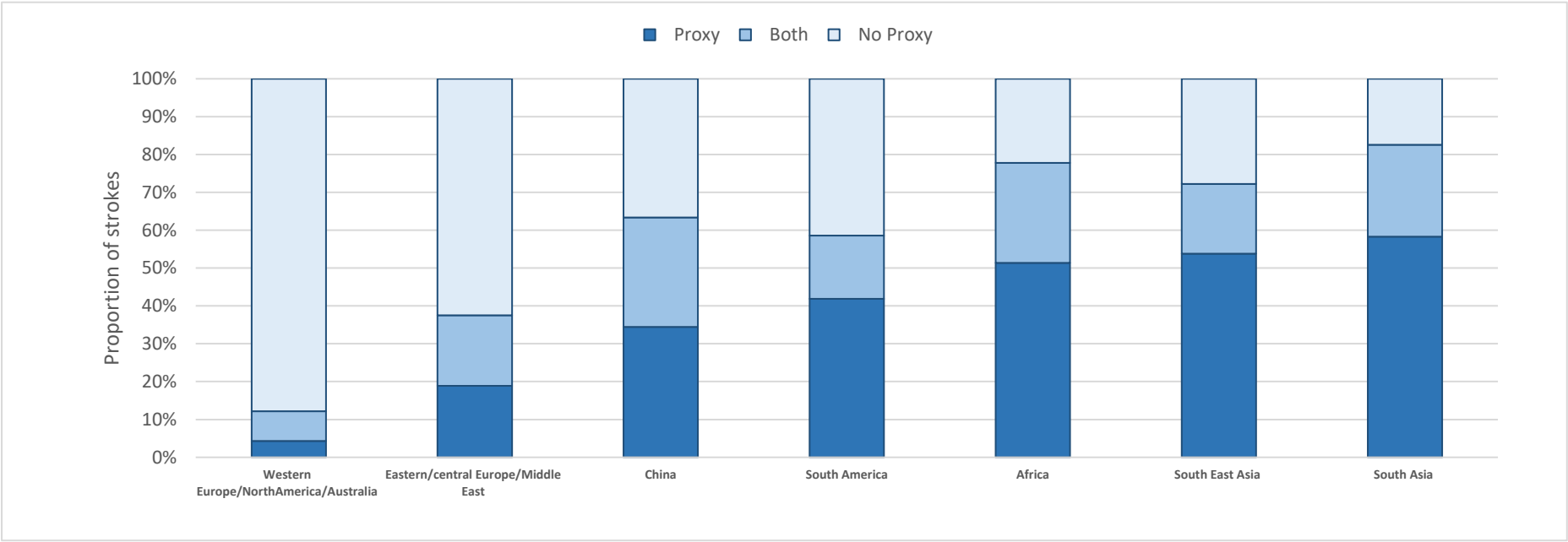


Figure 4-2 Reports use of proxy by increasing stroke severity represented by modified Rankin scale. The left is a stacked column chart reporting the proportion of strokes by MRS reliant on use of proxy or assistance of proxy. The dark blue represents use of proxy alone, while light blue represents assistance of a proxy. Reliance on proxy incrementally increases with increasing stroke severity (p-value < 0.05). This is further illustrated on the right through a violin plot reporting increasing probability of proxy use with increasing stroke severity and reduction in non-use of proxy with increasing stroke severity.

4.2.4 Variations in Use of Proxy Respondents by Region

Use of proxy varied significantly by region, ranging from 4.3% (n=82) in Western Europe, North America and Australia to 53.8% (n=460) of South East Asian participants (Figure 4-3). On multivariable analysis, after adjusting for demographic factors and stroke severity, the significant association of proxy use was maintained in all regions with South East Asia demonstrating the greatest association (aOR 38.29; 95% CI 27.35-54.12), with the lowest magnitude of association with Eastern/central Europe and Middle Eastern countries (aOR 3.7; 95% CI 2.70-5.11) (Table 4-3). Non-use of proxy would have resulted in 43% (n=4966) fewer cases of stroke being enrolled from low- and middle-income countries.

Figure 4-3 Regional Variation and Use of Proxy



No Proxy	1682 (87.8%)	870 (62.5%)	1461 (36.7%)	609 (41.4%)	216 (22.2%)	238 (27.8%)	497 (17.4%)
Both	152 (7.9%)	259 (18.6%)	1150 (28.9%)	246 (16.7%)	257 (26.4%)	157 (18.4%)	696 (24.3%)
Proxy	82 (4.3%)	263 (18.9%)	1375 (34.5%)	616 (41.9%)	500 (51.4%)	460 (53.8%)	1670 (58.3%)

Figure 4-3 reports a stacked column chart of proxy use by region. The dark blue represents use of proxy alone, lighter blue represents assistance of a proxy and lightest blue represents non-use of proxy. The proportion of strokes by proxy use is represented for each region. This figure represents the regional variation associated with proxy use with highest proportion of proxy use among African, South East Asian and South Asian populations with over half of strokes from these regions reliant on use of proxy.

4.2.5 Variations in Use of Proxy Respondents by Education Status

We report a reduction in proxy use as level of education increased among participants. Proxy respondents completed the questionnaire alone among 25.7% (n=728) who attended trade school, college or university (reference), 30.9% (n=1093) of those who completed schooling between ages 9-12 years (OR 1.35; 95% CI, 1.2-1.51, p-value <0.001), 38.0% (n=1877) of those who completed schooling between ages 1-8 years (OR 2.35; 95% CI, 2.11-2.62, p-value <0.001) and 58.9% (n=1269) of those who received no education (OR 7.89; 95% CI, 6.82-9.14, <0.001). This significant association was maintained on multivariable analysis after adjusting for other demographic factors and stroke severity (Table 4-3).

4.2.6 Other Factors Associated with Proxy Respondent Use

Compared to participants who were never married, proxy use was higher in those who were separated or divorced (aOR 1.71; 95% CI, 1.12-2.61), those who were married or living with a partner (aOR 2.02; 95% CI, 1.49-2.74) or widowed participants (aOR 1.65; 95% CI, 1.17-2.34). We report variation in proxy use among different occupations. Occupation influenced use of proxy, with general labourers, farmers and housewives accounting for 68.2% (n=3298) of proxy-alone who competed questionaries. On univariate analysis, the occupations with greatest association of proxy use were housewives (OR 6.3; 95% CI, 5.34-7.43, p-value <0.001) and those on disability benefit (OR 3.9; 95% CI, 2.93-5.21, P-v <0.001). This association was maintained on multivariable analysis adjusting for other demographic factors and stroke severity; housewives (OR 1.82; 95% CI, 1.37-2.41) and those on disability benefit (OR 1.71; 95% CI, 1.11-2.65).

Proxy-alone competed questionaries in 36.4% (n=4282) of those with no functional impairment (MRS 0) versus 40.2% (n=234) participants pre-existing disability (MRS 2-5).

There was no significant association of pre-existing functional impairment (MRS 2-5) (OR 1.09; 95% CI, 0.80-1.48, on multivariable analysis, p-value=0.213) with proxy use (Table 4-3).

Table 4-3 Association of demographic factors and stroke severity with use of proxy respondent versus patient respondent

Demographic Factor		Univariate Model Odds Ratio (95% CI)	Model 2 Odds Ratio (95% CI)	Model 3 Odds Ratio (95% CI)
Age Per Decade				
		1.10 (1.07-1.13)	1.03 (0.99-1.07)	1.16 (1.10-1.21)
Age (years)				
	<40	1.0	1.0	1.0
	40-59	1.07 (0.89-1.28)	1.17 (0.92-1.5)	0.99 (0.76-1.3)
	60-79	1.31 (1.09-1.57)	1.23 (0.97-1.56)	1.36 (1.03-1.78)
	≥80	1.57 (1.28-1.94)	1.3 (0.99-1.72)	2.07 (1.48-2.89)
Sex				
	Male	1.0	1.0	1.0
	Female	1.32 (1.22-1.43)	1.12 (1.01-1.24)	0.88 (0.76-1.02)
Marital Status				
	Never married	1.0	1.0	1.0
	Married/Living with Partner	1.98 (1.62-2.43)	2.91 (2.22-3.83)	2.02 (1.49-2.74)
	Widowed	2.68 (2.15-3.35)	2.17 (1.60-2.96)	1.65 (1.17-2.34)
	Separated/divorced	0.90 (0.68-1.19)	1.08 (0.74-1.57)	1.71 (1.12-2.61)
Education				
	Trade School/College/University	1.0	1.0	1.0
	None	7.89 (6.82-9.14)	7.44 (6.13-9.04)	2.89 (2.28-3.67)
	1-8 years	2.35 (2.11-2.62)	2.81 (2.43-3.26)	1.37 (1.13-1.66)
	9-12 years	1.35 (1.20-1.51)	1.78 (1.53-2.08)	1.44 (1.20-1.74)
Region				
	Western Europe/North America/Australia	1.0	1.0	1.0
	Eastern/central Europe/Middle East	6.15 (4.76-8.03)	3.82 (2.83-5.20)	3.7 (2.70-5.11)
	Africa	45.39 (34.70-60.03)	19.39 (14.05-27.01)	13.76 (9.79-19.51)
	South Asia	67.64 (53.36-86.85)	32.88 (24.82-44.05)	20.50 (15.15-28.04)
	China	18.32 (14.59-23.31)	25.30 (19.42-33.38)	15.87 (11.83-21.54)
	South East Asia	39.30 (30.11-51.85)	44.83 (32.42-62.59)	38.29 (27.35-54.12)
	South America	20.82 (16.33-26.85)	9.02 (6.75-12.17)	6.40 (4.70-8.78)
Occupation				
	Professional	1.0	1.0	1.0
	Business/Clerical/Police	2.22 (1.87-2.64)	2.03 (1.61-2.55)	1.30 (1.00-1.70)
	Farmer/General and Skilled Labour	2.24 (1.95-2.59)	2.34 (1.95-2.82)	1.16 (0.92-1.46)

	Housewife	6.30 (5.34-7.43)	5.14 (4.08-6.50)	1.82 (1.37-2.41)
	Disability/Social Security	3.90 (2.93-5.21)	2.59 (1.77-3.78)	1.71 (1.11-2.65)
	Other	1.14 (0.92-1.40)	1.35 (1.03-1.78)	1.60 (1.14-2.22)
MRS preadmission				
	0	1.0	1.0	1.0
	1	1.13 (0.99-1.30)	0.53 (0.44-0.64)	0.77 (0.63-0.96)
	2-5	1.03 (0.86-1.24)	0.43 (0.34-0.55)	1.09 (0.80-1.48)
MRS at time of stroke				
	0	1.0	1.0	1.0
	1	2.09 (1.34-3.42)	2.11 (1.34-3.49)	2.27 (1.41-3.82)
	2	6.03 (3.94-9.74)	5.59 (3.61-9.13)	6.73 (4.24-11.21)
	3	16.87 (11.08-27.18)	12.01 (7.80-19.55)	13.85 (8.77-22.98)
	4	39.87 (26.15-64.30)	17.90 (11.58-29.18)	20.95 (13.21-34.90)
	5	174.36 (111.37-287.35)	37.63 (23.56-63.05)	39.20 (23.81-67.39)
Aphasia				
	No	1.0	1.0	1.0
	Yes	4.02 (3.69-4.39)	2.18 (1.95-2.44)	2.44 (2.15-2.78)
Homonymous hemianopia				
	No	1.0	1.0	1.0
	Yes	1.46 (1.27-1.67)	0.76 (0.63-0.92)	1.24 (0.98-1.56)
Level of Consciousness at time of stroke				
	Alert	1.0	1.0	1.0
	Drowsy	15.48 (13.77-17.44)	7.00 (6.15-7.97)	5.88 (5.05-6.86)
	Unconscious	43.26 (32.61-58.76)	11.94 (8.76-16.63)	9.59 (6.85-13.69)

MRS= Modified Rankin Scale
Analysis was performed using the logistic regression model.
Model 1 Univariate
Model 2 Adjusted for age/sex/MRS at time of stroke/aphasia/homonymous hemianopia/Level of consciousness
Model 3 Adjusted for age, sex, marital status, education status, region, occupation, preadmission MRS, MRS at time of stroke, aphasia, homonymous hemianopia, Level of consciousness at time of stroke

4.2.7 Measurement of Stroke Risk Factors by Proxy Respondent Type

Multivariable unconditional logistic regression analysis was performed for all stroke by respondent type (Table 4-4) for the ten modifiable risk factors by the INTERSTROKE working group. This analysis demonstrated that self-reported history of hypertension, smoking, diet, physical activity, heavy alcohol intake (defined as more than five drinks in one episode at least once per month), psychosocial factors, cardiac causes and ApoB/ApoA1 ratios were associated with risk of all stroke across all groups. Waist to hip ratio and self-reported history of diabetes were associated with risk of all stroke in cases reported by the individual, but there was no association among cases reported by proxy alone; waist to hip ratio OR 1.20; 95% CI, 1.05-1.36 (individual reported) Vs OR 1.08; 95% CI, 0.95-1.22 (proxy reported). The magnitude of association of psychosocial factors with all stroke was higher among individual reported cases (OR 2.73; 95% CI, 2.19-3.40) than proxy reported cases (OR 1.86; 95% CI, 1.44-2.40).

Table 4-4 Multivariable Analyses for All Stroke by Sources of Information for Cases

Risk Factors	Patient	Proxy	Both
	OR (99% CI)	OR (99% CI)	OR (99% CI)
Self-reported history of hypertension or blood pressure ≥140/90mmHg	2.77 (2.49-3.09)	3.10 (2.76-3.47)	2.85 (2.50-3.25)
Current smoker	1.74 (1.54-1.97)	1.53 (1.34-1.75)	1.55 (1.34-1.80)
Waist-to-hip ratio			
T2 vs T1	1.20 (1.05-1.36)	1.08 (0.95-1.22)	1.38 (1.19-1.60)
T3 vs T1	1.54 (1.36-1.74)	1.09 (0.95-1.25)	1.33 (1.14-1.55)
Diet (mAHEI score)			
T2 vs T1	0.94 (0.84-1.06)	0.76 (0.68-0.86)	0.82 (0.71-0.94)
T3 vs T1	0.79 (0.70-0.90)	0.65 (0.57-0.74)	0.72 (0.62-0.84)
Regular physical activity	0.66 (0.57-0.76)	0.48 (0.39-0.60)	0.56 (0.44-0.70)
Self-reported history of diabetes or HbA1c ≥6.5%	**1.23 (1.10-1.39)**	**1.06 (0.94-1.20)**	**1.17 (1.02-1.35)**
Alcohol intake			
Low/moderate	1.07 (0.94-1.21)	1.00 (0.86-1.16)	1.16 (0.99-1.36)
High/Heavy episodic	2.16 (1.70-2.76)	1.50 (1.08-2.07)	1.85 (1.34-2.55)
Psychosocial factors	2.73 (2.19-3.40)	1.86 (1.44-2.40)	2.33 (1.76-3.09)
Cardiac causes	2.97 (2.51-3.51)	3.73 (3.03-4.61)	3.32 (2.64-4.19)
ApoB/ApoA1 ratio			
T2 vs T1	1.21 (1.07-1.37)	1.21 (1.05-1.39)	1.21 (1.04-1.41)
T3 vs T1	1.68 (1.48-1.91)	1.93 (1.69-2.21)	1.69 (1.45-1.97)
Cumulative PAR, %	89.2 (86.8-91.3)	90.3 (87.3-92.7)	89.1 (85.4-91.9)

OR=odds ratio; PAR= population attributable risk CI=confidence interval; T=tertile; mAHEI=modified alternative healthy eating index; Apo=apolipoproteins. The variables age, hypertension, smoking, waist-to-hip ratio, diabetes, physical activity, mAHEI, alcohol intake, psychosocial factors, apolipoproteins, and cardiac causes were included in all models.
For unconditional model, sex and region were also added to the multivariable model.

4.3 Discussion

In this large international case control study, we report that use of proxy resulted in greater representation of patients with severe stroke, women, older age groups, those less educated and participants from low- and middle-income countries. Proxy use was higher in patients with severe stroke who presented with aphasia or had homonymous hemianopia. Our findings suggest that non-use of proxy respondents would have resulted a in major selection bias and under-representation of key populations.

To our knowledge, this is the largest study to demonstrate effective use of proxy in observational stroke research, highlighting utilisation of proxy respondents as an effective means of improving recruitment. Our study advances knowledge in utility of proxy respondents in international research studies, and report that non-use is expected to result in a major selection bias, that varies by region. In particular, we found that proxy respondent use was more prevalent in low- and middle-income regions. The reason for variation by country income level is likely to be multifactorial; related to greater stroke severity, lower levels of formal education achieved, and perhaps cultural factors, beyond the scope of these analyses. Severe strokes and fatal strokes are more prevalent in low- and middle-income countries, thought to be largely due to a higher proportion of intracerebral haemorrhage, which we report in the INTERSTROKE study (138).

We report in Figure 4-3 that over half of South Asian and African cases of stroke would have been at risk of exclusion from this pivotal study. Inclusion of a representative population in stroke research is challenging, particularly in studies that require questionnaire-based information. The primary objective of the INTERSTROKE study was to estimate the importance of modifiable risk factors for stroke and to quantify the population attributable risk (PAR). Including a population with severe stroke is important, given that some risk factors may vary by stroke severity. For example, atrial fibrillation is associated with a 2-fold increase in stroke severity, and, if patients with severe stroke are not represented in the study, it will result in an underestimate of the PAR associated with atrial fibrillation. In our study, 73.9% of participants with a mRS of 3-5 required a proxy respondent, either alone or in combination. Non-use of proxy respondents would have resulted in this cohort being excluded from participation or incomplete information collection. Stroke was the second leading cause of disability adjusted life years for those

aged 50 years and older in the 2019 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) (141), emphasising the need to ensure that those who experience severe strokes are represented within research studies to truly identify risk factors to target for modification at an individual and at a population level.

Non-use of proxy would have resulted in a lower representation of certain patient populations, where relative importance of some key risk factors may vary. For example, proxy use was more prevalent in patients with certain occupations, such as 31.3% (n=1423) fewer labourers (general or skilled) and 54.5% (n=1288) fewer housewives being enrolled which is of particular relevance in low- and middle-income countries. Non-use of proxy would have resulted in 58.5% (n=1245) fewer cases from participants who never received formal education compared to 25.9% (n=427) of cases who received third level education (aOR 2.89; 95% CI, 2.28-3.67; p-value < 0.05). We have demonstrated that through the use of proxies, valuable information can be obtained on those less educated, allowing greater representation of this cohort in clinical research. These observations are relevant to research in other diseases, particularly in populations with cognitive impairment and dementia, where proxy respondents are also integral.

Our findings suggest that non-use of proxy would have resulted in the exclusion of more women than men and support the use of proxy respondents to increase female participation in stroke research. This was not significant following adjustment for demographic factors and features associated with severe stroke, however we know women are already at higher risk of disabling strokes (142) so further consideration must be given to cultural and demographic factors influencing participation. Women are generally underrepresented in stroke trials, with reported barriers including caregiving

responsibilities, perceived risks associated with participation and trial specific design factors such as age cut off (143).

Underrepresentation of older age groups is a limitation of stroke research studies. In this study, non-use of proxy would have resulted in 34.2% (n=2516) fewer participants aged under 65 and 40.1%(n=2450) fewer participants aged 65 and older. We report that 10.1% of all cases of stroke were over the age of 80 years and were twice as likely to require the use of proxy. Prevalence of stroke is almost ten times greater among those over the age of 65 years of age (144) compared to younger populations. Older adults are at greater risk of death and dependency after stroke (145,146) however many clinical trials exclude this cohort, not just on the basis of age but on criteria which disproportionately affect older persons including functional limitations and serious chronic illness (147).

