Exploration of Adulthood Diet Quality in Relation to Walking Speed Indicating Physical and Cognitive Function in Later Life

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Abstract

Rationale: The proportion of adults aged above 60 is rapidly increasing and by 2050 they will comprise almost one fourth of total world population. However, with moderate disability rates also increasing, there is great need for older people to maintain overall well-functioning. Physical and cognitive functioning play a major role in daily activities and determine life quality of older people. Maintaining walking ability is crucial for independent living and walking speed is predictive of overall health, survival and better physical and cognitive functioning. Rates of functional decline vary interindividual and between sexes, with women living longer but with higher comorbidity rates than men. Part of this variability in functional trajectories is attributable to modifiable lifestyle factors, with diet being of great interest. Specific nutrients and presumably healthy diets have been associated with better physical and cognitive performance in older people.

Research gap: Evidence for diet quality in line with current dietary guidelines and objective measures of well-functioning, important for older people, is limited. In addition, considering well-known differences in eating and ageing trajectories between men and women, it is highly underexplored whether the effect of diet on overall functioning of older people is sex-specific. Finally, evidence for whether accumulation of healthy dietary exposure over time may exert additional benefits on overall functioning in later life, is scarce.

Aim: To investigate the overall and sex-specific prospective associations between diet quality in late midlife and over a 27-year period in adulthood and objective measures of walking speed in older life, indicating survival and physical and cognitive functioning.

Methods: This thesis used dietary data (five-day food diaries) of men and women from four time points of the 1946 MRC National Survey of Health and Development birth cohort (N=5,362) when participants were at ages 36, 43, 53 and 60-64 and measures of walking speed from the Insight 46 (N=502), its clinical sub-study, when participants were at age 69-

71. Diet quality was defined by the Healthy Eating Index-2015 at each age (low: 0 – high: 100). Prospective associations with walking speed at age 69-71 were assessed for diet quality (a) in late midlife (age 60-64) and (b) over adulthood (from age 36 to 64), considering major demographic, health and lifestyle factors from age 36 to 64.

Sample size: At least one valid dietary assessment was available for n=480. Walking speed was available for n=474 and among men (51%) and women in the Insight 46, dietary data was available as follows: n=313 (age 36), n=369 (age 43), n=346 (age 53), n=444 (age 60-64). Final sample size ranged from n=331 (Chapter 4) to n=437 (Chapter 6).

Results: Diet quality improved over adulthood (age 36: HEI=47 ± 11 vs age 64: HEI=62 ± 13). Women had higher diet quality than men at each age (β=4 HEI points, 95% CI: 3, 6; $p<0.05$). Men had faster absolute values of walking speed than women at age 69-71 (1.39 m/s ± 0.15 vs 1.32 m/s ± 0.14, $p<0.05$), which was attenuated after controlling for anthropometric differences ($p= 0.85$). Main analysis showed there was a null overall association between diet quality in late midlife (β: 0.01 m/s, 95% CI: -0.01, 0.02) and over adulthood (β: 0.02 m/s, 95% CI: -0.02, 0.03) and walking speed in later life. Sex-specific analysis showed a positive association between diet quality in late midlife and faster walking speed in women independently of other factors (β: 0.02 m/s, 95% CI: 0.01, 0.04), but null associations for men (β: -0.01 m/s, 95% CI: -0.03, 0.01). When walking and performing a cognitive task, there was indication of a positive association between diet quality and walking speed in women (β: 0.03 m/s, 95% CI: 0.01, 0.05) and an inverse association in men (β: -0.02 m/s, 95% CI: -0.05,-0.01). Finally, starting with and maintaining high diet quality over adulthood was associated with faster walking speed in later life in women (β: 0.04 – 0.06 m/s, 95% CI: 0.01, 0.11), thus reflecting better functioning and longer survival, but not men (β: -0.01 m/s, 95% CI: -0.02, 0.01); yet the association was not independent of other lifestyle factors.