There are limitations to be considered when using proxy respondents. Subjective domains may be reported differently by proxies and patients, especially in those with significant cognitive impairment (148). Proxy respondent bias can occur, with measures such as quality of life influenced by the caregivers own quality of life, financial situation, ability to do things for fun and age (149). Avoiding proxy respondent bias is challenging, however making an informed decision of the key measurements to include in the study and being aware of hidden constructs that are at most risk of proxy bias is essential in interpreting study results. In the INTERSTROKE study, we ensured inclusion of measurements which could be endorsed objectively and Table 4-4 demonstrates the similar magnitude of association of modifiable risk factors for all stroke among cases, whether reported by patient alone or by proxy.

Other limitations include not measuring pre-existing mild cognitive impairment, dementia or other neurocognitive disorders which may have influenced the need for proxy

respondent. As these conditions contribute to severity of functional impairment, modified Rankin score prior to the stroke was used as a surrogate to adjust for pre-existing functional and cognitive impairment. In addition, this study did not measure deafness or conditions causing visual impairment which is relevant as sensory impairment may impact need for proxy.

4.4 Conclusions

This study demonstrates that in the absence of proxy respondents, key demographic populations and those with disabling strokes would have been excluded from this large, international observational study. Inclusion of proxy respondents in INTERSTROKE has ensured that the findings identified are representative of the global population. We recommend that clinical researchers investigating acute stroke should consider inclusion of proxy respondents as a method to represent these populations and reduce selection bias.

4.5 Statement of Ethics

The study was approved by local ethics committees at all recruitment sites and written informed consent was obtained for all participants.

4.6 Funding Sources

The INTERSTROKE study is funded by the Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, Canadian Stroke Network, Swedish Research Council, Swedish Heart and Lung Foundation, The Health & Medical Care Committee of the Regional Executive Board, Region Västra Götaland, and through unrestricted grants from several pharmaceutical companies with major contributions from Astra Zeneca, Boehringer Ingelheim (Canada), Pfizer (Canada), MERCK, Sharp and Dohme], Swedish Heart and Lung Foundation, UK Chest, and UK Heart and Stroke. The study funders had no role in study

design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Chapter 5

Household-level Lifestyle Interventions for the Prevention of Cognitive Decline - A Systematic Review and Meta-analysis

Maria Costello, Christine McCarthy, Conor Judge, Karen Dennehy, Clodagh McDermott, Tomás Ó Flatharta, Martin O'Donnell, Michelle Canavan- Lifestyle interventions for the prevention of cognitive decline; have we targeted the wrong unit for randomisation? A Systematic review and Meta-analysis. 17th EuGMS, 11 to 13 October 2021, Athens (Conference Poster)

Maria Costello, Christine McCarthy, Conor Judge, Karen Dennehy, Clodagh McDermott, Tomás Ó Flatharta, Martin O'Donnell, Michelle Canavan - Household-level lifestyle interventions for the prevention of cognitive decline; A Systematic review. Archives of Gerontology and Geriatrics, Volume 98,2022, 104565, https://doi.org/10.1016/j.archger.2021.104565.

Introduction

With an ageing population, the prevalence of dementia is increasing and is predicted to affect 75 million people worldwide by the year 2030 (2). A previous Delphi consensus study has supported the need to target modifiable lifestyle factors including physical inactivity, smoking and mid-life obesity to prevent dementia and promote healthy cognitive functioning in later life (30). Since then, there have been several large randomised controlled trials (RCTs) published targeting multicomponent lifestyle interventions at an individual level focusing on "at risk" populations (150–153). More recently, twelve modifiable lifestyle and environmental risk factors have been identified which are suspected to account for 40% of all cases of dementia, highlighting key targets for intervention (29) and the need for collaborative international trials.

While individual-level interventions are important, consideration may also be given to targeting the lifestyle and health behaviours of households instead of individuals alone, which may advantage the individual and household members. Caregivers within households may experience benefits from targeted lifestyle interventions given the proposed association between caregiving and mortality (20,154). It has been previously demonstrated that household members share risk factors, including lifestyle behaviours (e.g. physical inactivity) (155), with clustering of risk factors among different dyad groups; spouses, parent-offspring dyads and siblings. Additionally, there are studies suggesting that individual-level lifestyle interventions for type 2 diabetes mellitus may be associated with more favourable risk factor profiles among household members (156). Therefore, the potential advantages of household-level interventions may include improved adherence with the intervention and ancillary benefits to other household members. A recent assessment of caregiving in the United States estimates that there has been a reduction in

care recipients (such as persons with dementia) living in their own home and they are now more likely to be living with their caregiver than in 2015 (157), supporting an expanding opportunity to consider household-level interventions.

The aim of this systematic review and meta-analysis was to assess the impact of household level lifestyle interventions on cognitive decline. Secondary outcomes included impact on functional outcomes, admissions to long term care, mood, caregiver burden and physical health outcomes for all participants.

5.1 Methods

We performed a systematic review and meta-analysis, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (158). The protocol for this study was registered with PROSPERO (identifier: CRD42020184387). There was no funding source for this study.

5.1.1 Search Strategy

A search strategy was designed for PubMed, MEDLINE, Embase, PsycInfo, CENTRAL and CINHAL for trials published from database inception until April 30th, 2020. Key search terms included *Dementia, Cognitive Impairment, Randomised Controlled Trial, Physical Activity, Exercise, Diet* and *Sleep*. The search strategy was reviewed by senior authors (MDC and MOD). The full search strategy for PubMed is in Table 5-1 and is representative of the terms used throughout all of the searched databases.

Table 5-1 Sample Search Strategy conducted for PubMed

Search number	Search Details	Results
12	(((((((("cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) OR "Dementia"[Title/Abstract]) OR "mild cognitive impairment"[Title/Abstract]) OR "Alzheimer s disease"[Title/Abstract]) OR "neurocognitive disorder"[Title/Abstract]) AND (("Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract]) OR "Strategy"[Title/Abstract])) AND (((((((("exercise"[Title/Abstract] OR "physical activity"[Title/Abstract]) OR "resistance training"[Title/Abstract]) OR "training"[Title/Abstract]) OR "activity"[Title/Abstract]) OR "Physical"[Title/Abstract]) OR "gym"[Title/Abstract]) OR "aerobic"[Title/Abstract])) OR (((((((("cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) OR "Dementia"[Title/Abstract]) OR "mild cognitive impairment"[Title/Abstract]) OR "Alzheimer s disease"[Title/Abstract]) OR "neurocognitive disorder"[Title/Abstract]) AND (("Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract]) OR "Strategy"[Title/Abstract])) AND ((((((("Diet"[Title/Abstract] OR "Nutrition"[Title/Abstract]) OR "Food"[Title/Abstract]) OR "healthy eating"[Title/Abstract]) OR "Dietary"[Title/Abstract]) OR "Mediterranean diet"[Title/Abstract]) OR "alcohol"[Title/Abstract])))) OR (((((((("cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) OR "Dementia"[Title/Abstract]) OR "mild cognitive impairment"[Title/Abstract]) OR "Alzheimer s disease"[Title/Abstract]) OR "neurocognitive disorder"[Title/Abstract]) AND (("Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract]) OR "Strategy"[Title/Abstract])) AND (("Sleep"[Title/Abstract] OR "Sleep-wake"[Title/Abstract]) OR "Circadian"[Title/Abstract]))) AND ((((((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type]) OR "randomized"[Title/Abstract]) OR "placebo"[Title/Abstract]) OR "randomly"[Title/Abstract]) OR "trial"[Title/Abstract]) OR "groups"[Title/Abstract])	4,728
11	"randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]	3,012,359
10	(((((((("cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) OR "Dementia"[Title/Abstract]) OR "mild cognitive impairment"[Title/Abstract]) OR "Alzheimer s disease"[Title/Abstract]) OR "neurocognitive disorder"[Title/Abstract]) AND (("Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract]) OR "Strategy"[Title/Abstract])) AND (((((((("exercise"[Title/Abstract] OR "physical activity"[Title/Abstract]) OR "resistance training"[Title/Abstract]) OR "training"[Title/Abstract]) OR "activity"[Title/Abstract]) OR "Physical"[Title/Abstract]) OR "gym"[Title/Abstract]) OR "aerobic"[Title/Abstract])) OR (((((((("cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) OR "Dementia"[Title/Abstract]) OR "mild cognitive impairment"[Title/Abstract]) OR "Alzheimer s disease"[Title/Abstract]) OR "neurocognitive disorder"[Title/Abstract]) AND (("Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract]) OR "Strategy"[Title/Abstract])) AND ((((((("Diet"[Title/Abstract] OR "Nutrition"[Title/Abstract]) OR "Food"[Title/Abstract]) OR "healthy eating"[Title/Abstract]) OR "Dietary"[Title/Abstract]) OR "Mediterranean diet"[Title/Abstract]) OR "alcohol"[Title/Abstract])))) OR (((((((("cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) OR "Dementia"[Title/Abstract]) OR "mild cognitive impairment"[Title/Abstract]) OR "Alzheimer s disease"[Title/Abstract]) OR "neurocognitive disorder"[Title/Abstract]) AND (("Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract]) OR "Strategy"[Title/Abstract])) AND (("Sleep"[Title/Abstract] OR "Sleep-wake"[Title/Abstract]) OR "Circadian"[Title/Abstract]))	17,613
9	((((((("cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) OR "Dementia"[Title/Abstract]) OR "mild cognitive impairment"[Title/Abstract]) OR "Alzheimer s disease"[Title/Abstract]) OR "neurocognitive disorder"[Title/Abstract]) AND (("Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract]) OR "Strategy"[Title/Abstract])) AND (((((((("exercise"[Title/Abstract] OR "physical activity"[Title/Abstract]) OR "resistance training"[Title/Abstract]) OR "training"[Title/Abstract]) OR "activity"[Title/Abstract]) OR "Physical"[Title/Abstract]) OR "gym"[Title/Abstract]) OR "aerobic"[Title/Abstract])	13,986
8	((((((("cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) OR "Dementia"[Title/Abstract]) OR "mild cognitive impairment"[Title/Abstract]) OR "Alzheimer s disease"[Title/Abstract]) OR "neurocognitive disorder"[Title/Abstract]) AND (("Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract]) OR "Strategy"[Title/Abstract])) AND ((((((("Diet"[Title/Abstract] OR "Nutrition"[Title/Abstract]) OR "Food"[Title/Abstract]) OR "healthy eating"[Title/Abstract]) OR "Dietary"[Title/Abstract]) OR "Mediterranean diet"[Title/Abstract]) OR "alcohol"[Title/Abstract])	3,452

7	((((((("cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) OR "Dementia"[Title/Abstract]) OR "mild cognitive impairment"[Title/Abstract]) OR "Alzheimer s disease"[Title/Abstract]) OR "neurocognitive disorder"[Title/Abstract]) AND (("Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract]) OR "Strategy"[Title/Abstract])) AND (("Sleep"[Title/Abstract] OR "Sleep-wake"[Title/Abstract]) OR "Circadian"[Title/Abstract])	1,753
6	(((((("cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) OR "Dementia"[Title/Abstract]) OR "mild cognitive impairment"[Title/Abstract]) OR "Alzheimer s disease"[Title/Abstract]) OR "neurocognitive disorder"[Title/Abstract]) AND (("Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract]) OR "Strategy"[Title/Abstract])	58,306
5	"exercise"[Title/Abstract] OR "physical activity"[Title/Abstract] OR "resistance training"[Title/Abstract] OR "training"[Title/Abstract] OR "activity"[Title/Abstract] OR "Physical"[Title/Abstract] OR "gym"[Title/Abstract] OR "aerobic"[Title/Abstract]	3,693,645
4	"Diet"[Title/Abstract] OR "Nutrition"[Title/Abstract] OR "Food"[Title/Abstract] OR "healthy eating"[Title/Abstract] OR "Dietary"[Title/Abstract] OR "Mediterranean diet"[Title/Abstract] OR "alcohol"[Title/Abstract]	1,156,074
3	"Sleep"[Title/Abstract] OR "Sleep-wake"[Title/Abstract] OR "Circadian"[Title/Abstract]	202,932
2	"Intervention"[Title/Abstract] OR "Treatment"[Title/Abstract] OR "Strategy"[Title/Abstract]	4,992,118
1	"cognitive impairment"[Title/Abstract] OR "cognitive decline"[Title/Abstract] OR "Dementia"[Title/Abstract] OR "mild cognitive impairment"[Title/Abstract] OR "Alzheimer s disease"[Title/Abstract] OR "neurocognitive disorder"[Title/Abstract]	234,116

5.1.2 Study Selection

5.1.2.1 Inclusion Criteria

- Randomised controlled trials (RCTs)
- Recruited participant with known or at risk of cognitive impairment and their household, and household unit was randomised to the intervention or control
- Living in community households
- Multiple or single component interventions of diet, exercise and/or sleep
- For trials of exercise, with multiple arms (e.g. individual and household), arms which targeted the household could be included
- Reported any of the following outcomes: change in cognitive scale or score, the development of dementia, mild cognitive impairment, cognitive decline or worsening of any of these outcomes, using standardised diagnostic criteria

5.1.2.2 Exclusion Criteria

- Studies including participants living in assisted living facilities, skilled nursing facilities or long-term care settings
- Studies with fifty participants or less and did not include a minimum number of households
- Studies with less than six months follow up between baseline and final cognitive testing
- Trials of pharmacological intervention, device intervention or nutritional supplement
- Trials where there was absence of a control group

The PICOT criteria (Population, Intervention, Comparison, Outcome, Time) are summarised in Table 5-2.

Table 5-2 PICOT criteria for study inclusion

PICOT Criteria	Inclusion	Exclusion
Population	Community level households including participants with known or at risk of cognitive impairment	Participants living in assisted living facilities, skilled nursing facilities or long-term care settings Studies which randomised a single individual in the household to receive the intervention
Intervention	Non-pharmacological lifestyle interventions; can be single or multiple component	Pharmacological or device related interventions; dietary supplements; interventions combining cognitive training
Comparison	Households receiving usual care	Households receiving another active lifestyle intervention, cognitive training or medication
Outcome	Change in cognitive testing and/or incidence of neurocognitive syndromes Admission to long term care Change in functional outcomes Change in mood Change in caregiver outcomes	
Timeframe	Greater than six months follow up between baseline and repeat cognitive assessment	

Following application of our initial eligibility criteria, we did not identify any eligible RCT. However, as part of our search, we identified trials that randomised dyads. We revised our eligibility criteria to also include trials recruiting dyads and retained all other eligibility criteria. We considered the unit of recruitment (dyad) to overlap sufficiently with a household. As we failed to identify RCTs in our initial search, we considered revision of our protocol to be appropriate and relevant to our central research question. These revised criteria are summarised in Table 5-3.

Table 5-3 Revised PICOT Criteria

PICOT Criteria	Inclusion	Exclusion
Population	Dyads of participants with or at risk of cognitive impairment and caregiver/other household member	Participants living in assisted living facilities, skilled nursing facilities or long-term care settings Studies which randomised a single individual in the household to receive the intervention
Intervention	Non-pharmacological lifestyle interventions; can be single or multiple component	Pharmacological or device related interventions; dietary supplements; interventions combining cognitive training
Comparison	Households receiving usual care	Households receiving another active lifestyle intervention, cognitive training or medication
Outcome	Change in cognitive testing and/or incidence of neurocognitive syndromes Admission to long term care Change in functional outcomes Change in mood Change in caregiver outcomes	
Timeframe	Greater than six months follow up between baseline and repeat cognitive assessment	

5.1.3 Data collection and extraction

Following removal of duplicates, titles and abstracts were screened by two reviewers (MMC and CMcC) using the Rayann web application which is a web-tool (Beta) designed to help

researchers working on systematic reviews to screen abstracts, upload full-text articles and export decisions (159). Full texts were obtained for potentially eligible studies following abstract review. Reference lists of randomised trials and previously published systematic reviews were reviewed for other potentially eligible articles. Full texts of remaining articles were independently assessed by two reviewers (MMC and CMcC), to determine whether studies fulfilled eligibility criteria. Disagreements were resolved by group consensus with the addition of a third review (MDC and MOD). Data were extracted independently by MMC and CMcC using a standardized data extraction form. These data included baseline demographics of participants, description of intervention, description of control, cognitive outcome measures, baseline/follow up/change in cognitive scores, incidence of dementia, incidence of mild cognitive impairment, baseline/follow up/change in functional outcomes, baseline/follow up/change in mood outcomes and admission to long-term care/institutionalisation. Admission to long term care was considered a surrogate for significant functional decline. If outcomes had repeated measures during the study, we reported outcomes at the point of longest follow-up.

5.1.4 Statistical Analysis

Statistical analyses were performed using the Metafor package (160) in R statistical software, version 3.5.3. For continuous outcomes (e.g. Mini Mental State Examination, Barthel Index), the mean change from baseline to follow-up was meta-analysed. If this was not reported, the mean between-group difference reported at follow-up was used. Standard errors (SE) were calculated by converting 95%, Confidence Interval (CI) using the following formula: $SD = \sqrt{N} \times (\text{upper bound of the CI} - \text{lower bound of the CI})/3.92$ (161). The difference in cognitive test score change between the intervention and control group was calculated when the difference was not reported in the trial. A pooled mean difference, with

95%, CI, was estimated using a random effects model and illustrated with forest plots. For one study (162) we pooled the mean standardised differences of all test scores and performed a meta-analysis to give a single mean standardised difference most representative of cognitive score outcomes for that study, because it reported multiple relevant constructs in its cognitive score (Figure 5-2). One study had three arms; home exercise, group-based exercise and control (163). For this meta-analysis, the group-based exercise arm was excluded.