Contribution to knowledge: This thesis provided novel insights of the impact of diet quality across various stages over adulthood on measures of overall functioning, which predict survival and are clinically relevant for older people. Furthermore, it added original evidence for sex differences modifying this relationship and most importantly it suggested that achieving and maintaining high diet quality the longest possible over adulthood is likely to yield additional benefits towards better age-related physical functioning, in particular in women

Presentations and Publications Relevant to Thesis

Tektonidis TG, Coe S, Esser P, Maddock J, Buchanan S, Mavrommati F, Izadi H, Schott JM, Richards M, Dawes H. Longitudinal Changes in Diet Quality over Adulthood and Physical Function in Older Life: Findings from a British Birth Cohort. Current Developments in Nutrition. 2020;4(Supplement_2):1495-1495. (Chapter 6)

Tektonidis TG, Coe S, Esser P, Maddock J, Buchanan S, Mavrommati F, Schott JM, Izadi H, Richards M, Dawes H. Longitudinal Changes in Diet Quality over Adulthood and Physical Function in Later Life: Findings from a British Birth Cohort. The American Society for Nutrition – 2020 Nutrition Meeting, Seattle, US, 1 – 4 June 2020. (Chapter 6)

Tektonidis TG, Coe S, Esser P, Maddock J, Buchanan S, Mavrommati F, Schott JM, Izadi H, Richards M, Dawes H. Diet quality in late midlife is associated with faster walking speed in later life in women, but not men: findings from a prospective British birth cohort. *The British journal of nutrition*. 2019:1-21. 111. (Chapter 4)

Tektonidis TG, Esser P, Coe S, Maddock J, Buchanan S, Mavrommati F, Schott J, Izadi H, Richards M, Dawes H. MON-LB692: Diet Quality in Late Midlife is Associated with Faster Walking Speed in Later Life in Women, but Not Men: Findings From a British Birth Cohort. *Clinical Nutrition*. 2019; 38:S316-S317. (Chapter 4)

Tektonidis TG, Esser P, Coe S. The Relationship of Lifetime Diet with Gait as an Indicator of Frailty. Postgraduate Research Symposium, Oxford Brookes University, Oxford, UK. (Chapter 4 & 5)

Tektonidis TG, Esser P, Coe S, Lightowler H. 0198-Older Age: Associations of diet and physical activity on gross motor function: a prospective cohort study in older adults in the UK. International Health Conference 2017: Oxford, UK, 29 June – 1 July 2017. (Chapter 3)

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This is maybe the first time I feel proud of myself regarding something I complete; I worked day and night, I pushed myself over my limits, I fought hard and I reached what I could not. Quoting the incomparable Nikos Kazantzakis:

"Μην καταδέχεσαι να ρωτάς: Θα νικήσουμε; Θα νικηθούμε; Πολέμα και φτάσε όπου δεν μπορείς!"

"Do not condescend to ask: Shall we conquer? Shall we be conquered? Fight on and reach what you cannot!"
N.K.

Statement of Contribution

This thesis is the outcome of the research work I have conducted since 1st February 2017 in the Centre for Movement, Occupational and Rehabilitation Sciences (MOReS) and the Oxford Brookes Centre for Nutrition and Health (OxBCNH), at Oxford Brookes University, in collaboration with the University College London (UCL).

Initially, I used a three-month period to extensively read the literature, identify the research gap and form the research question. I then prepared, drafted and submitted my research proposal alongside the variable request plan (diet and covariate list at each time point) to UCL / MRC to access the NSHD / Insight 46 dataset. I also prepared and submitted the ethical approval form to the Research Ethics Committee, Oxford Brookes University.

Once the project was officially approved, I analysed a total of 1,000 walks (250 participants x 4 walks each) to obtain data on walking speed in the Insight 46, using a bespoke gait analysis software (DataGait). I then conducted an extended literature review to identify and select the optimal tool to assess diet quality. A significant part of my contribution, was modification, conversion and calculation of the Healthy Eating Index (HEI), which I used to asses diet quality at all ages (36, 43, 53, 64). This was a substantial amount of work, which I would like to highlight. To successfully generate HEI-2015 at each age, I used resources from the UK National Diet and Nutrition Survey; the US Department of Agriculture, the US Food Patterns Equivalent Database and the UK Food Composition Database. The total step-by-step procedure can be seen in 3.3.2 The Healthy Eating Index (Conversion/Modification of HEI-2015) and in Appendix 3.

Following estimation of diet quality and walking speed values, I conducted the statistical analysis throughout the project, including all descriptives, main analysis and trajectory analysis (supervised by Dr Izadi). To establish validity of my findings, I attended a number of statistical courses on advanced statistical modelling.

Upon analysis, I structured and drafted all chapters of the current thesis and revised it until a final form was approved by the supervisory team. I also confirm that all discussion points and conclusions deriving from this work, are my original contribution.

Finally, I have also presented part of this work in two conferences, I have published one paper (Chapter 4) and two abstracts (Chapter 4 & 6) as first author and I am currently working on two manuscripts (Chapter 6). In conclusion, I hereby confirm that throughout the project I have worked independently and, unless otherwise stated, this thesis entirely reflects my individual contribution.

Table of Contents

Abbreviations

24HRs	24-hour recalls
95% CI	95% Confidence Intervals
aHEI	Alternative Healthy Eating Index
AIC	Akaike Information Criterion
β	beta coefficient
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BSD	Baltic Sea Diet
cm	centimetre
CMI	Cognitive-Motor Interference
CoM	Centre of Mass
CVD	Cardiovascular Disease
DASH	Dietary Intervention to Stop Hypertension
FFQ	Food Frequency Questionnaire
FPED	Food Patterns Equivalents Database
g	gram
GBTM	Group-Based Trajectory Modelling
HCS	Hertfordshire Cohort Study
HEI	Healthy Eating Index
HEI-2015	Healthy Eating Index version of 2015
I-ADL	Instrumental-Activities of Daily Living
ICC	Intraclass Correlation Coefficient
IGC	Individual Growth Curve
IMU	Inertial Measurement Unit
kg	kilogram
LMM	Linear Mixed Model
m	meter
MedDiet	Mediterranean Diet
MRC	Medical Research Council
MUFAs	Mono-unsaturated fatty acids
n	number of participants
NDNS	National Diet and Nutrition Survey
NSHD	National Survey of Health and Development
OGA	Observational Gait Analysis
OMCS	Optical Motion Capture Systems
PUFAs	Poly-unsaturated fatty acids
RCT	Randomized Clinical Trial
s	second
SD	Standard Deviation
SE	Standard Error
T2D	Type 2 Diabetes
UK	United Kingdom
US	United States of America
USDA	United States Department of Agriculture
WS	walking speed
ΔBIC	Difference in Bayesian Information Criterion
ω-3	omega-3 fatty acids

List of Tables

List of Figures

Chapter 1 - Introduction

1.1 Summary

Life expectancy is increasing worldwide but this does not necessarily translate into healthy ageing. Maintaining overall well-functioning with ageing, while living independently, is a major challenge in older people. Walking ability is involved in several daily activities and may predict survival rates in older people. It also reflects age-related well-functioning including physical and cognitive status. Among other modifiable lifestyle factors, a healthy diet may be important to maintain age-related well-functioning. This chapter will provide a general introduction to ageing and health, with main focus on physical and cognitive aspects. It will also reflect on methods to assess diet and walking performance, in particular walking speed. All fundamental concepts and terminology to be used across this thesis are introduced.

1.2 Life Expectancy Trends and Ageing

According to the World Health Organization (WHO) [1] and the United Nations [2] the proportion of adults aged over 60 worldwide will double from 13% (962 million) in 2017 to 22% (2.1 billion) by 2050. All regions (except Africa) will have at least 25% or more of their population being over the age of 60 (Figure 1.1). In addition, by 2020 this age group will outnumber all children aged up to five years, with the rate of increase being about 3% per year [1]. To date, Europe has the highest percentage of population of people aged over 60, one out of four citizens [2].