5.1.5 Risk of Bias

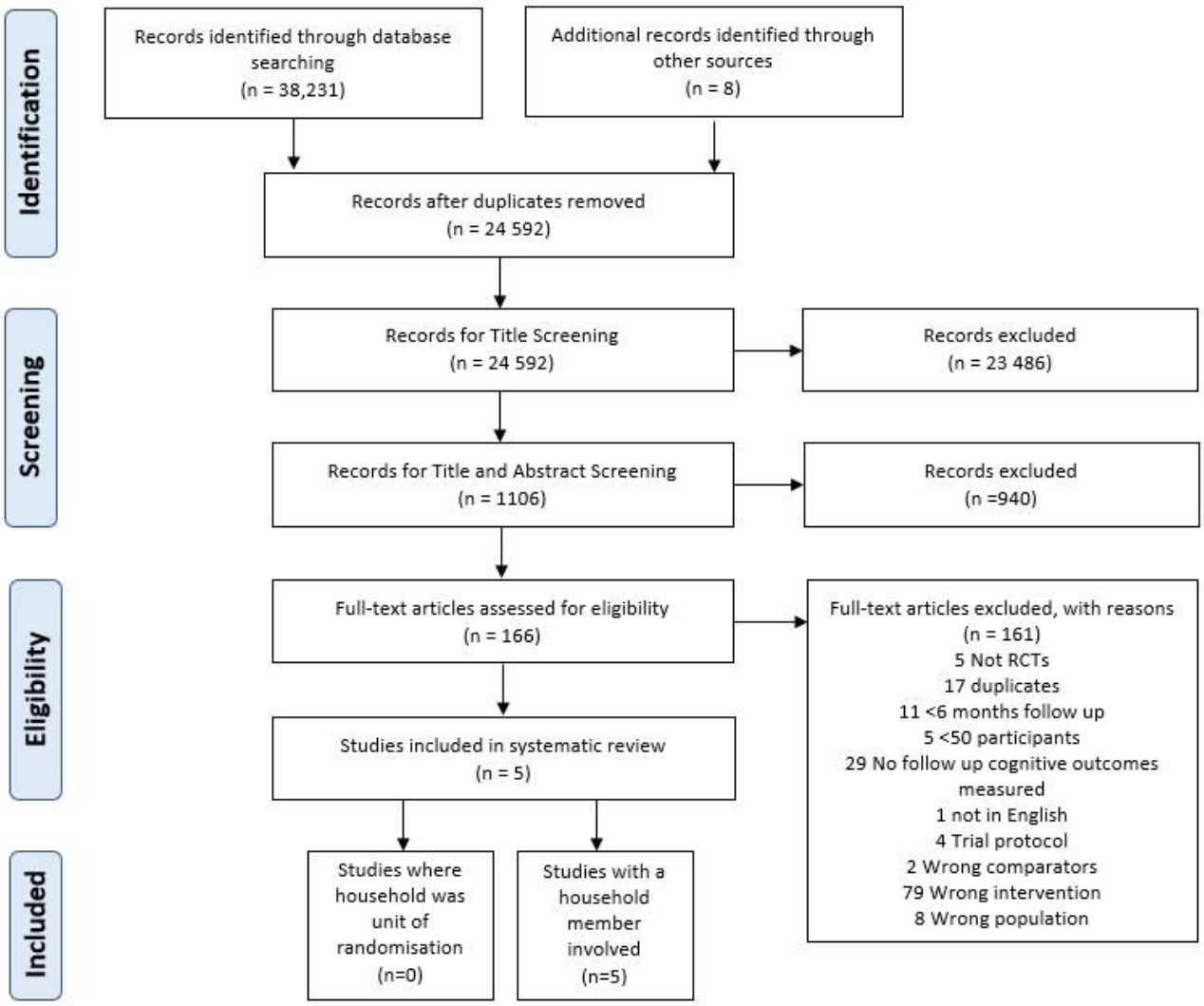
Risk of Bias was assessed using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB2) (164), which measured adequacy of randomisation, deviation from intended interventions, management of missing outcome data, measurement of reported outcome and selection of reported results. Risk of bias assessments were performed independently by reviewers (MMC and KD) and disagreements were resolved by a third reviewer (CMcC). A summary table of the results were created (Figure 5-5, Figure 5-6). Publication bias was assessed using a funnel plot (Figure 5-7).

5.2 Results

5.2.1 Search Results

Following our electronic search, 24,592 records were identified following removal of duplicates. Titles were screened and 1106 remained for abstract review. 166 articles were then reviewed as full texts for eligibility of our revised search criteria. Reasons for exclusion during the selection process are detailed in Figure 5-1.

Figure 5-1 PRISMA Flow Diagram



We identified no clinical trials which randomised households to receive a lifestyle intervention incorporating sleep, diet, exercise, or a combination of all three for preventing cognitive decline.

5.2.2 Included Study Characteristics

Following revision of our search and eligibility criteria, five studies (162,163,165–167) met eligibility, which randomised dyads comprising of caregivers, spouses or other household member(s) along with the person at risk of or with cognitive decline. These studies recruited

1721 participants. Two studies evaluated dietary interventions (165,167) and three were interventions targeting increased physical activity (162,163,166). Two studies were conducted in Spain (165,167), one in England (166), one in Finland (163) and one in the Netherlands (162). No study described the household unit i.e. if there were other individuals outside of the dyad living within the household. Four studies randomised patients with an established diagnosis of dementia or Alzheimer's disease (162,163,166,167) and the remaining study enrolled participants who required the assistance of a caregiver for activities of daily living (165). Baseline study characteristics are described in Table 5-4 and cognitive test outcomes are described in Table 5-5 and Table 5-6. Two studies reported change in MMSE (163,167) from baseline to follow-up, one study reported change in a battery of neuropsychological tests at baseline and follow up (162), one reported follow up Pfeiffer score (165) and one reported follow up Mini-Addenbrooke's Cognitive Examination (166). The Pfeiffer score is a short portable mental status questionnaire for the assessment of organic brain deficit in older individuals (168) (Appendix 6). Time from baseline cognitive testing to repeat cognitive testing ranged from six months to two years.

Table 5-4 Summary table of study characteristics

Study	Intervention	Control	N	Primary outcome	Secondary outcome	Cog impaired Population description	Caregiver population description	Female n (%)	Mean age at baseline years (INT)	Mean age at baseline years (CONT)	Time interval for outcome measurement (months)
FINALEX (2016) Finland	(1) Custom Home Exercise: 1 hour twice a week for 12 months (2) Group exercise *(excluded)*	Usual care plus general written advice on diet and exercise	210	Physical functioning and mobility	Cognition	Diagnosis of AD made by a physician using standard criteria	All were spouses of participants	81 (38.6%)	77.7 (5.4)	78.1 (5.3)	12
Prick et al (2017) Netherlands	30 minutes of active exercise at least 3 days a week. Delivered by personal coach in 8 sessions to dyads in own homes	General information on dementia plus 3 phone calls,	222 *	Cognition	Compliance	Diagnosis of dementia made by a physician	Family caregivers	100 (58.8%)	76.0 (7.6)	78.0 (7.2)	6
Fernandez-Barres et al (2017) Spain	Caregiver and PWD received individual session to explain the project and causes and consequences of malnutrition. Group caregiver educational sessions performed and further individual dietary monitoring of the patient in the presence of caregiver	No nutritional intervention	173	Nutritional status	Activities of daily living, cognition and mood	52.6% had cognitive impairment	Majority informal caregivers	118 (68.2%)	84.3 (6.7)	85.4 (7.6)	12
TACIT (2019) UK	Tai Chi intervention for PWD and caregiver comprising of (1) Tai Chi classes, (2) home-based Tai Chi practice (3) behaviour change techniques	Usual Care	170 **	Timed get up and go test	Functional balance, fear of falls, quality of life, global cognitive functioning	Diagnosis of dementia in their NHS health record	Caregivers living with person with dementia	34 (40%)	77.9 (8.3)	78.2 (7.5)	6
NutrALZ (2011) Spain	Dietician led educational training in nutrition, supervised monitoring of weight and decision tree to help with malnutrition risks	Usual Care	946	ADL and IADL	Nutrition, cognitive function, caregiver burden	Diagnosed with dementia according to standard criteria	Family caregiver	644 (68.1%)	79.4 (7.0)	78.6 (7.5)	12

INT: intervention; CONT: control; AD: Alzheimer's Disease; PWD: persons with dementia; HE: Home Exercise; NHS: National Health Service *111 Dyads **85 Dyads

Table 5-5 Summary table of study outcomes measured

Study	Cognitive Outcomes Measured	Mood outcomes Measured	Functional outcomes measured	Caregiver burden outcomes Measured	Lifestyle intervention	Baseline cognitive scores (INT)	Baseline cognitive scores (CONT)	FU Cog scores (INT)	FU Cog score (CONT)	Change in cog score (INT)	Change in cog score (CONT)
FINALEX (2016) Finland	MMSE	Neuropsychiatric index, Cornell depression scale	FIM	ZBI	Physical Activity	17.8 +/- 6.6	17.7 +/-6.2	NR	NR	1.63 (95% CI = -2.64 to -0.61)	-1.08 (95% CI = -2.17– 0.02)
Prick et al (2017) Netherlands	WMS-R Digit Span BW 8 WT recognition 8 WT delayed 8WT Immediate RBMT faces RBMT pictures BADS key search GIT Fluency animals GIT Fluency professions WMS-R Digit span FW	NR	NR	NR	Physical Activity	*	*	*	*	NR	NR
Fernandez-Barres et al (2017) Spain	Pfeiffer's test	Geriatric Depression Scale	Barthel Score	NR	Diet	3.2±3.3	3.9±3.1	3.4±3.1	4.1±3.2	0.2	0.2
TACIT (2019) UK	Mini-Addenbrooke's Cognitive Examination	NR	NR	ZBI	Physical Activity	16.2 (4.9)	15.1 (4.3)	14.5 (6.4)	13.7 (6.3)	-1.7	-1.4
NutriALZ (2011), Spain	MMSE	Cornell depression scale	ADL and Lawton IADL	ZBI	Diet	14.7 ± 6.0	16.0 ± 6.25	12.8 (12.1 to 13.6)	14.3 (13.6 to 15.0)	-2.21 (95% CI = -2.68 to -1.74)	-2.21 (95% CI = -2.60 to -1.82)

INT: Intervention; CONT: Control; FU: Follow up; MMSE: Mini Mental State Examination; FIM: Functional Independence Measure; NR: Not Reported; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily living; WMS- R: Wechsler Memory Scale Revised; BW: Backwards; FW: forwards; 8WT: 8 Word Test; RBMT: Rivermead Behavioural Memory Test; BADS: Behavioural Assessment of Dysexecutive Syndrome; ZBI=Zarit Burden Interview

* Table 5-6

Table 5-6 Cognitive Scores from Prick et al.

Cognitive Score	INT baseline estimate	INT baseline SD	INT follow-up estimate	INT follow-up SD	CONT participants	CONT baseline estimate	CONT baseline SD	CONT follow-up estimate	CONT follow-up SD
WMS-R Digit Span BW	5.46	2.53	5.02	2.53	54	5.57	2.81	5.7	2.74
8 WT recognition	11.74	3.87	11.05	3.77	54	11.28	4.53	10.82	4.96
8 WT delayed	0.84	1.46	0.74	1.55	54	1.06	1.83	1.15	1.99
8WT Immediate	17.54	6.67	17.67	7.84	54	17.43	8.44	18.03	10.35
RBMT faces	29.6	5.97	30.44	5.66	54	30.65	4.8	30.7	5.48
RBMT pictures	66.96	10.63	64.39	13	54	66.31	11.2	66.37	12.94
BADS key search	5.95	3.86	5.4	3.25	54	6.58	4.75	5.4	3.25
GIT Fluency animals	10.51	5.25	9.56	5.67	54	11.15	7.42	11.25	7.1
GIT Fluency professions	7	4.06	7.21	4.64	54	7.78	5.36	8.32	6.21
WMS-R Digit span FW	10.68	3.2	10.4	3.76	54	10.46	2.79	10.53	3.45

INT: Intervention; CONT: Control; WMS- R: Wechsler Memory Scale Revised; BW: Backwards; FW: forwards; 8WT: 8 Word Test; RBMT: Rivermead Behavioural Memory Test; BADS: Behavioural Assessment of Dysexecutive Syndrome

5.2.3 The association of Lifestyle Interventions with Cognition

For one study, (162) we meta-analysed estimates from ten cognitive tests performed from baseline to follow up to produce a summary cognitive score to compare against the other four trial cognitive test outcomes Figure 5-2.

Figure 5-2 Summary score of cognitive outcomes (Standard Mean Difference) for Prick et al.

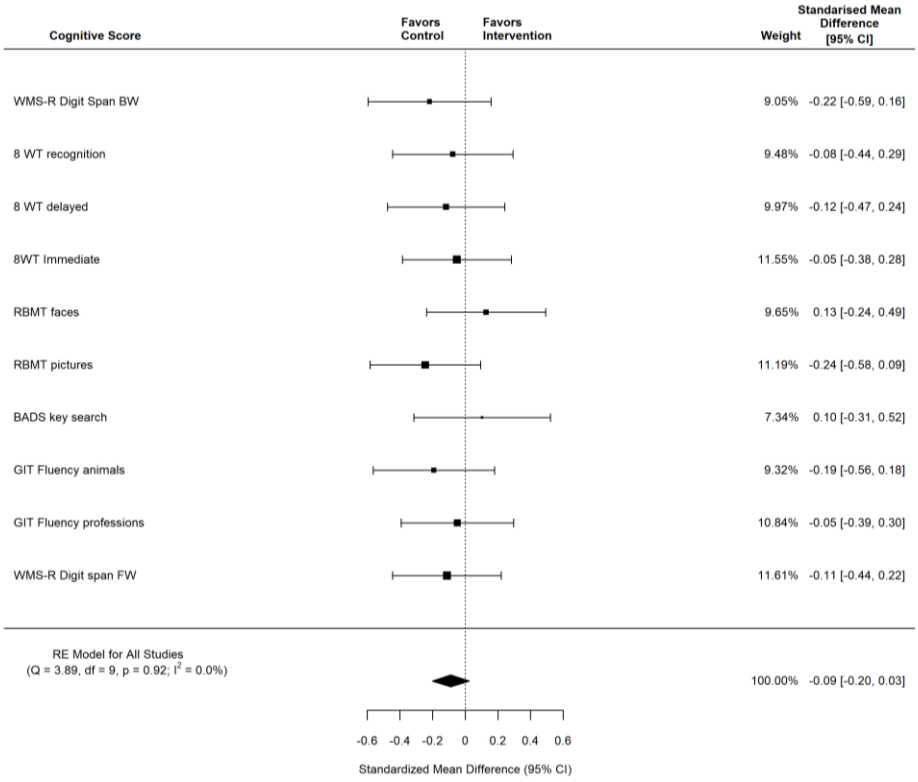


Figure 5-2- Forest plot of cognitive outcomes of participants in Prick et al (162). Forest plot comparing the standardised mean difference of cognitive outcome scores measured in this study within the non-pharmacological intervention cohort versus those randomised to control. The squares and bars represent the mean values and 95%, confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical line represents the line of no effect.

A meta-analysis of trials targeting exercise revealed no significant difference in standardized mean cognitive score between groups 0.96 [95% CI, 0.87 to 1.07] and similarly in an analysis confined to trials targeting diet there was no significant difference in standardized mean cognitive score between groups 0.93 [95% CI, 0.73 to 1.18] (Figure 5-3).

Figure 5-3 Association of cognitive scores with lifestyle interventions

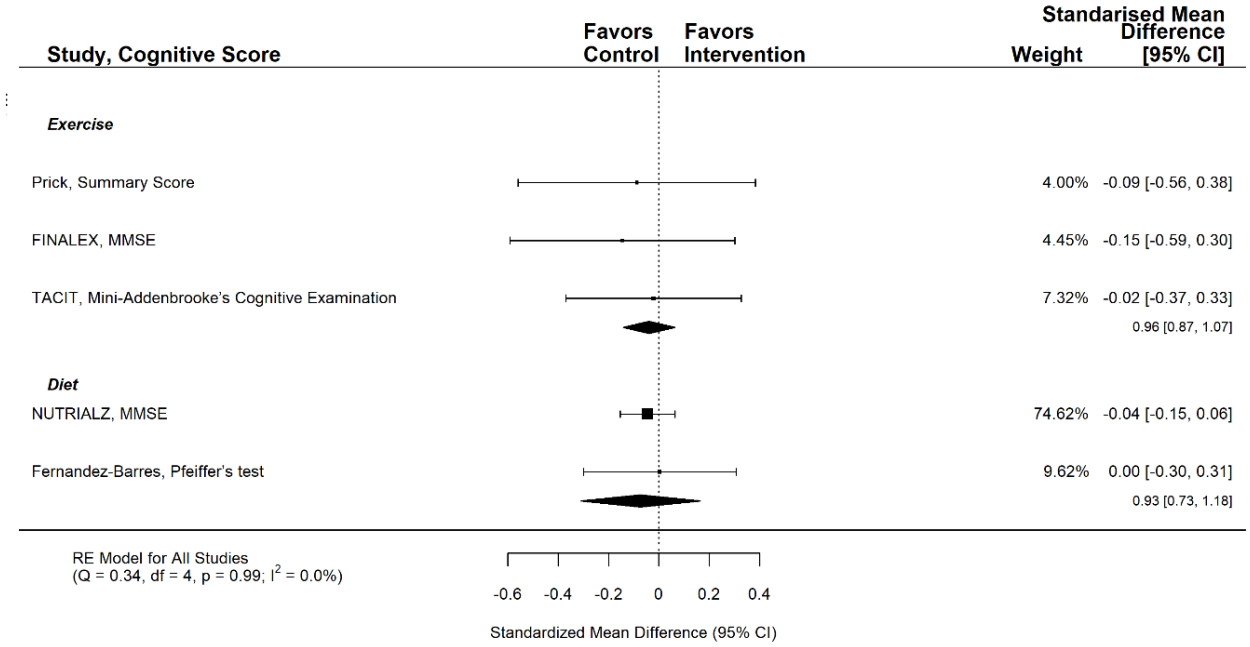


Figure 5-3- Forest plot of cognitive scores for each study. Forest plot comparing the standardised mean difference of cognitive outcome scores within the non-pharmacological intervention cohort of each study versus those randomised to control. The squares and bars represent the mean values and 95%, confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical line represents the line of no effect.

5.2.4 The association of Lifestyle Interventions with Functional Outcomes

Three studies reported functional outcomes at baseline and follow up, employing Functional Independence Measure (FIM) score in one trial (163,169), Barthel Index score in one study (165), and one reported change in activities of daily living (ADL) along with the Lawton Instrumental ADL measure (167). In an analysis confined to trials targeting diet there was no significant difference in standardized mean cognitive score between groups 0.03 [95% CI, -0.27 to 0.33] (Figure 5-4).

Figure 5-4 Association of change in functional outcome scores with dietary interventions

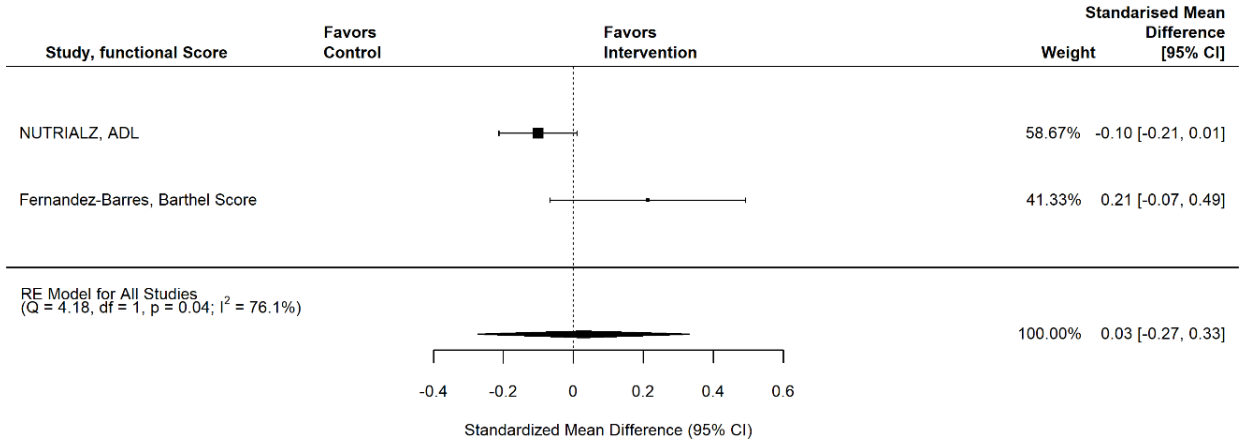


Figure 5-4- Forest plot of Association of change in functional outcome scores with Dietary interventions. Forest plot comparing the standardised mean difference of functional outcome scores within the dietary intervention cohort versus those randomised to control. The squares and bars represent the mean values and 95%, confidence intervals of the effect sizes, while the size of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical line represents the line of no effect.

5.2.5 The association of Lifestyle Interventions with Long-term Care Admissions, Mood and Caregiver Burden

All studies reported the proportion of participants admitted to long-term care during follow up which totalled 128 participants across intervention and control groups. There was no meaningful difference in admissions among both cohorts. Three studies measured mood at baseline, but only one study measured mood on follow up (165). In this study, there was no significant change in mood outcomes in those randomised to receive dietary intervention compared to control. Caregiver burden was measured at baseline in three studies using the Zarit Burden Interview, but only two reported change in caregiver burden on follow up (166,167). In both studies, there was no significant difference in caregiver burden between intervention and control groups. No study reported on cognitive or physical health outcomes in caregivers.