In particular for the United Kingdom (UK), life expectancy over age 65 has increased from 8% to double this proportion (16%) during the last two centuries, although no further improvements have been shown after 2011 [3] (Figure 1.2). This is mainly due to a combination of lower mortality rates of cardiovascular (CVD) and metabolic disease (in high-income countries), less child deaths (in low-income countries) and lower overall mortality from infectious diseases [4]. Advances in medical healthcare and socioeconomic-lifestyle changes also favour this trend

[4]. Still, the rate of increase remains lower than in other comparable countries internationally, due to particularly high number of deaths between 2015 and 2017 in the UK, according to the Office of National Statistics [3].

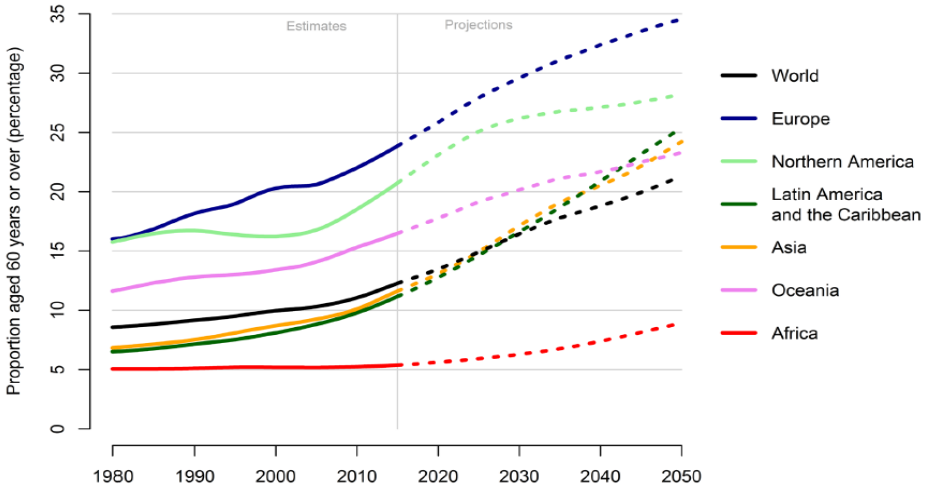

Figure 1.1 Percentage of population aged over 60 by region, 1980-2050[1]

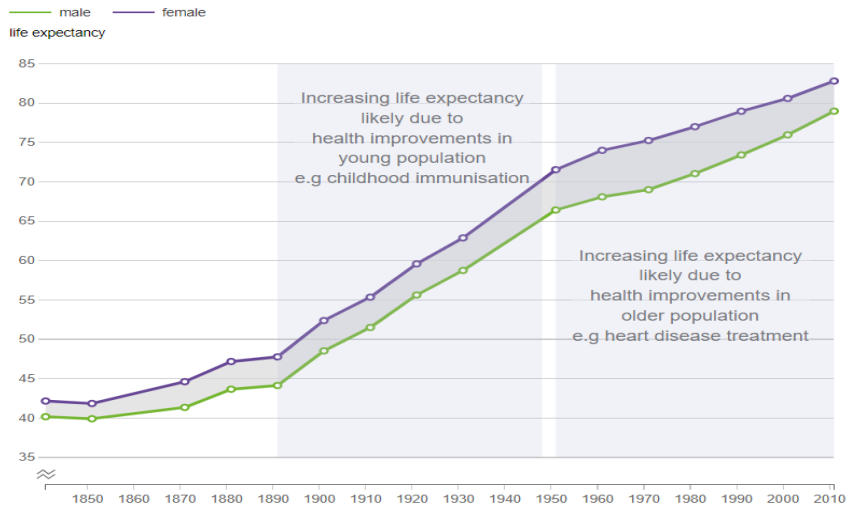

Figure 1.2 Life expectancy at birth, England and Wales, 1841-2011[2]

[1] Source [2].
[2] Source [3].

1.2.1 Maintaining Well-Functioning

With life expectancy increasing, there is great need for older people to maintain overall well-functioning, mainly physical and cognitive functioning [1]. Both elements should play a major role in daily activities of older people and often dictate quality of life with ageing. Achieving healthy biological ageing requires "*maintenance, post maturity of physical and cognitive functioning for as long as possible, which delays the onset and rate of functional decline*" according to the Conceptual Framework of Healthy Ageing [5].

Physical function is a key component of healthy ageing because it is involved in most basic activities of daily living (ADL). From walking to dressing, most self-care activities rely on sufficient physical resources, mainly reflected by the musculoskeletal system, which is considered a prerequisite by the International Classification of Impairments, Diseases, and Handicaps [6]. Reduced physical capacity can lead to loss of independence, shorter survival and huge cost implications for health and social care systems [7, 8]. Ageing populations who lose independent mobility have less chances to contribute in the community, higher likelihood of social isolation and disease and a poorer quality of life [9]. In turn, maintaining optimal levels of physical functioning is linked to lower rates of adverse health outcomes, disability and subsequently death [5, 8, 10]. In particular for older people, maintaining physical functioning is important for the delay of age-related conditions such as osteopenia and sarcopenia [11], which are significantly related to risk of falls and fractures [12].

Several everyday tasks include problem-solving, speed processing and memory capacity, all of which comprise the cognitive domain [13]. For example, driving ability or likelihood of staying in high intellectual capacity jobs are of great importance and both rely on cognitive status. Evidence has linked higher cognitive ability to higher work performance, occupational level, prestige and income [14]. Living independently with ageing is another crucial concept for older people as most instrumental activities of daily living (IADL) such as shopping, taking medications, managing finances, require sufficient cognitive resources [14, 15]. Finally,

cognition is inversely linked with adverse health outcomes, such as risk of depression [16] and comorbidities [17]. Therefore, maintenance of cognitive function is a major element of healthy ageing, as it contributes to overall quality of life and lower risk of chronic disease and mortality [13, 14, 18].

1.2.2 Health Decline

A longer lifespan is assumed to bring great potential for individuals, their families and communities and national policies should face challenges that longer life expectancy entails. Older people can extend the period of education, of self-improvement and self-completion and can contribute in several ways to society [1]. Unfortunately, observed longer life expectancy does not necessarily translate into 'healthy' years, as evidence suggests [19, 20]. Although severe disability has declined over the last 30 years, the trend is not the same for mild to moderate disability [3]. Indeed, declines in physical and mental capacity are apparent with ageing because of biological and social changes. The aggregation of lifetime damage at molecular and cellular level has detrimental impact on the quality of life of older people. This is expressed by elevated inflammation and oxidative stress and in combination with unpleasant life experiences such as social isolation, transition from work to retirement or loss of family members, often results in loss of independence, higher risk of chronic illness and, ultimately, death [4].

Physical Decline

Unavoidably, ageing comes with structural, molecular and cellular unfavourable changes that gradually accumulate over the lifespan [1]. Average decline in physical capacity accelerates up to 20% per 10 years in people aged over 70 [21].Yet, those changes are not linear or universal for all age groups, and trajectories of ageing differ between individuals in so that people in their 70s may or may have not declined substantially [1]. This is mainly because individuals vary in terms of disease proneness and exposure to environmental factors such as

physical activity and diet. Nonetheless, the musculoskeletal system is a good reflector of physical function in later life [22] and its progressive impairment will eventually lead to physical decline and decrease in physiological reserve [1, 23]. For example, bone and mass volume decline for both sexes, leading often to osteoporosis and higher risk of hip and forearm fractures [23]. After achieving a peak in early adulthood, muscle mass and strength start declining with ageing in both sexes, with women having on average lower lifetime muscle mass [1]. Similar patterns occur for bone mass and density, in particular for postmenopausal women, who suffer from age-related joint and bone degradation, resulting in discomfort, pain and decline in mobility [1, 23].

The underlying mechanisms of motor decline are complex and not within the scope of this thesis but number of adverse alterations in genome, protein and hormone expression contribute, alongside unfavourable changes in stem and bone cells [23]. Eventually the musculoskeletal system will deteriorate, as response to simultaneous age-related declines in all above mentioned systems [23].