5.2.6 Reported Adherence to Lifestyle Interventions

Three studies reported on adherence to lifestyle interventions. Adherence was variable ranging from 35% in one study (162), to 92.9% in another study (163) . The two studies targeting nutrition (165,167) did not comment on adherence. All five studies reported on loss to follow up (n=413, 23.9% of total participants) with common reasons being death, institutionalisation, and medical complications.

5.2.7 Risk of Bias

Risk of bias was assessed in all five studies (Figure 5-5, Figure 5-6). The overall risk of bias was deemed low in three studies (162,163,166), and for the remaining two trials there were some concerns (165,167). In both studies there were some concerns around measurement of outcome data driven by the possibility that knowledge of the assigned intervention could

influence participant-reported outcomes and observer-reported outcomes. The randomisation process was adequate in all five studies and there were low levels of concerns around deviations from intended interventions, missing outcome data and selection of the reported result. There was no evidence of publication bias as illustrated by a contour enhanced funnel plot, which was symmetrical around the point estimate however there were a low number of studies to report on in this review (Figure 5-7).

Figure 5-5 Cross Tabulation Risk of Bias

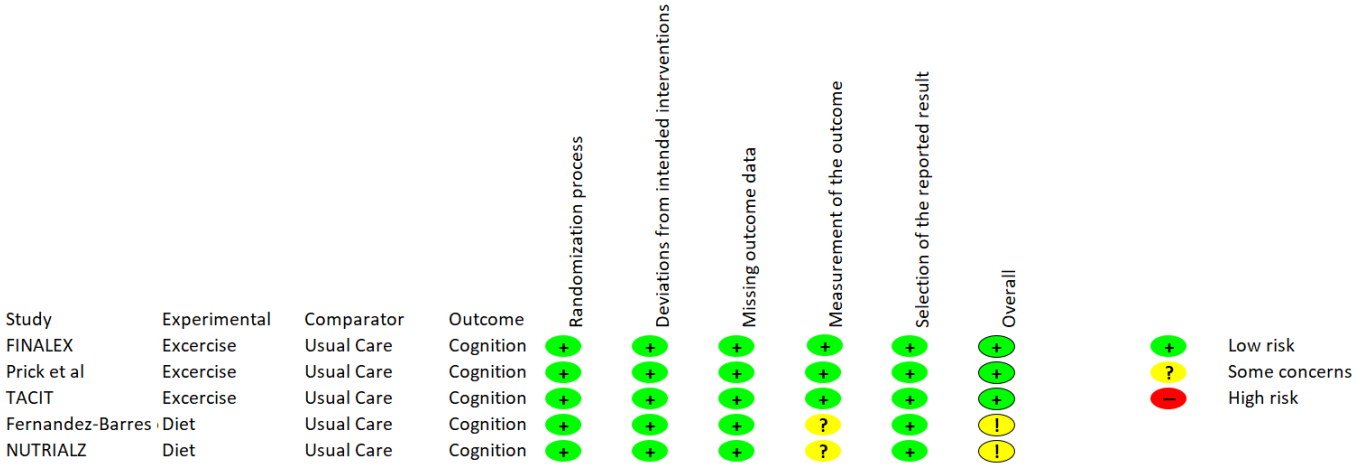


Figure 5-5 represents risk of bias among all five studies. This was generated using the Cochrane Risk of Bias 2 tool. https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

Figure 5-6 Risk of Bias Summary

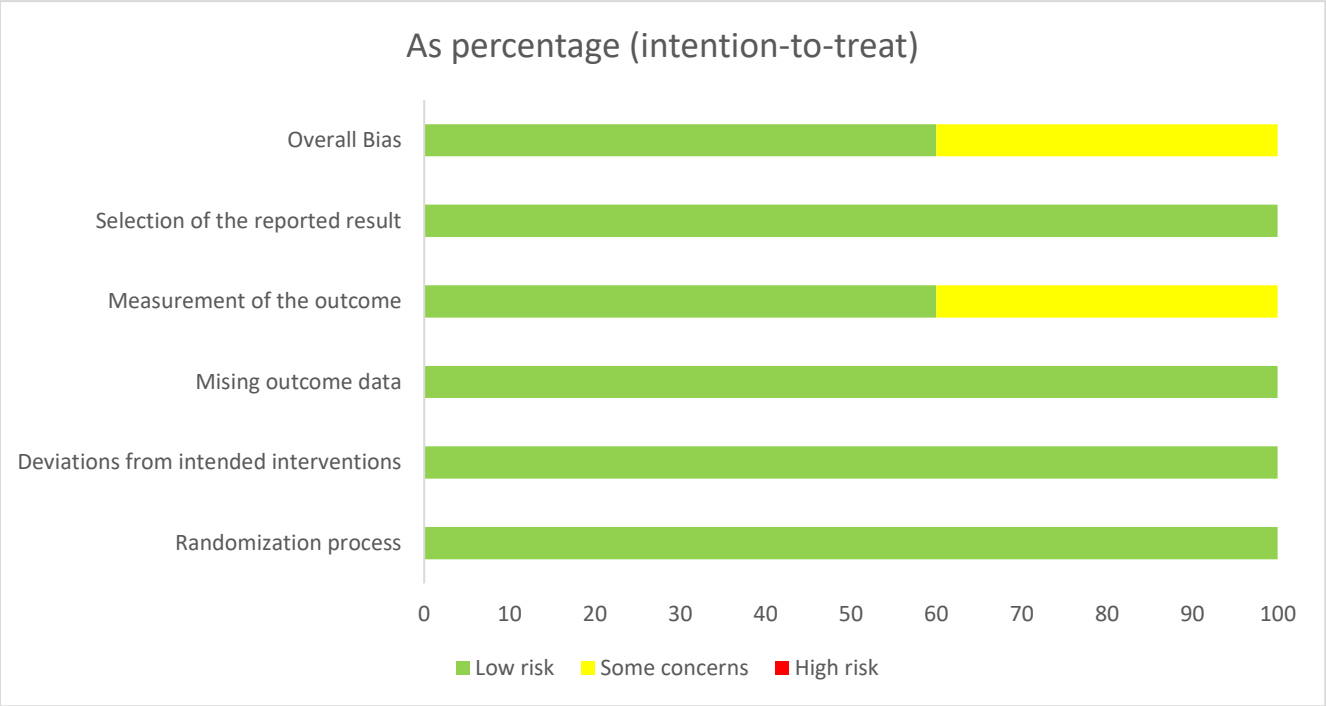


Figure 5-6 was generated using the Cochrane Risk of Bias 2 tool.

https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

Figure 5-7 Standard funnel plot

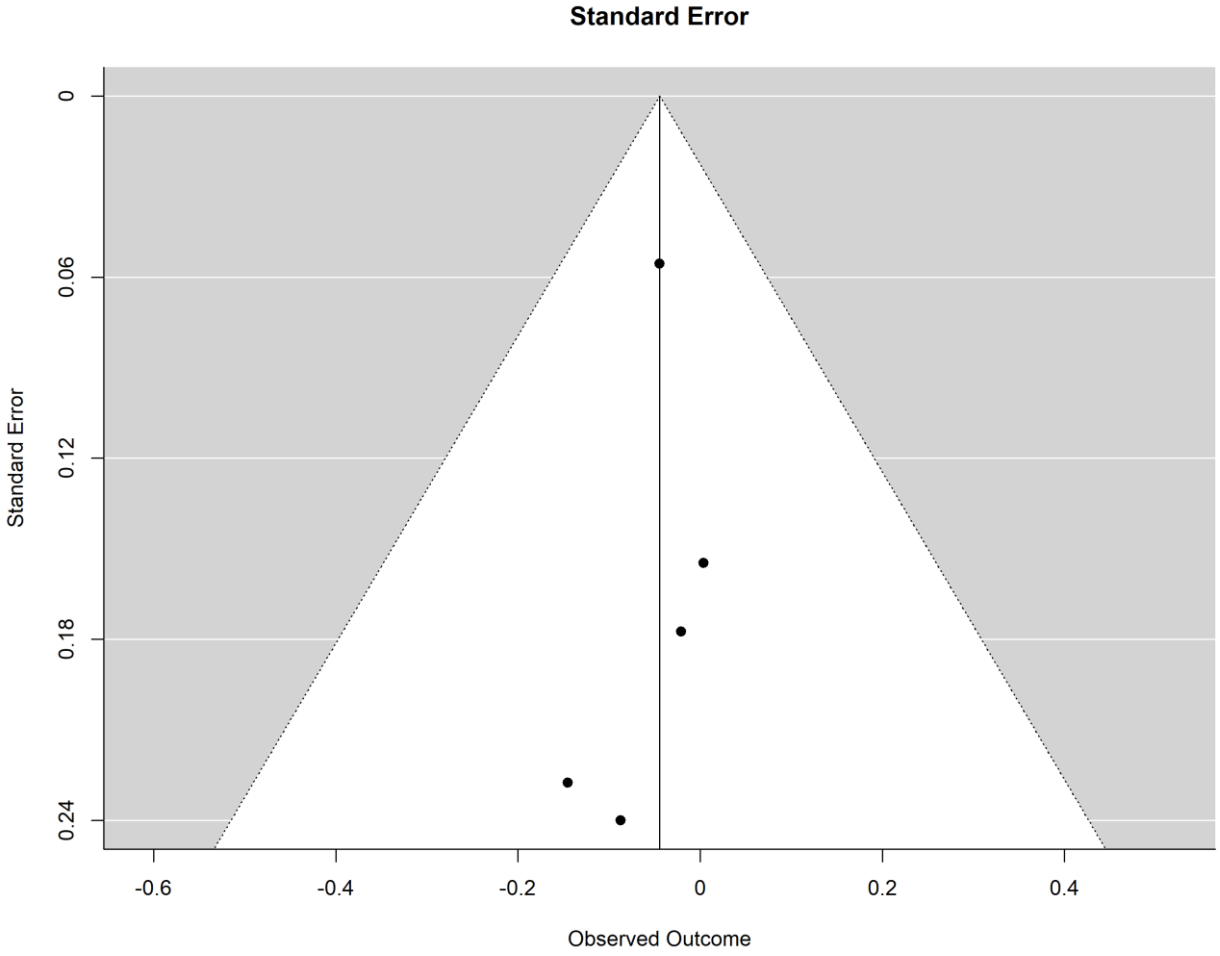


Figure 5-7: Standard funnel plot for all five trials

5.3 Discussion

In our review, we did not identify clinical trials that randomised households of individuals with cognitive impairment to lifestyle intervention(s) of diet, exercise, or sleep, for the prevention of cognitive decline. However, we identified trials that recruited household-like units of participants, usually dyads, where the intervention incorporated participant(s) in addition to individuals with cognitive impairment. We found that dyad-targeted dietary and exercise interventions had no significant impact on cognitive testing or functional outcomes, but small sample sizes included in those trials precludes definitive conclusions, as more modest effects may be present.

Definitions of "households" vary, but are most commonly defined as "those who dwell under the same roof and compose a family" or "a social unit composed of those living together in the same dwelling" (170). There are advantages to targeting lifestyle interventions at a household level, as many health behaviours cluster within families and co-habitants. In other populations, trials have employed households as units of randomisation, and these have primarily focused on dietary or physical activity interventions to reduce the risk or severity of childhood obesity, within a family (171,172). For example, the Healthy Homes/Healthy Kids trial, randomised families to the intervention and was designed to measure body mass index (BMI) outcomes in both children and parents and to additionally determine household behaviours that would influence dietary choices (70). The rationale for this type of study design is based on the influence of caregivers within households on lifestyle behaviours, for example the responsibility for meal preparation and grocery provision often lies with caregivers. This is particularly relevant in the household where there is an individual with cognitive impairment and targeting the caregiver as an equal part

may increase the benefit given shared behaviours. It may result in increased adherence and better feasibility when the household rather than the individual is enrolled.

Although dietary interventions primarily randomise the individual, given the concept of shared mealtime and food preparation within a household one can hypothesise that individually targeted dietary interventions may impact on health behaviours of other household members. Beyond logical inference, there is evidence to support a household-level effect of lifestyle intervention. A follow-up study of the Women's Health Trial (WHT), an RCT designed to assess the feasibility of a low-fat dietary intervention among women at moderately increased risk for breast cancer, found that husbands of women who received the intervention consumed significantly less dietary fat than husbands of those in the control group. It was suggested that these findings were likely due to passive involvement, by eating low-fat diet meals prepared by their wives (73). This study demonstrated that health behaviour in those households changed and was sustained beyond the individuals randomised to the trial. It may be more relevant to focus on the household unit as the target of for lifestyle interventions rather than the individual, given that households are likely to share many lifestyle traits such as degree of sedentary activity, dietary habits and smoking (173).

Non-pharmacological interventions for dementia including multicomponent training (exercise and cognitive training) and support programmes have been evaluated extensively but have achieved varying levels of efficacy (174,175). These include interventions such as group support meetings, training in behavioural management for caregivers, family counselling, emotional support for caregivers and regular home-based occupational therapy visits. Previous reviews of dyadic interventions have focused on outcomes such as

acceptability, feasibility, impact on caregiver burden, impact on behavioural symptoms of the individual with dementia (176,177) rather than cognitive or functional outcomes of the individual or the caregiver. Additionally, these reviews did not comment on adherence to the intervention. This is reflected in our literature search which did not uncover any household targeted lifestyle intervention for the prevention of cognitive decline.

5.3.1 Limitations

There are several limitations to this study. First, we did not identify any trial which truly represented the household as a unit of randomisation for the evaluation of lifestyle interventions for the prevention of cognitive decline. Given this, our strategy was revised following our initial search. Second, we had limited information for dyad based trials on relationships between caregiver and care recipient in addition to living circumstances and other household members. Studies including dyads did not report on cognitive outcomes or physical health outcomes of the caregivers. Third, we note that there was heterogeneity among the cognitive and functional outcome tools of measurement in our analysis with different measurements used across the five studies. This highlights the role for standardised core outcome sets for interventions trials in this population.

5.4 Conclusions

To our knowledge, there has been no household level RCT exploring a lifestyle intervention for the prevention of cognitive decline. Our revised criteria to include studies of dyads showed these interventions had no significant impact on cognitive function but illustrate feasibility of these types of trials. Future trials of lifestyle-based interventions for the prevention of cognitive decline should consider targeting households as the unit of randomisation to explore cognitive and physical health benefits for all household members

in addition to added benefits of greater adherence and sustainability of positive health behaviours.

Chapter 6

Are Clinical Trials Randomising Households to Lifestyle Interventions for the Prevention of Cognitive Decline Feasible? Semi-Structured Interviews to Determine the Beliefs, Preferences, and Deterrents for Households Impacted by Dementia.

6.1 Introduction

Rates of dementia are increasing in Ireland (178). Approximately 180,000 people in Ireland are currently or were previously carers for a family member or partner with dementia (18) and there are many others unaccounted for who are providing care and support structures in informal ways. There is considerable regional variation in the prevalence of dementia across Ireland with the highest proportions reported in the West of the country (179), which has an estimated population of 453,109, most of whom are living in rural areas.

Household-level interventions of lifestyle interventions primarily targeting obesity have been trialled within the paediatric population and in indigenous communities (where health councillors made regular home visits to Aboriginal Households and supported the setting of dietary and physical activity goals) (70,180), but there has been no randomised controlled trial (RCT) targeting household-level interventions for the prevention of cognitive decline. There have been small clinical trials enrolling dyads but these have included little information on household structure or caregiver network (162,165,167) and focused on individual-level outcomes (i.e. individual with cognitive impairment) rather than health outcomes for the entire household.

Overall, individual-level randomised trials of short-term, single domain lifestyle interventions have not demonstrated a large, meaningful effect. The Finnish intervention study to prevent cognitive decline and disability (FINGER) (153) randomised individuals to a multidomain intervention (including physical activity, dietary advice and cognitive training) demonstrating improvement in global cognitive functioning at 2 years follow up, and from this trial the World-Wide FINGERS network has been established bringing together global trials with methodological features in common with the original FINGER study (181).

Beyond this, consideration should be given to household level interventions (where the unit of randomisation is the household rather than the individual) to determine if a greater, sustainable effect on cognition can be achieved. Social contact has been identified as a protective factor in dementia prevention, and engaging with family regularly plays a prominent role (29). Household level interventions may confer benefit beyond the individual with cognitive impairment, with collateral benefits for all household members. Family members who provide informal care duties for the individual with cognitive impairment, may also be at risk of emotional and physical strain leading to adverse health outcomes, physical injury, change in immune response and lack of engagement with their own preventative health strategies (20,154). From the findings in Chapter 2 and Chapter 3, we identified that higher duration caregiving of adults was associated with an increased frequency of unhealthy cardiovascular behavioural risk factors (shorter sleep durations, poor diet, increased BMI and smoking) and this cohort may be at higher risk of mortality. This highlights the role of identifying 'at risk' caregivers, for example those caregiving for individuals with dementia who often require high intensity care, for targeted preventative health strategies. Apart from cognitive and physical health benefits for the participants, targeting a household may improve the feasibility and sustainability of change in lifestyle by changing the culture within the home. Given the prevalence of dementia, any strategy shown to benefit overall brain health is of use, and if individuals feel they are taking control to prevent further cognitive deterioration this may be, in itself, of benefit (182). All members of households affected by dementia may benefit from targeted lifestyle interventions.

6.2 Study Aim

The aim of this study was to explore the feasibility and attitudes towards introducing lifestyle-based interventions in households affected by dementia. Our aim was to better understand the beliefs of the household members around lifestyle factors such as sleep, diet and physical activity and their link with dementia; what challenges households affected by dementia might face in changing lifestyle factors; and how feasible it would be to sustain change among all household members.

6.3 Methods

6.3.1 Design

We collected data from participants using semi-structured interviews (SSI). The qualitative method of thematic analysis (183) was used. This method was chosen given that it is the most common form of qualitative analysis and provided a flexible approach given that the interviews were adaptable to participants. We explored the opinions and beliefs of household members on pre-determined topics of interest and spent time exploring in depth any factors which were of importance to any household member.

6.3.2 Ethical Approval

Ethical Approval for this study was obtained from the Ethics Committee at University Hospital Galway (UHG).

6.3.3 Participants

Two investigators (MMC and CMcC) identified, screened, contacted, obtained verbal consent, and interviewed household members. Study participants were identified prospectively though the dedicated Memory Clinic service, Department of Geriatric Medicine, University Hospital Galway between October 2020 and May 2021. Consecutive

patients referred to the clinic, living in a community-dwelling household, were invited along with their household members to participate in a semi-structured interview. Information regarding the study was given to all potential participants and follow-up phone contact was made to explain the aim of the study and to re-iterate that participation was voluntary. Written consent was obtained from all household members who participated in the study.

Interviews were carried out among each household separately, to ensure all household members had the opportunity to give their opinion. In light of the COVID-19 pandemic, interviews took place online using the secure, web-based video platform recommended by the Health Services Executive (HSE) for patient clinician interaction. One household completed the interview via telephone due to internet connectivity issues and one household elected to be interviewed face-to-face at the request of the individual with cognitive impairment.

6.3.4 Sample Size

Eight households in total were recruited for this study. Unlike quantitative research where statistical guidelines exist for sample size calculation, there remains practical uncertainty around sample size justification in qualitative research (184). Our initial goal was to meet thematic saturation (whereby further interviews would have yielded no new themes) (185) however there were several practical factors which influenced the size of the sample. These included difficulty in getting household members to be available at the same time to complete interviews together, challenges in prospective recruitment due to interruption of services during peak waves of the COVID-19 pandemic and a limited pool of potential participants given many individuals attending the memory clinic were living independently. Although the sample size appears small, and it was difficult to judge when thematic

saturation was reached, detailed information was gathered, and similar concepts were repeated among households suggesting appropriate thematic conclusions could be made in this small in-depth study. In addition, the households included varied in sex, urban versus rural location and relationship to other household members allowing for diversity of perspectives.

6.3.5 Data Collection

In advance of the interviews taking place, a standardized interview guide was developed for use by investigators. During each interview, one researcher took the lead as interviewer and the other acted as moderator and facilitated if any technical challenges arose for participants. The interview guide was developed via research group consensus. Questions were developed around pre-determined topics and specific follow up questions were used to explore themes and specific opinions that participants volunteered. If there was a particular area of interest for participants, this was explored in further detail.

Open-ended questions were aligned according to the following subtopics; attitudes towards lifestyle factors; beliefs towards sleep, diet, exercise in cognition specifically how they contribute to dementia and the ability to modify them; barriers and challenges to individuals/households in changing lifestyle behaviours, self-efficacy and feasibility in changing lifestyle behaviours and willingness to participate in trials exploring lifestyle factors as a household (Table 6-1). During the course of the interview, participants were shown a video of a sample behavioural intervention targeting sleep called Sleepio to explore attitudes towards digital interventions (186). No formal measurements of sleep, diet or physical activity were taken as part of this study.

Table 6-1 Interview Topics for all household members

Topic 1	General attitudes to sleep, diet, physical activity, and cognition.
Topic 2	Barriers & challenges to lifestyle change
Topic 3	Self-efficacy/feasibility of changing lifestyle behaviours
Topic 4	Willingness to participate in household level clinical trials

Interviews were recorded with permission of all participants. This was to allow for detailed analysis of the responses to be performed. The interviews were transcribed according to topic response and were organised in a systematic way. Any identifying information disclosed during the interview process was not included in the interview transcriptions.

6.3.6 Data Analysis

Interview transcripts were analysed by two investigators, MMC and CMcC. Interview notes were reviewed to identify common themes within the identified subtopics. Inter and intra household disagreements and agreements were noted. Quotations, when relating to a specific topic, were recorded where relevant, and could be contributed from any household member. Key phrases and themes were quantified during the analysis with frequency taken as a marker of importance among households.

6.4 Results

6.4.1 Demographics and Household Characteristics

In total, eight households participated in the semi-structured interviews with a total of eighteen participants. The characteristics of the households are outlined in Table 6-2. Of the 8 individuals with cognitive impairment, 75% (n=6) were male, with a median age of 78.5

(range 71-87) years and all had cognitive test scores that were considered impaired (median Montreal Cognitive Assessment Score 14/30 [range 10-23]). Duration of symptomatic cognitive decline ranged from 1 to 5 years, 2 of 8 required assistance with personal activities of daily living (PADL) and all required assistance or were dependent for instrumental activities of daily living (IADL). All were living in the West of Ireland. In terms of the relationship to the person with dementia, among the 10 household members that participated, 50%(n=5) were spouses, 30% (n=3) daughters, 10%(n=1) a son and 10% (n=1) a daughter-in-law.

Table 6-2 Demographic details of study participants

Household	Sex of PWD	Age of PWD (yrs)	Neurocognitive Disorder	Cognitive Test Results	PADL	IADL	Sex of other Household member(s)	Relationship to PWD	Formal Home Supports
1	Male	71	Alzheimer's Disease	MoCA 13/30	I	A	Female	Wife	None
							Female	Daughter	
2	Male	73	Mild Cognitive Impairment	MoCA 23/30	I	A	Female	Wife	None
3	Male	78	Mixed vascular and Alzheimer's Disease	MoCA 15/30	A	A	Female	Daughter-in-law	None
							Male	Son	
							Male	Grandson	
4	Female	87	Alzheimer's Disease	MoCA 19/30	I	A	Female	Daughter	None
5	Female	79	Mixed vascular and Alzheimer's Disease	MoCA 10/30	A	D	Male	Son	Home Help
6	Male	86	Mild Cognitive Impairment	ACE-III 73/100	I	A	Female	Wife	None
7	Male	80	Lewy Body Dementia	MoCA 14/30	I	A	Female	Wife	Home Help
							Female	Daughter	
8	Male	77	Vascular Dementia	MoCA 14/30	I	A	Female	Wife	None

PWD=Person with Dementia; ACE-III=Addenbrooke's Cognitive Examination III; MoCA= Montreal Cognitive Assessment; PADL= Personal Activities of Daily Living; IADL=Instrumental Activities of Daily Living; I=Independent; A=Assistance Needed; D=Dependent

6.4.2 Responses to Interview Topics

6.4.2.1 General Attitudes to Sleep, Diet, Physical Activity and Cognition

The majority of participants rated their sleep as good or very good (n=13), two persons with cognitive impairment described their sleep as poor and three household members without cognitive impairment described their sleep as poor or very poor. Of the households where members reported very poor sleep, the person with cognitive impairment within the household described their own sleep as very good. All interviewees, including those with cognitive impairment reported sleep as being important or very important to themselves.

Six households felt that sleep was important in protecting brain reserve and memory function. One daughter commented “If you don't sleep your brain isn't given time to process or charge". Two households did not place much importance on the relationship between sleep and cognitive function with one spouse noting that her husband [with cognitive impairment] always had much better sleeping patterns and “his memory is worse”. Of the households who felt it was important they noted that reduced sleep resulted in mental slowing and difficulty concentrating; “I’m not as sharp as I'd like to be if I don't sleep well” [daughter-in-law, Household 3]; “when you’re that tired…. you can't think straight"[person with cognitive impairment, Household 4]. All households reported poor concentration if insufficient sleep the night before.

Six participants reported getting 7-8 hours of sleep per night, three reported greater than 8 hours of sleep per night and half of participants (n=9) reported less than six hours of sleep per night. Only one household reported that all members had similar sleeping habits; other households reported variation in time to bed, time to getting up and daytime napping. In one household, the person with cognitive impairment had visual hallucinations at night-

time and, although he did not report poor sleep, this led to sleep disturbance for other household members who would wake in response to his interactions and need to re-orient him on a regular basis.

Interviewees self-reported having a healthy or very healthy diet (n=17) with one household member reporting poor diet due to snacking and “comfort eating”. Perceptions of healthy diet included eating fresh fruit and vegetables, consumption of fish 1-2 times per week, and reduced intake of red meat. In Household 1, the spouse had been recently diagnosed with coeliac disease, which had resulted in a switch to gluten-free meals for the entire household. Other than one household, all reported having the same diet intake at mealtime within the household. In Household 3, the son adopts a vegan approach intermittently, which means two separate dinners are prepared. In six households, the person with cognitive impairment was dependent on other household members to decide which food was in the house and for meal preparation while in Households 4 and 5 these responsibilities were shared among members. No household reported that the person with cognitive impairment was the main meal preparer.

All households reported that diet was important or very important in protecting brain reserve and memory function: “you hear about omega and cod liver oils….we specifically eat fish regularly as supposed to be good for brain” [Household 2]. Most households (n=6) were uncertain of the exact mechanism through which diet and cognition might be linked but were able to contribute specific foods they felt were good for cognition with fresh fruit and vegetables rated highest, followed by fish. Household 1 commented that alcohol was “definitely bad for the memory”. No household named a specific dietary type

(e.g. Mediterranean). Household 2 commented “I don’t like the word diet; it sets you up to fail. I prefer healthy eating or way of eating" [spouse].

Physical activity patterns varied among and within households. Most interviewees reported walking as their main form of physical activity. Households 1, 6 and 7 reported “lack of interest” in physical activity among the individuals with cognitive impairment and they were less active than other members within households. Household members without cognitive impairment reported higher levels of physical activity, with many spouses achieving a walk of thirty minutes 4-6 times a week. Others reported participating in yoga, swimming, and outdoor exercise classes and in Households 6 and 8 the spouses spent a lot of time gardening. Six households reported enjoying exercise, one household did not overly enjoy exercise and one household reported having “to endure” physical activity. Half of households participated in physical activity together (mainly walking), while the remaining half preferred to exercise separately.

All households reported that physical activity was important, with two households reporting that it was very important, in protecting brain reserve and memory function. Households reported many different ways in which physical activity played a role in preserving cognition; "I see exercise as the pump to keep the brain going" [daughter-in-law, Household 3]; "Exercise is an activity, you need to have your wits about you…being safe…concentrating on what is around you" [person with cognitive impairment, Household 2]. Six households reported physical activity as being important to relax and relieve stress to help with cognitive function. Other reported benefits included environmental change, being outdoors and socially interacting with others.

6.4.2.2 Barriers and Challenges to Individual/Household in Changing Lifestyle Factors

Three households stated they would be interested in changing their sleep habits using a lifestyle intervention, one household was potentially interested, and the remainder were not currently interested. Half of households felt it would be easier to improve sleep quality at an individual-level, compared to improving it among the whole household while the remainder had no opinion on the matter. Household 7 had the most uncertainty around this as, due to Lewy body dementia, visual hallucinations were very prominent for the individual with cognitive impairment at night-time. The main barrier to changing sleep quality at a household-level was reported to be the inter-individual variation of sleep patterns within the household.

The majority of households (n=7) reported that it would be easier to change the dietary habits of the entire household rather than that of an individual alone. Most reported no concerns around the need to change diet or the benefit of dietary change, however, the individual with cognitive impairment from Household 8 wished to be certain any dietary initiatives would not interfere with his medications. Cost or sourcing produce was not a concern among any household.

Three households felt it would be easier to improve physical activity levels as a household unit than at an individual-level, three households felt it would be easier to improve at an individual-level and the remaining two households felt it would depend on the type of physical activity and the routine of the household. The main barriers to implementing a new physical activity programme were risk of physical injury and falls, followed by change in routine.

Household income was discussed with all households to determine if any participants had concerns about financial limitations in implementing behavioural change. There were no concerns disclosed, with many having good access to quality food produce and living nearby green spaces where physical activity could easily take place.

6.4.2.3 Self-efficacy and Feasibility in Changing Lifestyle Factors

Half of participants reported that it would be difficult to change sleep habits and that any change would be difficult to sustain long-term while the remainder had no opinion of this. In comparison, all households felt it would be feasible to change and sustain dietary habits, especially if there was regular support, recipe ideas and that the foods recommended tasted nice. Five households felt it would be realistic to change physical activity levels among all household members while the remainder felt it would not be realistic or were uncertain. When asked about methods to overcome barriers to improving physical activity clear instructions, regular support and enjoyment were mentioned most frequently. Household 3 commented it would help "if people were taught self-compassion and awareness of self…highlighting that journey would be possible for anyone at any age" [daughter-in -law]. Six households felt that of the three specific lifestyle factors (sleep, diet and physical activity), diet would be the easiest lifestyle habit to change in a household while the remaining two ranked physical activity [household 2] and sleep [household 3] as easiest to change. Half of households felt it would be difficult to try and change all three lifestyle habits in combination with the remainder uncertain if it could be achieved.

6.4.2.4 Willingness to Participate in Trials Exploring Lifestyle Factors as a Household

Five households reported that an online intervention would be easy for them to use especially if via smartphone or tablet application. The remaining three households stated

they would find it difficult with main concerns being computer literacy and need for technical support from children outside of the home. Five households had no issues with internet connectivity while the remainder reported intermittent difficulties with Wi-Fi. All had internet available in their homes. Seven households reported that at least one member would have no issues with typing, with one household reporting the person with cognitive impairment would be especially limited as he had no experience of using computers or typing on a smartphone. Only one household (Household 6) reported that they could be limited due to hearing issues.

Six households were very interested in participating in a future clinical trial to improve cognition by introducing sleep, dietary and/or physical activity interventions and which did not involve any pharmaceutical agents. The remaining two households stated they were "potentially" or "maybe" interested. With regards to trial outcomes, fitness, stimulation of memory and improvement in blood pressure were most frequently mentioned as being of importance to interviewees, followed by laboratory measurements of blood glucose and cholesterol levels. Regular support from trial staff, reminders and regular education were mentioned as ways to ease participation and avoid dropping out of the trial with one household mentioning that virtual calls and assessments would make it easier to participate due to their rural location.

6.5 Discussion

In this study we used semi-structured interviews to explore themes relating to the beliefs, preferences, barriers of lifestyles (diet, sleep, and physical activity) among households where a member had cognitive impairment. We further explored attitudes towards household-level lifestyle interventions, and online modes of intervention among

households. The identified themes are summarised in Table 6-3. Key information which emerged included the complexity of sleep within households, the willingness to trial dietary interventions, the motivations to participate in physical activity and the openness to digital interventions. With no clinical trial to date targeting the household as the unit of randomisation for lifestyle interventions for the prevention of cognitive decline, the themes which we have identified can be used to inform and plan for future research studies.

Table 6-3 Themes arising from semi-structured interviews

Themes
Household members without dementia were more likely to report poor sleep habits
Sleep habits were perceived to be much more related to the individual and the household and would be the hardest to change and sustain change within households
Although most participants had healthy diets, most were interested in making a change if it would be of benefit to cognition
Participants felt there was a strong link with nutrition and cognition
Physical activity is challenging to adapt due to lack of motivation and focus when individuals are cognitively impaired and additional barriers to changing lifestyle interventions concentrated around risk of harm
Motivations for physical activity in households are far beyond strength and cardiovascular benefit; more prominently it used for relaxation and social interaction.
Digital or online based interventions were appealing with virtual visits highlighted as a method to improve trial participation
Regular support and reminders would be beneficial to support behavioural change

The first theme that emerged was that household members without cognitive impairment were more likely to report poor sleep than those with cognitive impairment. There are multiple possible factors involved including caregiver burden, disruption of sleep routine, difficulty falling back asleep after assisting with nocturnal care needs and poor sleep hygiene such as over-reliance on caffeine to compensate for this (187). The complexity of this was highlighted among Household 7, where the person with Lewy Body Dementia had frequent nocturnal visual hallucinations which led to sleep disturbance for his spouse.

Following on from this, a key second theme that emerged was that sleep habits were perceived by most interviewees to be more related to the individual than the household, and that sleep would be the hardest lifestyle habit to change. Many participants were not aware of non-pharmacological strategies to improve sleep. When provided with a sample online sleep behavioural intervention, participants were uncertain and neutral about its application. There was uncertainty around approaching it as a household rather than as an individual. To date, most RCTs exploring household-level interventions targeting sleep have been aimed at families with young children as an intervention to prevent childhood obesity, however, parental or caregiver sleep is rarely measured alongside child sleep habits (188). Future trials of sleep and cognition should include measurement of sleep of all household members, reasons for disruption, compensation mechanisms alongside objective sleep measurements.

Another theme which emerged was that although most participants had healthy diets, most were interested in making a change and felt there was a strong link with nutrition and cognition. Each household was easily able to volunteer foods that they felt were beneficial for overall brain health. Throughout the interviews it was clear that household members all ate similarly, and if there were dietary restrictions or specific food dislikes for one individual, all members tended to adapt their diet accordingly. Our study supports current evidence that family and the household environment remains the most continuous factor which influences dietary behaviours (189) and should be considered a key level at which a targeted intervention can be delivered.

Higher income does not always equate to better diets among households. Economic development can lead to increased food security but also lead to higher fat and processed

food consumption (190). Having greater food access and options therefore does not always equate to a better diet which may have regional implications for population based dietary interventions. The participants in this study did not consider cost or sourcing produce to be a barrier, instead highlighting that recipe ideas or methods to incorporate certain food groups would be of greater practical benefit.

Another emergent theme were the challenges relating to changing physical activity behaviours. First, three households commented that it was very challenging to motivate the person with cognitive impairment to exercise. Interestingly, on further exploration, these individuals were very physically active when younger, involved regularly in team sports and took organisational roles within clubs. It has been previously reported that persons with dementia are more likely to abandon recreational and physical activities spaces (191). Participation in physical activity, particularly group based activities has been shown to be of benefit for cognition (192,193) but based on our interviews, physical activity interventions need to account for difficulties with focus and attention and not deviate greatly from routine. Many households also expressed that physical injury and risk of falls would be a concern with this type of intervention. Future trials should ensure that physical activity goals are easily incorporated into daily routine, with regular reminders that are achievable for all household members. The incentive for physical activity for most of our interviewees was stress relief and change of environment. Previous individual-level trials of physical activity in older persons demonstrated that a targeted custom physical activity intervention was effective in reducing major mobility disability (194) and therefore it is worth investigating if there is benefit for those with cognitive impairment and their households to offset significant functional decline.

A further theme which emerged was that digital or online based interventions were appealing to all households. Very few described challenges with internet access or sensory issues which would adversely impact engagement with online applications. For one individual, this study was the first time he had participated and engaged in a video-based call and found it very user friendly. He stated it had increased his confidence in participating in a future trial incorporating digital technology. Another household promoted the use of virtual trial visits as they were based rurally and attending in person would be time consuming and stressful. Involving patients with dementia in designing and adapting of online interventions is crucial to ensure engagement and acceptability (195). Given the recent surge in information communication technology, piloting new applications is essential, however, our interviews suggested that many participants were already empowered to use technology, frequently using messaging services and video calling to maintain communication among family members outside of the home. Most had greatest comfort with smartphones and tablets and noted little need for computer or laptop-based activity which should be considered when choosing a digital application host.

An important theme which emerged was the need for regular support and reminders for any household participating in a lifestyle intervention trial. Most concern around participation was due to uncertainty about how and when to incorporate changes. Many felt that reminders or messages about small adaptations on a regular basis would be achievable rather than a single educational seminar at the beginning of the trial. There was a sense among participants that personalising the interventions would allow change to be sustainable and that would allow for better support within households. The use of smart technology to encourage health behaviour change has not been found to be superior to traditional methods following acute myocardial infarction and stroke (196,197), however,

our findings suggest it may have a beneficial role for the cognitively impaired population and their households in allowing a trial intervention to be more feasible.

6.5.1 Strengths and Limitations

The main strength of this study is the novel use of semi-structured interviews to explore perspectives of all household members on lifestyle intervention trials. Given the lack of trials randomising at a household-level, this study provides in-depth insight into the beliefs, preferences, and deterrents of potential participants. Using small semi-structured interviews, rather than larger focus groups, allowed for the person with cognitive impairment and their household members to voice their opinions comfortably and freely. Although other methodological approaches such as surveys provide more structured data, this approach allowed subjects to express a deeper thought process around topics and give commentary on aspects that were of most importance to them.

An additional advantage of conducting the interviews over a web-based video platform was twofold. First, participants were able to have the interviews take place from the comfort of their own home, allowing a relaxed atmosphere and greater open discussion around the relevant topics. Second, this was a method to practically explore digital literacy, ease, and comfort of using online applications among our memory clinic attendees which is relevant for any future clinical trial incorporating technology.

Another strength to this study was the variation in household relationships, with participation from children as well as spouses. This gave additional insights and different perspectives of household members on lifestyle behaviours among different generations, however, we found that diet and physical activity behaviours were similar despite age gaps.

A limitation to this study was identifying suitable participants. Many of our memory clinic attendees live independently supported by family members who do not live within the same household structure. Consideration, in future trials, should be given to the definition of a household; as within West of Ireland populations, many family members live in very close proximity and meals are often shared with regular visits throughout the day although families may not be living under the same roof. In addition, our sample size could be criticised as being small, and may not be truly representative of our region, but given practical limitations in recruitment, rich data was still extracted and can be used to inform future study design.

A further limitation to the study was that we did not show sample applications that a trial would use to affect change in diet and physical activity. An area for future patient and public involvement would be to hold focus groups to discuss an appropriate user-friendly digital application that would be acceptable for all household participants.