Cognitive Decline

Similar to physical function, cognition also deteriorates with ageing, with slopes of decline being different between cognitive domains [1, 13]. Of various factors, education background across lifespan is strongly related to alterations in cognitive reserve between individuals, resulting in some domains decreasing at early adulthood while others deteriorate in older age [13]. In addition, factors such as socioeconomic status, lifetime experiences, chronic disease prevalence and environmental factors such as mental training, diet and physical activity, significantly influence rates of cognitive decline with ageing [1]. Finally, interpersonal variability in adaptation and expression of cognitive decline is further determined by intelligence markers and psychological factors such as emotional well-being, anxiety and depression [14].

While some cognitive domains show resilience to brain ageing, domains such as conceptual reasoning, executive function and most importantly perceptual-motor function, the “fluid cognition”, achieve its peak until the 30s, and gradually declines with ageing [14]. This leads to declines of overall cognitive capacity and available attentional resources, in particular when undergoing complex tasks [1, 13]. On the contrary, other domains such as concentration, distraction, gained knowledge, vocabulary and experiencing concepts, the “crystallized cognition”, remains quite robust, if not improves, across the lifespan [1, 13].

Cognitive decline is mainly related to brain changes during ageing. Excessive levels of inflammation and oxidative stress lead to neurobiological modifications such as distorted cellular signalling, beta-amyloid accumulation, increased neuro apoptosis and loss of plasticity of synapses, all contributing to neuro degeneration [24]. Furthermore, grey matter volume, responsible for muscle control and sensory perception, starts declining after the 20s, while there is also moderate loss of hippocampal and white matter volume, even with healthy ageing [13]. On the contrary entorhinal cortex volume, which is important for navigation and time perception, does not decline substantially with healthy ageing, but mainly during extensive damage such as in case of dementia [13, 25].

1.2.3 Sex Differences in Ageing

Ageing, no matter how “healthy”, will inevitably lead to overall health decline and eventually death. However, trajectories of ageing and functional decline, are well known to differ between sexes mainly due to genetic, environmental and hormonal factors [26]. Women have longer survival than men but they also have higher rates of morbidity [1]. The concept of so-called “longevity” suggests that in order to compensate for less absolute physical strength and functional capacity at early adulthood, women tend to decline at slower rates with ageing and become vulnerable to “terminal” health deterioration later than men [27]. On the contrary, men are physically more robust than women and have been consistently found to have faster

walking speed [28], higher bone mass [29], muscle mass and strength [30] and better physical performance [31]; yet physical decline with ageing is much steeper [32]. Although, skeletal muscle decline occurs in both sexes with ageing, the ratio of steroid hormones will drastically determine muscle wasting [30]. Testosterone is highly anabolically active leading to more muscle mass in men and recent evidence suggests that oestrogen levels may downregulate muscle and bone loss, which occurs more often in postmenopausal women [30]. Finally, due to different hormonal profiles, men and women respond different to muscle wasting age-related conditions, such as sarcopenia and cachexia. For example, although women decline less steeply than men, they start with weaker musculoskeletal system, resulting in higher sarcopenia prevalence [30].

Similar to physical status, cognitive function follows steeper declines among older men with healthy ageing compared to women, who also benefit from overall higher cognitive function in middle age [33]. Variation is large, with some evidence suggesting better cognitive profile in older men regarding spatial ability versus better cognitive ability in reasoning and verbal communication in women [33]. For example, it has been suggested that women are likely to depend more on the central nervous system to compensate for lower muscle strength and therefore even slight changes may result in worse functioning compared to men [33]. Women have been reported to have in general better structural brain profile regarding grey and white volumes than men [34, 35]. In addition, men have lower cortical thickness and faster thinning of it [36], alongside with faster age-related declines in frontal and temporal brain volume [37]. These differences are partially attributable to sex steroid hormones, similar to differences seen in the musculoskeletal system. For example, it has been suggested that testosterone may have a major role in structuring, organizing and activating spatial ability in older men [38], whereas estradiol levels, naturally high in pre menopause women, have been found to be at highest concentrations in the prefrontal cortex [39]. The latter may partially explain observed sex differences of stress levels in the prefrontal cortex, favouring women, when walking tasks involve cognitive workload [40].