6.6 Conclusions

This study identified that sleep, diet, and physical activity are justifiable targets for intervention at household-level for those affected by cognitive impairment. In addition, there may be cumulative benefits to targeting more than one lifestyle activity in need of intervention, further adding to the potential of this type of trial methodology. Barriers to this centre around acceptability of digital intervention, concern around risk of injury and perceptions of sleep behaviour among different household members. Further studies are needed to determine what digital intervention would be most acceptable and the best methods to support trial participants, both in person and using virtual visits. Future clinical

trials should include households affected by cognitive impairment in protocol planning to maximise study feasibility.

6.7 Declarations

6.7.1 Ethics approval and Consent to Participate

Ethical Approval for this study was obtained from the Ethics Committee at University Hospital Galway (UHG). Written consent was obtained for all household participants.

6.7.2 Consent for Publication

All participants provided verbal consent for publication at time of interview. This was recorded. All participants were informed that the contents of the interview would be kept confidential, and no individual participant or household would be identified in any future communication or publication.

6.7.3 Availability of Data and Materials

Relevant extracted data are included within the main body of the manuscript and the tables. Recorded interview transcripts are securely maintained with the authors of the study.

6.7.4 Acknowledgements

We are grateful to all households who participated in this study.

Chapter 7

Designing Clinical Trials of Household Level Lifestyle Interventions for the Prevention of Cognitive Decline: the Challenges and the Opportunities

7.1 Background and Rationale

Incidence of dementia is projected to increase in developing countries (3). Without significant community level interventions aimed at prevention and treatment of this syndrome and its consequences, this condition will continue to incur incremental societal cost (198). Large scale, simple, cost-effective public health measures which are achievable by households across a variety of geographical locations for the prevention of cognitive decline is essential.

Non-pharmacological interventions targeting individuals with dementia such as multicomponent training and support programmes have been evaluated but have achieved varying levels of efficacy (174,175). These include interventions such as group support meetings, training in behavioural management for caregivers, family counselling, emotional support for caregivers and regular home-based occupational therapy visits. There have been several studies on psychoeducational interventions with the primary outcome focusing on behavioural management of the individual with dementia, mental health outcomes of caregivers and caregiver quality of life (199).

In Chapter 5, we report findings from a systematic review exploring Household-level lifestyle interventions for the prevention of cognitive decline. Our findings suggest a deficit in household-level lifestyle interventions for prevention of cognitive decline and related outcomes. Individuals with dementia are more reliant on family members for assistance (200), often with whole households collaborating together for caregiver tasks (201). Given that household members share many common lifestyle behaviours, consideration should be given to targeting the household to modify health behaviours. Previous trials which have successfully targeted the household investigating dietary or physical activity interventions to

reduce the risk or severity of childhood obesity within a family (171,172), and the shared behaviour principals are applicable to households affected by cognitive impairment.

Given the importance of lifestyle factors in risk of dementia, simple lifestyle interventions which target households rather than individuals may have group-level health benefits.

7.2 Evidence to Date on Multicomponent Interventions for Dementia Prevention

Our focus of interest is on non-pharmacological preventative lifestyle strategies targeting vascular risk and physical health namely diet, exercise, sleep which are thought to impact cognitive outcomes (202). In 2015, a systematic review and Delphi consensus study supported midlife obesity, physical inactivity and smoking as targets for intervention (30). This review was based mainly on observational studies and highlighted the importance of the need for well-designed multicomponent randomised controlled trials (RCTs) to further identify targets of interest.

Since then, there have been several large European multicomponent intervention trials published; PreDIVA (150), which targeted community dwelling older adults and was delivered within primary care settings, the MAPT trial (203) which included cognitive training and randomisation to a dietary supplement, FINGER (204) which incorporated cognitive training alongside dietary and exercise intervention and HATICE (151) which used a coach led e-health platform based around goal setting and education around lifestyle habits. These RCTs as part of the European Dementia Prevention Initiative have targeted interventions at an individual level focusing on “at risk” populations. These clinical trials support targeting lifestyle factors for dementia prevention and have highlighted the benefit of a utilising a multicomponent rather than single component intervention. Physical activity

and vascular health have been identified as key areas to target in high risk populations (29) and consideration should be given to targeting behavioural lifestyle factors in particular.

PreDIVA demonstrated no difference in dementia incidence between intervention and control groups, however in participants who had untreated hypertension who adhered to treatment during the trial there was a reduction in Dementia incidence. MAPT failed to demonstrate any impact of a multidomain intervention and polyunsaturated fatty acids on cognitive function. FINGER showed more promise by demonstrating that a multidomain intervention could improve or maintain cognitive functioning among an older population, and that the intervention was acceptable and feasible. From these trials, it has been identified that selecting the correct target population at the right time is essential and that the content of the intervention is pivotal emphasising the important role of feasibility trials in this domain (204). Future clinical trials should explore the influence of caregivers within households on lifestyle behaviours given where responsibilities lie, for example for meal preparation, motivation to exercise. This is particularly relevant in the household where there is an individual with cognitive impairment and targeting the caregiver as an equal part may have added benefits given shared behaviours. It may result in increased adherence and better feasibility when the household rather than the individual is enrolled compared to previous individually targeted multicomponent intervention trials.

7.3 Evidence for Targeting Behavioural Risk Factors for Dementia Prevention and for Considering the Household as the Unit of Randomisation

During the course of this thesis, three behavioural risk factors of interest for the prevention of cognitive decline and as potential targets for improving the health of caregivers have emerged; namely sleep, physical activity and diet.

7.3.1 Definition of a Household

Definition of a household is of great consideration in trial design and is impacted by local, societal, and cultural factors. A household is traditionally defined as several persons who live in the same dwelling. Consideration should be given to the inclusion of groups of individuals who share the same meals, grocery provision and have physical contact on a consistent and regular basis, most likely living in very close proximity as meeting the definition of a household. Recruitment in certain countries or rural environments may be limited by only including the traditional definition of household. Further feedback from individuals with cognitive impairment and their caregivers should be used to inform the structure of an eligible household.

7.3.2 Sleep

Epidemiological studies have identified poor sleep as a risk factor for dementia and good quality sleep as having a role in maintaining brain health. Sleep patterns change with ageing and multiple lifestyle factors and co-morbidities can contribute to poor sleep hygiene. Pharmacological interventions for sleep are associated with significant adverse effects particularly in the older population so trialling a non-pharmacological strategy to improve sleep habits and overall brain health is of interest. Digital cognitive behavioural therapies targeting habits have shown promise for cognitive performance (205) but have not been trialled beyond the individual level.

To date, most RCTs exploring household level interventions targeting sleep have been aimed at families with young children as an intervention to prevent childhood obesity however parental or caregiver sleep is rarely measured alongside child sleep habits (188). Gender also plays a role with the “night shift “ of caregiving duties often disproportionately

placed on women, with more responsibility for feeding and often due to overall gendered expectations (206).

Other factors influencing differences and similarities in disordered sleep among household members include working night shifts, screen time exposure, and cultural practices like napping and co-sleeping and frequency of caregiving. Among caregivers of adults with dementia, quantity of caregiver sleep is similar to quantity of care recipient sleep with higher frequency of night time awakenings among caregivers looking after those with higher falls and behavioural issues (207,208). Disrupted sleep therefore may have a role to play in in caregiver health outcomes and provides a potential target for further intervention in households affected by cognitive impairment.

7.3.3 Diet

Dietary changes are controversial in dementia prevention with previous focus placed on specific vitamin, mineral, and dietary supplements. There has a been greater exploration of whole-diet options in more recent years. Observational data suggests the Mediterranean diet (high intake of vegetables, legumes, fruits, nuts, cereals, and olive oil; low intake of saturated lipids and meat) has benefit (43) however further randomised trials are required to support this. The WHO guidelines have recommended this diet for dementia prevention given the possibility of dementia risk reduction and the lack of harm associated with this regime. Careful consideration must be given to how dietary adherence is measured within future trials for dementia prevention. There is definite opportunity to consider the incorporation of metabolomics as a novel method to measure Mediterranean diet exposure (209). A metabolic signature, comprised of 67 metabolites has been recently identified within the PREDIMED cohort, which measured adherence to the Mediterranean diet and

predicted cardiovascular risk independent of known cardiovascular risk factors (210). The metabolome helps overcome some of the inherent difficulties in measuring dietary outcomes in studies including self-reporting bias, accuracy of nutrient plasma levels and enables adherence to an entire diet to be explored rather than one specific component.

Households and dietary behaviours are intrinsically linked. There are several food related household factors which impact the nutrition of the individual. Household income affects access to food, with certain food preferences greater among lower income families with selection based on affordability rather than taste. Change in food pricing has greatest impact on the consumption patterns among lower income households.

Household occupations in low- and middle-income countries also impacts dietary behaviour. Households involved in farming will be more likely to consume and have access to their own produce. Households that are not involved in agricultural practice may be limited by cost in accessing farm-grown products. In addition, the role of time as an economic commodity must be considered. If women are working in labour roles for long hours, food pattern consumption shifts, for example, from homemade to commercially made produce. Household roles can impact food behaviours, with those earning most in households often the main decision maker in choice and allocation of food. Family and the household environment remains the most continuous factor which influences dietary behaviours (189) and should be considered an opportunistic level at which an intervention can be directed.

7.3.4 Physical Activity

Sustaining mid-and later life physical activity has been established as a key action to reduce long-term dementia risk (29) however studies on exercise are complex. A specific exercise

intervention has not been yet identified, although the WHO have advised that aerobic exercise is likely beneficial for dementia prevention. Exercise programmes bring inherent limitations such as cost of equipment, location, and other limitations in the setting of physical comorbidities.

A meta-analysis of observational studies has supported the role of any level of physical activity (low, moderate or high) as being a protective factor in maintaining cognitive performance compared to being sedentary (211). A Cochrane review comparing aerobic physical activity programmes with any other intervention or no intervention for cognitive function found benefit but recommended that further trials are required to determine if any form of exercise is sufficient for benefits on cognition or if a specific aerobic component is required (57). Targeting volume of physical activity rather than specific physical activity type may be a more meaningful and achievable intervention for studies on dementia prevention.

There are several socioeconomic factors which influence level of physical activity in adulthood that often are applicable to all household members including higher level of education and being from more advantaged social classes (212). Further consideration must be given to the influence of household behaviours on physical activity of the individual, including level of activity of other members, influence of chronic disease, interest in participation with other household members, level of mobility, and musculoskeletal issues. In addition, exploring motivations behind physical activity participation is of relevance; is the intent to improve cardiovascular fitness or are there other needs being met including stress relief, social interaction, and sense of purpose within group-based activities.

7.4 Evidence for Targeting Behavioural Risk Factors in Caregivers

Many studies to date have focused on the psychological impact of caregiving but very few have explored the impact of caregiving on lifestyle risk factors. Many non-communicable diseases e.g. cardiovascular disease and diabetes develop over time with chronic stressful states being implicated, including caregiving for heavily dependent individuals. It is therefore worth exploring health behaviours further in this cohort of individuals and estimating if there is a benefit to endorsing healthy lifestyle behaviours among this group.

In a previous study of caregivers of hospitalised cardiovascular patients, caregiver burden including impact on time and sleep, affected health behaviours and impacted caregiver ability to maintain regular physical activity and healthy eating habits (213). Caregivers of those needing assistance with activities of daily living have also been identified as a cohort more likely to have negative health behaviours with sense of self-control also contributing to poor lifestyle habits (214).

Given that many individuals with dementia require assistance with activities of daily living and have non-cognitive components to their condition that can lead to lack of sleep and disruption of routine for caregivers, targeting lifestyle habits of caregivers of dementia alongside the care recipient will likely be of benefit, not only from an adherence and feasibility perspective but is likely to confer health advantages to all parties. The findings in Chapter 2 and Chapter 3 highlight the likely beneficial role of targeting “at risk” caregivers, i.e. those providing greatest duration and intensity of care to vulnerable adults who are most likely at risk of adverse health outcomes due to caregiving.

7.5 Benefits of Including Caregivers in Lifestyle Interventions Trials

There are several benefits to the inclusion of caregivers in future clinical trials of lifestyle interventions for the prevention of cognitive decline. Caregivers of those with dementia are thought to be more at risk of negative health behaviours and the stress process theory of caregiving and less likely to engage in self-care (107,215,216). This group may be more likely to benefit from public health interventions, particularly those who deliver longer durations of care as emerged in Chapter 2 and Chapter 3. Their inclusion in clinical trials will lend insights into the benefit of lifestyle behavioural change in caregiver health outcomes.

Outside of being a target of interest, caregivers can assist with trial retention. Caregivers can help act as proxy respondents to ensure completion of outcome data for participants with cognitive impairment, for shared behavioural outcomes. Salthouse et al determined previously that attrition of those with cognitive impairment from clinical research is often due to mortality, morbidity, mobility and motivation (217). In Chapter 4 we demonstrated the benefit of including proxy respondents to ensure true representation of vulnerable populations in clinical research which is applicable to those with cognitive impairment with caregivers being able to support care recipients and help overcome the magnitude of overall attrition.

As highlighted in Chapter 6, household members with cognitive impairment are likely to be reliant for instrumental activities of daily living and therefore navigating lifestyle interventions alone and unsupported would be challenging. By using caregivers to act as the primary conduit for the trial intervention, this may result in greater acceptability and feasibility among all participants.

7.6 Role of Adaptive Design Methods

Given the challenges in measurement and adaptation of behavioural risk factors, future trials incorporating households affected by cognitive impairment should consider using adaptive design methods. There is no “one size fits all” model for dementia prevention and for some households targeting physical activity and sleep may be of greater relevance than targeting diet and vice versa. In addition, within households, there may be differences in the behaviours that the caregiver and the individual with cognitive impairment should be attempting to improve, or there may be a difference in optimal goals based on pre-existing lifestyle factors. Micro randomisation is a novel method which can address the need for modification of lifestyle interventions throughout the trial without undermining the validity and integrity of the study.

Micro randomisation can be used to optimise the components of the proposed behavioural intervention. The rationale behind employing this technique is to further balance the impact of unobserved factors to different intervention groups. In a future trial incorporating this methodology, through repeated randomisation, we can reduce the possible reasons why one intervention group has a better outcome than another (218). This technique is particularly suited to behaviours being investigated as part of a lifestyle intervention trial as it provides more personalised reminders which are likely to be a more successful way of targeting participants. This method will help inform for future bespoke lifestyle intervention prescribing based on the pre-existing behaviours of the household. Micro randomisation will also be of use to determine if success of the intervention is impacted by certain contexts for example the impact of good or bad weather or time of day on encouraging tailored physical activity.

7.7 How Micro Randomisation Would Work?

Consider a future, ideal clinical trial looking at household-level lifestyle interventions for the prevention of dementia, specifically targeting sleep, diet and physical activity which would employ use of micro randomisation. In such a proposed trial, each participant-time point will be randomized between intervention or no intervention (delivery of a contextually tailored activity suggestion for either sleep, diet, physical activity or no suggestion). This is outlined in Figure 7-1. I will now describe the specific proposed components about how micro randomisation would work within an ideal trial setting.

7.7.1 Intervention Components

Within this proposed trial, baseline measurements of exposure to sleep, Mediterranean diet and physical activity will impact how interventions are sequenced and promoted at what intensity and to which household member. For example, if sleep is determined to be adequate at time of trial enrolment but the participant is mainly sedentary, greater emphasis will be placed on physical activity as a target. However, if sleep measurements throughout the trial change and worsen, the trial intervention will adapt to begin to target sleep behaviours.

7.7.2 Intervention Options

A household-level multicomponent proposed trial would incorporate multiple interventions using this methodology. Sample dietary intervention options could include (A) suggestion of a snack incorporating the principles of a Mediterranean diet (B) no suggestion. Intervention options could be informed by healthy eating index (HEI) scores and other dietary questionnaires submitted by the participant. To support this, the Second Nature Programme digital application (219) could be adapted to the Mediterranean principles to provide

behavioural support to help participants incorporate dietary changes. Sample physical activity intervention options could include (A) suggestion of anti-sedentary activity e.g. walk using prompt (B) no suggestion. The intervention will ideally be informed by previous step count/physical activity targets reached daily and weekly which could be measured and supported using Fitbit devices. A sample sleep intervention could be (A) Avoid decaffeinated drinks after 4pm and turn off screens 30 mins before bedtime (B) no suggestion. Prompts could be informed by sleep patterns and information logged by participants, with the proposed option to do this using the online application Sleepio (205) which will be used create a bespoke behavioural intervention plan. Measurement of sleep could also be completed using a Fitbit device further informing the micro randomisation algorithm.

7.7.3 Distal Outcome

The proposed distal outcomes of interest in a possible trial of this kind would be monthly physical activity levels measured using a fitness tracker (step count, periods of moderate to high physical intensity activity), sleep using Pittsburgh Sleep Quality Index (PSQI) score and HEI scores to assess diet. Additional options to measure dietary adherence could include the interrogation of weekly grocery purchases. Careful consideration would need to be taken during the development of a trial protocol to ensure that measurement of diet is acceptable and feasible to participants and will be subject to the least amount of bias.

7.7.4 Proximal Outcome

The proximal outcome measure during a proposed trial of this kind would be the interaction with application (e.g. Fitbit) following push notification e.g. steps taken, dietary habits entered, sleep activity that night.

7.7.5 Decision Points

Within a proposed trial protocol decision-making points would need to be established. Possible proposed points would include breakfast time, mid-morning, lunch time, mid-afternoon, dinner time, evening time, pre-bedtime.

7.7.6 Observation of Context

In a proposed trial of this kind, several observed contexts would need to be accounted for. These would include weather, time of day, day of the week, previous day/week's eating habits, previous sleeping habits across the week, previous day/week's physical activity, interaction and level of movement following previous push notifications.

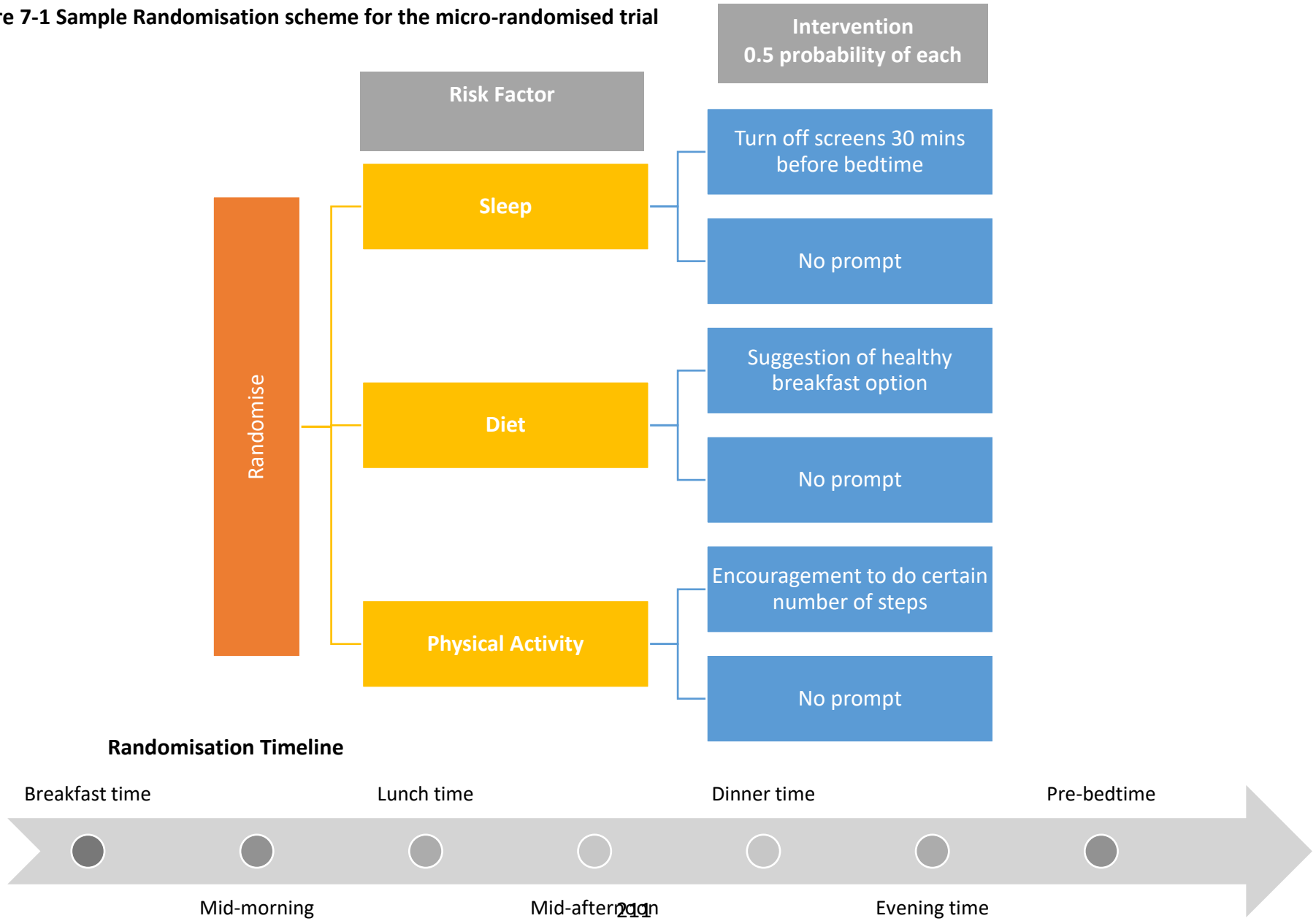
7.7.7 Availability Conditions

Within a trial protocol, availability would need to be specified i.e. highlighting that notifications would be unavailable if settings for push notifications on tablet or smartphone were turned off.

7.7.8 Randomization probabilities

In a proposed trial of this kind, participants who are available to receive a notification at a decision point would be randomised with a 0.5 probability to receive (A) a tailored physical/dietary/sleep activity and a 0.5 probability of receiving (B) no suggestion. In the possible scenario where participants have met recommended physical activity targets, optimal sleep habits, balanced caloric intake there would be no prompt for that risk factor on that day.

Figure 7-1 Sample Randomisation scheme for the micro-randomised trial



7.8 The Hawthorne Effect

The Hawthorne effect(220,221) poses risk to the validity of a household level lifestyle intervention trial and is another challenge to consider. Households in a proposed trial of this design will be aware their lifestyle habits are being observed and this may influence their behaviours. The role of micro randomisation in this setting has a significant role in mitigating the Hawthorne effect. Participants would be aware that the intervention may target sleep, diet and exercise, but will be unaware of how frequently they will be assigned to a prompt versus no prompt and how their achievements will reduce need to randomise for that particular risk factor. If a participant under the Hawthorne effect strives and meets the recommended physical activity targets for example, they will be randomised to no prompt. Even if observation is influencing their health behaviours, this will still meet the objective of this trial to determine which of the digital interventions to modify household-level lifestyle risk factors is effective.

7.9 Sample Size Considerations

A key outcome of interest for a possible trial of this kind would be to determine if the introduction of a multicomponent digital behavioural intervention is feasible among households affected by cognitive impairment.

A systematic review and meta-analysis performed as part of this thesis (Chapter 5) failed to identify any randomised clinical trial targeting households for prevention of cognitive decline and related outcomes making sample size calculations challenging for a proposed feasibility trial. There is little published guidance available on calculating sample sizes for feasibility studies (222), however this does not mean that a sample size cannot be justified.

Pilot studies previously exploring digital based interventions experienced a 30% recruitment rate in a study targeting households (223) and 38% in a study targeting older persons (224). If we were to consider a potentially eligible population from a memory clinic cohort of 300 patients of which approximately 75% (n=225) would live within a community household structure. Based on a 30% successful recruitment of the eligible population (n=225) this would give a total target sample size of 68, aiming for 34 households in each study arm. This is in keeping with previous recommendations of recruiting a minimum of 30 patients to estimate a parameter in pilot studies (225).

The other consideration is if micro randomisation is used within the trial. Overall, less participants would be required than a traditional randomised controlled trial. Differences due to exposure to the intervention would not only be explored between subjects but also within subjects dependent on the pattern and frequency of micro randomisation throughout the trial.

7.10 Measuring Trial Feasibility

Feasibility of a proposed multicomponent digital behavioural intervention targeting diet, exercise and sleep among households will be an essential trial outcome. Within a proposed trial, feasibility could be evaluated via the following parameters

- Eligibility rate. This will be calculated as the proportion of patients attending a memory clinic service that would meet the eligibility criteria for the trial.
- Recruitment rate. This will be calculated as the number of households who consent to participate divided by the number of eligible households approached
- Reason for Decline. Eligible households who decline to participate in the trial would be asked to volunteer a reason

- Retention rate. This would be calculated as the number of households who complete all outcome measures divided by the number who only record baseline measurements
- Adherence to the intervention This would be monitored by looking at the frequency of interaction with the digital application including logging onto the application, entering habits and level of interaction to work through the suggested changes.
- Discontinuation or non-adherence Where possible, reasons for this would be documented.

In a possible trial of this design, to troubleshoot early, a phone call would be made to prompt a response if outcome measures have not been logged within 7 days of being due or if there is inactivity with the intervention noted. If participants discontinue with intervention, then any completed outcome measurements will be retained for analysis with participant consent.

A trial of this kind could be considered feasible if greater than 70% of households participate successfully in the intervention and complete all outcome measures. Adjustments to the trial protocol should be considered if the rate is 65-70%. If the described rate is less than 65%, the intervention and/or process of the clinical trial will require significant change.

7.11 Role for Patient and Public Involvement

For a proposed trial to be successful, patient and public involvement (PPI) will be essential. In Chapter 6, I outline some of the preferences and deterrents for households to participate in a trial of this kind. With attrition rates a concern for trials involving participants with cognitive impairment, PPI can be used to identify potential barriers leading to loss to follow up in advance of a trial protocol being completed. In addition, PPI can be used to ensure

there is clarity around methodology of trial design and to determine the acceptability of a digital based lifestyle intervention. PPI can ensure that a trial design is relevant, that outcomes are clinically meaningful and improve the overall quality of the study (226). PPI can additionally act as a form of peer review, and assist with promoting trial recruitment and dissemination of findings among patient advocacy groups (227).

A proposed trial incorporating micro randomisation to households impacted by cognitive impairment would require further PPI involvement, building on the findings concluded in chapter 6. A greater focus would need to be placed on digital intervention acceptability among all household members to troubleshoot any significant limitations that might arise. Additionally, practical aspects of logging outcome measures should be explored to determine challenges that may emerge around data collection.

7.12 Criteria for Risk factors to Target

Based on the findings outlined in Chapter 2 on the literature to date, there are lifestyle risk factors that warrant further exploration in households affected by cognitive impairment. For each risk factor we have generated a list of criteria to consider within a future trial protocol which are outlined in Table 7-1. Each risk factor is explored within this table by each criterion in terms of being positive (+), negative (-) or neutral (N). The risk factors have been informed by the evidence based on behavioural risk factors among those with cognitive impairment, caregivers of those with cognitive impairment and by the semi-structured interviews performed as part of this thesis in Chapter 6.

Table 7-1 Criteria for lifestyle risk factors to target in randomised trials of households affected by cognitive impairment

Risk Factor	Prevalence in caregiver	Prevalence in person with AD	Amenable to household intervention	Technology feasibility	Amenable to micro randomisation
Sleep disturbance	+	+	-	+	+
Poor Diet	N	N	+	+	-
Lack of Physical Activity	-	+	+	+	+
Elevated Body Mass Index	+	N	+	+	+
Smoking	-	-	+	+	+
High alcohol Intake	-	-	+	+	+

+=Positive; -=negative; N=Neutral

7.13 Conclusions

When designing clinical trials to address lifestyle habits of households affected by cognitive impairment there is no "single size fits all" model. In truth, given variation among households, their structures and habits some households will require certain risk factors to be modified compared to others.

Recognition of the value of non-medical interventions or "social prescribing" is increasing but research is required to determine who will benefit the most and how it can be cost effective. Targeting those with dementia given the impact on cognitive and functional wellbeing is of interest but does require the support of the household. Exploring if the intervention has benefit on household members is therefore of interest and is supported by the findings which have emerged throughout this thesis.

Given the complex relationship of lifestyle factors and that deficits are not uniform among groups, novel methods including micro randomisation can be used to overcome many of these inherent challenges. Use of adaptive design reflects the lived experience of variation of these habits among household structures. Planning for future trials in this space should incorporate PPI to further determine type of technology to incorporate, household eligibility criteria and attitudes towards the micro randomisation process.

Chapter 8 Overall Conclusions

8.1 Summary and Conclusions

Increased life expectancy is likely to result in greater numbers of older individuals living with the cognitive and functional consequences of dementia placing significant demand on strained healthcare systems (228). Informal caregivers will continue to play a vital role in co-ordinating care needs, assisting with personal activities and monitoring for complications and decline, supporting these vulnerable individuals to remain living within their own homes. The consequences of such considerable effort on the health of the caregivers themselves is therefore an essential priority for public health intervention and investing in the household unit of those with cognitive impairment should be considered a future cost-saving measure for healthcare organisations worldwide. This thesis highlights the complex relationship between caregiving and health outcomes and suggests there is a threshold of caregiving of adults (≥7 hours per week) which leads to negative health implications, supporting that there is a specific cohort vulnerable to the stress caregiver model. Further dedicated research is required to identify this threshold to better inform policy around home help provision.

In this thesis, I examined the impact of caregiving on cardiovascular risk factors and mortality, demonstrating the role to identify specific cohorts of caregivers (i.e. those delivering greatest intensity of adult caregiving) who may benefit from targeted intervention. I further identify the important role of caregivers as proxy respondents in clinical research, to offset selection bias, ensuring appropriate representation of those with significant functional impairment, older participants and those of lower socioeconomic status in observational studies. Additionally, I explore the attitudes of households affected

by cognitive impairment through semi-structured interviews, to help inform future lifestyle intervention targets and strengths and limitations to randomising the entire household. To conclude I discuss the future opportunities in designing novel trials of lifestyle interventions, emphasising with equal importance the health outcomes for both the caregiver and the person with cognitive impairment.

8.2 Chapter 2

In this chapter, I explored the association of caregiving with prevalence of cardiovascular risk factors, with a particular focus on lifestyle risk factors including diet, physical activity, and sleep. This was evaluated in the large prospective cohort study, the NIH-AARP Diet and Health Study.

For this chapter, I developed the research question and the statistical analysis plan with MOD and MDC, I sourced and cleaned the data, performed all statistical analysis in R, I collated and interpreted the results, created the figures and drafted the manuscript.

In these analyses, I identified a complex association of caregiving with prevalence of cardiovascular risk factors. Overall, the analyses suggested mainly positive relationship of self-reported caregiving with lifestyle traits for example, those reporting caregiving of adults more likely to be physically active. However, on analysis based on duration of caregiving it emerged that higher duration caregiving of adults was associated with an increased frequency of unhealthy cardiovascular behavioural risk factors, namely shorter sleep durations, poor diet, increased BMI and smoking. This highlights the role of identifying ‘at risk’ caregiver populations for targeted preventative health strategies.

8.3 Chapter 3

Following on from Chapter 2, to further explore the impact of caregiving on health outcomes I explored the association of caregiving with all-cause mortality and cause specific mortality within the same cohort from the NIH-AARP, using the findings from Chapter 2 to explore lifestyle factors that mediate the association.

For this chapter, I developed the research question and the statistical analysis plan with MOD and MDC, I performed all statistical analysis in R and RevMan 5.3 with CJ, I collated and interpreted the results, created the figures, drafted the manuscript and performed an updated literature review to add our findings to a recently published meta-analysis on informal caregiving of adults and all-cause mortality.

Again, an interesting relationship between caregiving and mortality emerged. The analyses demonstrated that overall caregiving, for adults, is associated with lower risk of all cause-mortality (HR 0.90; 95% CI 0.88-0.93) and mortality from cardiovascular (HR 0.90; 95% CI 0.86-0.95) and non-cardiovascular causes (HR 0.89; 95% CI 0.86-0.92). However, there was an attenuation in magnitude of risk observed as duration of caregiving increased. It emerged that among individuals providing adult caregiving for 7 hours per week or more, there was no significant association with risk of mortality, on multivariable analyses.

These findings support the results from Chapter 2, that there is a role to identify a cohort who may be at risk of mortality due to higher durations of caregiving of adults, for health prevention strategies.

8.4 Chapter 4

In this chapter, I evaluated the role of proxy respondents in the large, international case control study INTERSTROKE, by estimating the magnitude of avoidable selection bias incurred if proxy respondents were not utilised. In addition, I reported on regional variations in prevalence and determinants of proxy use.

For this chapter, I developed the research question and the statistical analysis plan with MOD and MDC, performed all statistical analysis in R (using the R package created by CJ), created the tables and figures and drafted and drafted the manuscript. Among 13,318 participants with acute stroke, questionnaires were completed by patients alone in 36.3% (n=4837), combination of patient and proxy together in 21.9% (n=2,910) and proxy alone in 41.8% (n=5571). In these analyses, use of proxy alone was greater in participants with severe stroke (4.7% with modified-Rankin score of 0 versus 80.5% in those with score 5; OR 174.36; 95% CI 111.37-287.35), older persons (43.8% of those aged 80 years and over versus 33.2% of those aged less than 40 years; age per decade OR 1.10; 95% CI 1.07-1.13), women (40.7% versus 34.3% of men; OR 1.32 95% CI 1.22-1.43); and those less educated (58.9% of those never educated versus 26.2% of those who attended third level education; OR 7.89; 95% CI 6.82-9.14).

This chapter demonstrates that use of proxy respondents enhances the generalisability of international research studies of stroke, by increasing representation of women, patients with severe stroke, older age, and lower education. This finding is applicable to individuals with cognitive impairment who have significant cognitive and functional limitations which often impede their participation in clinical research. This chapter highlights the importance of the role of caregivers acting as proxy respondents to support participation and adherence

within clinical research. It provides further evidence to therefore consider targeting the household as the unit of randomisation can enhance the inclusion of older, functionally impaired individuals and protect against study attrition rates.

8.5 Chapter 5

To further assess the effect of targeting lifestyle behaviours of households on cognitive outcomes I conducted a systematic review and meta-analysis of randomised controlled trials where households were randomised to receive a lifestyle intervention for the prevention of cognitive decline. For this chapter I developed the research question in conjunction with collaborators. I designed the electronic search strategies, the data abstraction sheets and the statistical analysis plan. I carried out title and abstract searching as well as full text reviews, in conjunction with collaborators, of included articles and then extracted relevant data. I collated the results, conducted risk of bias assessments and the meta-analysis, and wrote the manuscript.

This systematic review had the following aims (i) to assess the impact of household level lifestyle interventions on cognitive decline and (ii) to assess impact on functional outcomes, admissions to long term care, mood, caregiver burden and physical health outcomes for all participants.

I identified no clinical trials which randomised households to receive a lifestyle intervention incorporating sleep, diet, exercise or a combination of all three for preventing cognitive decline. Following this, I revised my eligibility criteria to also include trials recruiting dyads given that this unit of randomisation overlaps sufficiently with a household. I subsequently identified five eligible RCTs (n=1721, with mean follow-up of 9·6 months) which randomised dyads, which evaluated diet (two trials) and physical activity (three

trials). There was no significant association of interventions with change in cognitive testing or functional outcomes, although trials were small with short-term follow-up.

The lack of household-level trials of lifestyle interventions for the prevention of cognitive decline highlights the deficit in our knowledge and limited the number of studies included in the meta-analysis. My systematic review also identified a lack of standardised outcome measures used across trials for measurement of cognition and function, which hindered my ability to reliably meta-analyse results among studies.

Future trials of lifestyle-based interventions for the prevention of cognitive decline should consider targeting households as the unit of randomisation to explore cognitive and physical health benefits for all household members in addition to added benefits of greater adherence and sustainability of positive health behaviours.

8.6 Chapter 6

Before proceeding with trials exploring household level lifestyle interventions for the prevention of cognitive decline, it is necessary to determine the preferences, deterrents and overall attitudes of potential participants recruited to a trial of this kind.

In this chapter, I conducted semi-structured interviews with households affected by cognitive impairment based in the West of Ireland. This was undertaken to better understand the beliefs of the household members around lifestyle factors such as sleep, diet and physical activity and their link with dementia; what challenges households affected by dementia might face in changing lifestyle factors; and how feasible it would be to sustain change among all household members.

For this study, I designed the study protocol, the standardised interview guide, participant information form, selected the sampling frame and applied to the local ethics

committee for study approval which was granted. Between October 2020 and May 2021, I carried out semi-structured interviews with eight households (consisting of 18 participants in total) using a secure web-based platform supported by CMcC. I arranged the web-based interviews, recorded the interactions with consent of all household members, transcribed the interviews, conducted summative content analysis to determine important themes and wrote the manuscript. I chose the medium of semi-structured interviews rather than a large focus group for the following reasons: feasibility of the study during the COVID-19 pandemic, to ensure that the person with dementia had a safe supportive environment to express their views, and to allow for deeper conversations around elements of lifestyle interventions for dementia that were of importance to participants.

In this qualitative study, several themes emerged; 1) household members without cognitive impairment were more likely to report poor sleep habits, and sleep was perceived to be the hardest behaviour to change; 2) diet generated most interest as a potential lifestyle intervention target as most participants believed there is a strong link with nutrition and cognition; 3) physical activity is challenging to adapt due to lack of motivation and focus when individuals are cognitively impaired. Barriers to study participation, including risk of harm, complexity of intervention and deviation from routine emerged during discussions. Ongoing public and patient involvement is essential for future trial design, specifically to explore feasibility of specific intervention types to change lifestyle behaviours.

8.7 Chapter 7

Building on my work in previous chapters, my final chapter explores the challenges and opportunities in designing clinical trials of household level lifestyle interventions for the prevention of cognitive decline. This review incorporates the findings of previous chapters

to build on the evidence to consider the household as the target unit for randomisation in lifestyle intervention trials, given the health benefits that may extend to caregivers and care recipients alike. Given the variation in lifestyle behaviours among and within households, this review explores the future opportunity to incorporate adaptive design methods such as micro-randomisation to enhance feasibility of trials of this nature. I outline the proposed methodology and criteria for risk factors to target, concluding that further engagement of households affected by cognitive impairment is necessary to determine acceptability of this type of trial design.

8.8 Future Directions

In conclusion, the caregiver plays an important role in lifestyle interventions for cognitive impairment. Inclusion of all household members in future clinical trials of lifestyle behavioural interventions may improve adherence with the intervention, retention rates, and avoid attrition of vulnerable individuals, and represent household-level outcomes (e.g. caregiver burden). Beyond this, certain caregiver populations may also benefit from targeted lifestyle interventions especially those delivering high intensity assistance to care recipients. With a growing ageing population, there is a need to ensure that informal caregivers are supported not only psychosocially but from early morbidity and mortality that may be a consequence of a long duration of burdensome caregiving. Targeting those delivering high intensity and durations of informal care for further exploration of cardiovascular and mortality risk will be of benefit, with a focus on establishing a specific threshold at which negative health effects emerge. At a practical level, such findings could be used to better inform policy around home care provision and supports for caregivers. Randomised controlled trials are necessary to evaluate the feasibility and efficacy of

household targeted interventions for this cohort, and there is an exciting opportunity to incorporate novel adaptive design methods to overcome many of the limitations experienced in previous multicomponent clinical trials targeting cognition.