1.3 Dietary Assessment Methods

Validity in assessing dietary intake is a major element of nutritional and medical research. Unlike other factors, dietary intake is very difficult to measure because of large variation in the type, quantity and frequency of food consumption and mainly due to overall subjective perception of food intake [41-43]. There is no method which can capture all these dimensions simultaneously and accurately. Dietary assessment is conducted directly by either objective observation or by self-report and dietary intake can also be reflected indirectly by biological markers [41, 42]. Depending on the research question and level of detail required, selection of appropriate methodology may differ. Nonetheless, non-valid dietary assessment "*may mislead comprehension of the effect of dietary intake on ageing and disease*" [41, 42].

1.3.1 Biological Markers

Proxy measures such as biological markers of metabolites of nutrients can directly reflect dietary intake and have been found to be independent of self-perception, mis-reporting and memory reliance [42]; yet their metabolism and absorption vary highly by age, sex and disease status [41, 42]. Therefore, although they may accurately reflect current levels of specific nutrients for individuals, they do not allow direct comparisons for the general public and they do not provide enough information on long-term adherence to dietary patterns and recommendations. In addition, the cost of laboratory analysis of nutritional biomarkers is a major issue in large-scale epidemiological studies [42].

1.3.2 Objective Methods

Objective methods include observation by duplicate diets or household food consumption records, performed by a trained researcher [41, 42]. The duplicate diet method replicates identical copies of dietary intakes of individuals, and then analyses those copies to estimate dietary exposure. The household food consumption record method collects detailed dietary information on all food (quantity, type, frequency, preparation and time of eating) consumed

in a household [41, 42]. It is understandable that both methods are not feasible options in large-scale epidemiological studies, due to high cost and time-related limitations and because people have increased food and snack consumption outside the home [41, 42].

1.3.3 Self-Report Methods

Self-report dietary assessment methods use answers from participants to accurately estimate dietary intake [41-43]. They can be grouped as: food diaries (estimated or weighed), 24-hour dietary recalls, food frequency questionnaires and dietary history/checklists. The first three are the primary dietary assessment tools in observational studies [41-43]. In general, all three methods involve assessment of food consumption and conversion of reported dietary intakes into food groups and nutrients [41-43]. Although in self-report methods there is potential for bias (recall[3], selection[4] or social desirability bias[5]), they also have important advantages when used in large-scale epidemiological studies [41-43]. They are affordable, easy to use and non-invasive and can capture both quantitative and qualitative dietary information.

24-Hour Recalls

24-hour recalls (24HRs) collect retrospective detailed information on food consumed over a specific period, usually the previous day or the preceding 24 hours [41-43]. The amount, type and brand (if possible) of the food in relation to a common size unit (cups, teaspoon, or bowl) are used to estimate portion size. In general, the more days of recall, the more accurate reflection of habitual intake. A range of three days for macronutrients to weeks for micronutrients has been proposed to assess accurately dietary intake [41-43]. 24HRs have a relatively small burden on participants; yet recall bias is a major issue [41-43]. Because of its

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[3] Defined as "*systematic error that occurs when participants do not remember previous events or experiences accurately or omit details*"[44]. Not considered a major source of bias in prospective cohort studies.
[4] Occurs when "*inclusion or follow-up of participants is related to both exposure and outcome, when their association might be different based on participation status*". See 7.3 Methodological Considerations.
[5] Defined as "*response bias that is the tendency of survey respondents to answer questions in a manner that will be viewed favourably by others*" [44]. See 7.3 Methodological Considerations.

high response rate, it is often used in national surveys as a measure of average levels of dietary intake in a population or to assess validity of Food Frequency Questionnaires.