Appendix 1 Agreement for the Transfer of De-Identified Human Data from the NIH-AARP Diet and Health Study

AGREEMENT FOR THE TRANSFER OF DE-IDENTIFIED HUMAN DATA

In response to the RECIPIENT's request for de-identified human data from approximately 566,398 participants collected under PROVIDER's approved protocol # OH95-C-N025 entitled "NIH-AARP Diet and Health Study" (DATA), the PROVIDER asks that the RECIPIENT and the RECIPIENT SCIENTIST agree to the following before the PROVIDER transmits the DATA:

1. The above DATA is the property of the PROVIDER and is made available as a service to the research community.

2. THIS DATA WILL NOT BE USED TO TREAT OR DIAGNOSE HUMAN SUBJECTS.

3. The DATA will be used for teaching or research purposes only.

4. The DATA will not be disclosed or further distributed to others without the PROVIDER's written consent. The RECIPIENT shall refer any request for the DATA to the PROVIDER.

5. The RECIPIENT SCIENTIST agrees to acknowledge the contribution of the PROVIDER in all written or oral public disclosures concerning RECIPIENT's research using the DATA, as is appropriate. RECIPIENT agrees to supply the PROVIDER with copies of public materials based on the use of the DATA.

6. THE PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE DATA WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. Unless prohibited by law, RECIPIENT assumes all liability for claims for damages against it by third parties which may arise from the use, storage or disposal of the DATA.

7. The RECIPIENT agrees to use the DATA in compliance with all applicable statutes, regulations, and policies.

8. The DATA is provided at no cost. Charges for preparation and delivery of the DATA are additional and must be paid by the RECIPIENT.

9. The DATA has been collected from human subjects. When NIH is the RECIPIENT, PROVIDER agrees the DATA has been collected in accordance with federal guidelines for "Protection of Human Subjects."

10. Personally identifiable information will not be provided. If the DATA being provided is coded, the PROVIDER will not release, and the RECIPIENT will not request, the key to the code.

11. RECIPIENT will not contact or make any effort to identify individuals who are or may be the sources of DATA without specific written approval from PROVIDER.

12. The following Confidential Information will be transferred: **none.**

All Confidential Information shall be clearly marked "CONFIDENTIAL" by the providing Party and maintained in confidence by the receiving Party for a period of five (5) years from the date of execution of this Agreement. Any Confidential Information that is orally disclosed must be reduced to writing and marked "CONFIDENTIAL" by the providing Party and such notice must be provided to the receiving Party within thirty (30) days of the oral disclosure.

For the purposes of this Agreement, Confidential Information does not include information which:

a. has been published or is otherwise publicly available at the time of disclosure to the receiving Party;
b. was in the possession of or was readily available to the receiving Party without being subject to a confidentiality obligation from another source prior to the disclosure;
c. has become publicly known, by publication or otherwise, not due to any unauthorized act of the receiving Party;
d. the receiving Party can demonstrate it developed independently, or acquired without reference to, or reliance upon, such Confidential Information; or
e. is required to be disclosed by law, regulation or court order.

13. DATA and Confidential Information will be used by RECIPIENT SCIENTIST solely in connection with the following Research Project:

Title: Association of Caregiving with Mortality: NIH-AARP Study

Background: Caregivers are those who provide regular, unpaid assistance with personal and instrumental activities of daily living to those with functional or cognitive impairment. The literature to date has mainly focused on the impact of caregiving on psychological health. The impact of being a caregiver on physical health and mortality outcomes has reported an increased in mortality among caregivers of individuals with dementia. Several studies have reported an association of caregiving with increased mortality, most notably when caregiving for persons with significant functional and behavioral issues. However, the factors mediating this association are poorly understood.

It is hypothesized that health outcomes in caregivers can be affected by several mechanisms including physical strain of delivering activities of daily living, physical impact of psychological distress, and the impact of caregiving on maintaining healthy diet, adequate sleep, exercise, and social interaction. These mechanisms need to be better understood to allow for targeted health interventions to improve clinical outcomes for caregivers. In addition, the association of caregiving and cause-specific mortality has not been studied and may lend insights into the mechanism underlying the association.

The NIH-AARP study provides opportunity to explore all-cause mortality and cause specific mortality of those caregiving to adults and explore factors that may mediate this reported association.

Objectives:

1. To determine the association of caregiving (frequency and type) with all-cause and cause specific mortality.
2. To explore factors (e.g. lifestyle) that may mediate the association of caregiving with mortality.

Summary of Experimental Plan:

Study population: All subjects within the NIH-AARP Diet and Health Study who completed dietary, physical activity and sleep information at baseline (1995-6) and completed final follow-up survey (2004-2006).
Exclusions: Those with missing information on sleep, diet, being a caregiver and physical activity.
Exposure: Reported caregiving for other adults or children for greater than 10 hours per week.
Outcome:
Primary outcome: Mortality and cause specific mortality for all participants.
Secondary outcome: Impairment in functional activities of daily living (ADL), as described in question three of the follow-up questionnaire.
Statistical analysis (including statistical method, covariates, and sensitivity analysis). Baseline descriptives will be reported for all participants. The variables will be reported by total cohort, primary outcome defined caregiver.* The change in magnitude of association with each cluster of variables introduced into the model will be explored. Hazard ratios and their 95% Confidence Intervals will be reported. Kaplan Meier curves will be reported for cause-specific categories of death with direct adjusted survival curves used to determine life years lost or gained by caregivers. Propensity score matching will be explored.

*Caregiver is defined as a person reporting more than 10 hours of caregiving per week. However, the association of lower intensity caregiving will be explored to determine whether a dose response exists for durations less than 10 hours. In addition, it is hypothesized that the type of caregiving (adult or child) may have differing magnitudes, and perhaps direction, of association with mortality, and will therefore, consider these two types of caregiving separately.

To further explore a population with a high probability of providing caregiving to a family member/spouse of friend, an analysis will be conducted that is confined to participants who are retired or working in occupations that are unlikely to be providing caregiving and are married or living with a partner. This will lead to a subgroup analysis by sex, age, retirement, education, race, physical activity, health screening participation and testing for interactions.

Contributions of the Parties:
PROVIDER will:

- Provide DATA to RECIPIENT;

- Participate in data interpretation; and
- Participate in manuscript preparation.

RECIPIENT will:

- Analyze and interpret DATA;
- Provide a copy of all research results to PROVIDER; and
- Prepare manuscript.

14. This Agreement is effective for a period of three (3) years from the date of final signature. Either Party may terminate this Agreement with thirty (30) days written notice to the other Party. When the Research Project is completed, this Agreement expires, or this Agreement is terminated, whichever comes first, RECIPIENT shall promptly return to PROVIDER or, at PROVIDER'S option, destroy all copies of DATA. Upon PROVIDER's request, RECIPIENT shall confirm in writing as to such destruction

SIGNATURES BEGIN ON THE NEXT PAGE.

RECIPIENT INFORMATION and AUTHORIZED SIGNATURE

Recipient Scientist: Dr. Maria Costello, MRCPI
Recipient Organization: The National University of Ireland Galway

_____ _____ **__Apr 22 2020__**
Signature of Authorized Official Date
Name: Prof Martin O'Donnell
Title: Director, HRB-Clinical Research Facility, NUI Galway, Galway Ireland

Address all correspondence related to this agreement to:

[insert address for notices]

PROVIDER INFORMATION and AUTHORIZED SIGNATURE

Provider Scientist: Dr. Rashmi Sinha
Provider Organization: National Cancer Institute

Virginia A. Deseau -S Digitally signed by Virginia A. Deseau -S Date: 2020.04.22 12:47:14 -04'00' 22 April 2020
Signature of Authorized Official Date
Virginia A. DeSeau, MS
Title: Senior Technology Transfer Manager

Address all correspondence related to this agreement to:

Technology Transfer Center
National Cancer Institute
9609 Medical Center Drive, Rm 1-E530 MSC 9702
Bethesda, MD 20892-9702 (for business mail)
Rockville, MD 20850-9702 (for courier service/visitors)

Appendix 2 Local Research Ethics Committee Approval Letter for NIH-AARP Study

Saolta
Grúpa Ollscoile Cúram Sláinte
University Health Care Group

Ospidéal na h-Ollscoile, Páirc Mheirlinne
Merlin Park University Hospital
GALWAY UNIVERSITY HOSPITALS

Clinical Research Ethics Committee
Room 59
First Floor
HR Building
Merlin Park Hospital
Galway.

20th May, 2020.

Dr. Maria Costello
SpR Geriatric Medicine
Department of Geriatric and Stroke Medicine
University College Hospital
Galway.

Ref: C.A. 2383 ***Association of Caregiving with Mortality: National Institute of Health-American Association of Retired Persons Diet and Health Study (NIHAARP)***

Dear Dr. Costello,

I have considered and reviewed the above submission, and I wish to confirm that I am happy to grant Chairman's approval to proceed.

'This submission has been reviewed from an ethical perspective only. It is the responsibility of the PI/sponsor/data controller and relevant Data Protection Officer to ensure and monitor compliance with any relevant legislation in the country where the study is due to take place or any local policy in the site where the study is due to take place.'

"Chairman's approval is normally ratified at the next Clinical Research Ethics Committee meeting. If any issues with your application are identified at the meeting we will contact you again"

Yours sincerely,

B. Gerard Loftus FRCPI,MD
Emeritus Professor of Paediatrics, NUI,Galway
Adjunct Professor of Paediatrics, IMU, Kuala Lumpur
Chair, Galway Clinical Research Ethics Committee.

Appendix 3 Participant Information Leaflet for Semi-Structured Interviews with Households Affected by Cognitive Impairment

The attitudes of households towards lifestyle changes for the prevention of cognitive decline

I would like to invite you to take part in a research study. Before you decide on becoming involved, you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Ask questions if anything you read is not clear or if you would like more information. Take time to decide whether or not to take part.

Who is conducting this study?

Dr Maria Costello (Principal Investigator and Data Controller) under the supervision of Professor Martin O' Donnell and Dr Michelle Canavan, Department of Geriatric and Stroke Medicine, University Hospital Galway.

Who I am and what the study is about

I am a Specialist Registrar in Geriatric Medicine, University Hospital Galway. I am currently undertaking a PhD in NUI Galway focusing on lifestyle changes within households affected by memory issues. The aim of this focus group is to get your insights on different health behaviours within your home, such as diet, exercise and sleep. The insights from this focus group will help develop a future clinical trial looking at ways to improve diet, exercise and sleep.

What will taking part involve?

Taking part in this project will involve a once off 60-90-minute discussion with you and those living in your home over video hosted chat. The discussion will be facilitated and structured using some interview questions. We will discuss

things like diet, exercise and sleep, your attitudes towards them and barriers in achieving them (e.g. "How much physical activity do you achieve on a weekly basis?") We will not discuss aspects of your medical history or other personal details. All members participating in this focus group will live in a home affected by memory problems. This focus group discussion will be led over the HSE recommended secure web-based platform "Webex" rather than in person, given restrictions related the COVID-19 pandemic. You will need to have internet access and computer, smartphone or other device compatible with Webex to participate. For the person attending the memory clinic we will record your latest memory test scores, and these will be anonymised also. You will not need to undergo re-testing as part of this study.

Why have you been invited to take part?

You have been invited to take part because you, or someone living in your household has memory problems and has been seen in the Memory Clinic service within the department of Geriatric Medicine University Hospital Galway.

Do you have to take part?

Participation in this focus group is completely voluntary and you or your household has the right to refuse participation, refuse any question and withdraw at any time without any consequence whatsoever.

What are the possible risks and benefits of taking part?

The main risk with this study is that some people feel embarrassed or under pressure when taking part in a group discussion. To help alleviate this the focus group will be moderated and you will not be forced to answer questions you are not comfortable discussing.

The benefit in participating in this study is that you will contribute to the design and structure of future clinical trials targeting households affected by memory problems. Your opinion is highly valued, and we can learn a great deal from you.

Will taking part be confidential?

Yes. Taking part in this study will be fully confidential. The focus group interview will be recorded but will exclude any information that emerges during the discussion that could be used to identify you. The focus group questions are not designed to extract any personal information. We will be collecting some non-anonymised data in the form of signed consent forms (including name, address and contact number) and these will need to be retained for the research study and will be done so securely. The audio recordings will also be stored securely as part of the study and will be password protected and coded not to include any personal information. The only situation where we might have to break confidentiality is if we have a strong belief that there is a serious risk of harm or danger to either the participant or another individual. Your identity will otherwise remain confidential. We do not wish to transfer your data to a country outside of the EU or an international organisation.

How will information you provide be recorded, stored and protected?

We will be processing your data on the legal basis of you providing your consent (see Article 6 and 9 of the General Data Protection Regulation 2016). Signed consent forms and original audio recordings will be retained in the clinical research facility, NUI Galway in a password protected device with all files encrypted until after the study has been published and PhD submitted. A

transcript of interviews in which all identifying information has been removed will be retained for a further two years after this. Under the freedom of information legislation, you are entitled to access the information you have provided at any time. You also have a right to lodge a complaint with the Data Protection Commissioner (https://www.dataprotection.ie/en/contact/how-contact-us).

What will happen to the results of the study?

The results of this study will be written up as part of a PhD thesis and will be put forward for publication in a journal. Study results may be presented at a conference and used in teaching presentations.

Has this Study been Reviewed by an Ethics Committee?

Galway University Hospital Research Ethics Committee have reviewed this study.

Who should you contact for further information?

If you would like any further information about the study, without any obligation to take part, please contact:

Dr Maria Costello, SpR Geriatric Medicine and PhD candidate

Clinical Research Facility National University of Ireland Galway

maria.costello@nuigalway.ie

Appendix 4 Consent Form for Semi-Structured Interviews with Households Affected by Cognitive Impairment

Participant Consent Form

People with cognitive impairment and their household members attitudes towards lifestyle changes for the prevention of cognitive decline:
Outcomes of a focus group study

1. I confirm that I have received a copy of the Information Sheet for the above study. I have read it and I understand it. I have received an explanation of the nature, purpose, duration and foreseeable effects and risks of the study and what my involvement will be.

2. I have had time to consider whether to take part in this study and I have had the opportunity to ask questions.

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

4. I understand that my consultant will be informed that I am taking part in this study.

5. I agree to take part in the above study. Yes ☐ No ☐

Name	Date	Signature
Name	Date	Signature
Name	Date	Signature

Contact number: _____

Please return this form in the postage paid envelope or return a scanned copy to:

Dr Maria Costello, HRB Clinical Research Facility, NUI Galway/maria.costello@nuigalway.ie

Thank you

Appendix 5 Ethics Committee Approval Letter for Semi-Structured Interviews with Households Affected by Cognitive Impairment

Saolta
Grúpa Ollscoile Cúram Sláinte
University Health Care Group

Ospidéal na h-Ollscoile, Páirc Mheirlinne
Merlin Park University Hospital
GALWAY UNIVERSITY HOSPITALS

Clinical Research Ethics Committee
Room 59
1st Floor
HR Building
Merlin Park Hospital
Galway.

27th August, 2020.

Dr. Maria Costello
SpR Geriatric Medicine
Department of Geriatric & Stroke Medicine
University College Hospital
Galway.

Ref: C.A. 2457 ***The Attitudes of households towards lifestyle changes for the prevention of cognitive decline***

Dear Dr. Costello,

I have considered and reviewed the above submission, and I wish to confirm that I am happy to grant Chairman's approval to proceed.

'This submission has been reviewed from an ethical perspective only. It is the responsibility of the PI/sponsor/data controller and relevant Data Protection Officer to ensure and monitor compliance with any relevant legislation in the country where the study is due to take place or any local policy in the site where the study is due to take place.'

Chairman's approval is normally ratified at the next Clinical Research Ethics Committee meeting. If any issues with your application are identified at the meeting we will contact you again.

Yours sincerely,

B. Gerard Ryan FRCPI,MD
Emeritus Professor of Paediatrics, NUI,Galway
Adjunct Professor of Paediatrics, IMU, Kuala Lumpur
Chair, Galway Clinical Research Ethics Committee.

Appendix 6 Pfeiffer Short Portable Mental Status Questionnaire (SPMSQ)

THE SHORT PORTABLE MENTAL STATUS QUESTIONNAIRE (SPMSQ)

Question	Response	Incorrect Responses
1. What are the date, month, and year?		
2. What is the day of the week?		
3. What is the name of this place?		
4. What is your phone number?		
5. How old are you?		
6. When were you born?		
7. Who is the current president?		
8. Who was the president before him?		
9. What was your mother's maiden name?		
10. Can you count backward from 20 by 3's?		

SCORING:*

0-2 errors: normal mental functioning

3-4 errors: mild cognitive impairment

5-7 errors: moderate cognitive impairment

8 or more errors: severe cognitive impairment

*One more error is allowed in the scoring if a patient has had a grade school education or less.
*One less error is allowed if the patient has had education beyond the high school level.

Source: Pfeiffer, E. (1975). A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. Journal of American Geriatrics Society. 23, 433-41.

Outputs Arising from This Work

Presentations

Maria Costello, Conor Judge, Martin J. O'Donnell, Michelle Canavan, Salim Yusuf on behalf of the INTERSTROKE investigators - Role of Proxy Respondents in International Stroke Research: Experience of the INTERSROKE Study. Oral presentation Galway University Hospital Research Day June 2021. Awarded Michael J O Donnell award in recognition of outstanding research by a registrar in medicine

Maria Costello, Christine McCarthy, Conor Judge, Karen Dennehy, Clodagh McDermott, Tomás Ó Flatharta, Martin O'Donnell, Michelle Canavan- Lifestyle interventions for the prevention of cognitive decline; have we targeted the wrong unit for randomisation? A Systematic review and Meta-analysis. 17th EuGMS, 11 to 13 October 2021, Athens

Publications

Maria Costello, Christine McCarthy, Conor Judge, Karen Dennehy, Clodagh McDermott, Tomás Ó Flatharta, Martin O'Donnell, Michelle Canavan - Household-level lifestyle interventions for the prevention of cognitive decline; A Systematic review.

Archives of Gerontology and Geriatrics, Volume 98,2022, 104565,

https://doi.org/10.1016/j.archger.2021.104565.

Papers Under Review

Maria Costello, Christine E. McCarthy, Jackie Bosch, Stephanie Robinson, Clodagh McDermott, Michelle Canavan, Martin J. O'Donnell - Are clinical trials randomising households to lifestyle interventions for the prevention of cognitive decline feasible? Semi-

structured interviews to determine the beliefs, preferences, and deterrents for households impacted by dementia. (Article under review with BMC Geriatrics, September 2021)

Other Publications during PhD

Practical tips for introducing high-fidelity simulation to undergraduates at a large scale: learning from our experience Walsh SM, **Costello M**, Murphy E, Lowery A, Reid McDermott B, Byrne D. BMJ Simul Technol Enhanc Learn. 2021 Mar 7;bmjstel-2021-000888. doi: 10.1136/bmjstel-2021-000888

"Increased Salt Intake for Orthostatic Intolerance Syndromes: A Systematic Review and Meta-Analysis." Loughlin, Elaine A., Conor S. Judge, Sarah E. Gorey, **Maria M. Costello**, Robert P. Murphy, Ruairi F. Waters, Diarmaid S. Hughes, Rose Ann Kenny, Martin J. O'Donnell, and Michelle D. Canavan. *The American Journal of Medicine* 133, no. 12 (2020): 1471-1478. https://doi.org/10.1016/j.amjmed.2020.05.028

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