Food Frequency Questionnaires

They are designed to assess habitual dietary intake, in terms of consumption frequency of a wide range of food items (usually 20-200), over a reference period, usually six to 12 months. Shorter Food Frequency Questionnaires (FFQs) can also collect information on specific foods rich in nutrients of interest or foods that are consumed sporadically [41-43]. They are widely used in retrospective nutritional studies to investigate relationships between dietary intake and disease because they rank intakes of individuals compared to others in the population. Therefore, they are not considered reference methods to assess accurate estimates of absolute dietary intake [41-43]. FFQs are easy to administer and have relatively low respondent burden; yet reported dietary intake is restricted to the items included in the food list and estimating portion sizes is challenging and may introduce measurement bias.

Food Diaries

Food diaries (also referred to as diet records) are prospective self-administered open-ended assessment tools which collect extensive information on the actual dietary intake over a specific period, ranging from one to multiple days [41-43, 45]. They can be weighed or estimated and thus reflect different levels of estimates of energy intake, macro- and micronutrients, food groups, foods and beverages. Food preparation, brand name of products, food outside home, timing and food environment are incorporated in this method. To reflect habitual intake, multiple days of diaries are needed, accounting for daily variation in diet [41-43, 45]. A minimum of three to a maximum of seven days is likely the optimal balance between accurate reporting and acceptable adherence burden [42]. Food diaries are appropriate for large-scale studies when detailed levels of food and nutrient intake of individuals are needed. Participants record intake of the “real-time” food eaten, hence reliance on memory is limited. Because of their open-ended nature, food diaries allow for cultural, ethnic and diverse group comparisons and

there is no restriction in reporting [41-43, 45]. On the contrary, food diaries require substantial time to analyse and high level of literacy and training of participants to accurately estimate portion sizes. In case of multiple days, it also requires a high level of motivation and adherence. Finally, although recall bias is not a major issue, participants may tend to alter their actual intake during the diary days, a phenomenon called “reactivity” [41-43, 45].

1.4 Gait

Gait, refers to locomotion of the human body by means of forward stepping which is achieved through the movement of the upper and lower limbs [46]. Gait is of great importance in everyday life as it is involved in numerous activities including work, commuting, and sports. Gait analysis refers to a broader spectrum to describe efficiency and quality of movement and assesses the act of walking, usually by performance of a standardized walk test [46]. Assessment is usually performed by use of technological equipment such as video, optical motion capture systems (OMCS) or inertial measurement units (IMU) [47, 48] and results in an extensive battery of walking parameters [46, 47, 49].

Gait analysis is widely used in clinical settings as a tool to record biomechanical measures and make clinical decisions. Gait analysis not only contributes in exploring walking patterns per se, but it also provides valuable information on a much broader range of functions, including neurological, skeletal and muscular dysfunction [50]. Indeed, it is often used with clinical examination to distinct diagnosis of similar neurological diseases, or to assess the severity, stage or nature of a disease [48]. The output of gait analysis, which is easy to conduct, is currently considered almost as repeatable as routine physical examination, due to advances in standardization and assessment methods. All these have led to gait analysis being generally offered as part of a routine healthcare visit , which highlights its clinical importance [50].

1.4.1 Gait Cycle

There are different models to describe a gait cycle and for this thesis the widely accepted model as described by *Whittle (2014)* [46] is briefly introduced. A complete gait cycle is defined as the motion from one foot strike (reference limb) to the following foot strike of the same limb. Each intermediate period is expressed as percentage of one complete gait cycle, meaning the initial foot strike is 0% and the successive foot strike of the same limb is 100%, which completes a gait cycle. When moving forward, the CoM shifts forward and the whole body tends to fall forward. The fall is prevented by the non-weight-bearing leg, which is then moved forward [46].

A simple although imperfect model to describe the act of motion is the inverted pendulum model (Figure 1.4*)*, in which the limbs behave as inverted pendulums resulting in the centre of the mass (CoM) shifting vertically by about 4cm and laterally by about 5cm [51, 52]. The main assumption of this model is that no mechanical work or knee torque is needed to move, lift or support body weight [52]. Despite its imperfections, the inverted pendulum model allows for an accurate and easy interpretation of the walking pattern and has been directly applied in human gait analysis [53].

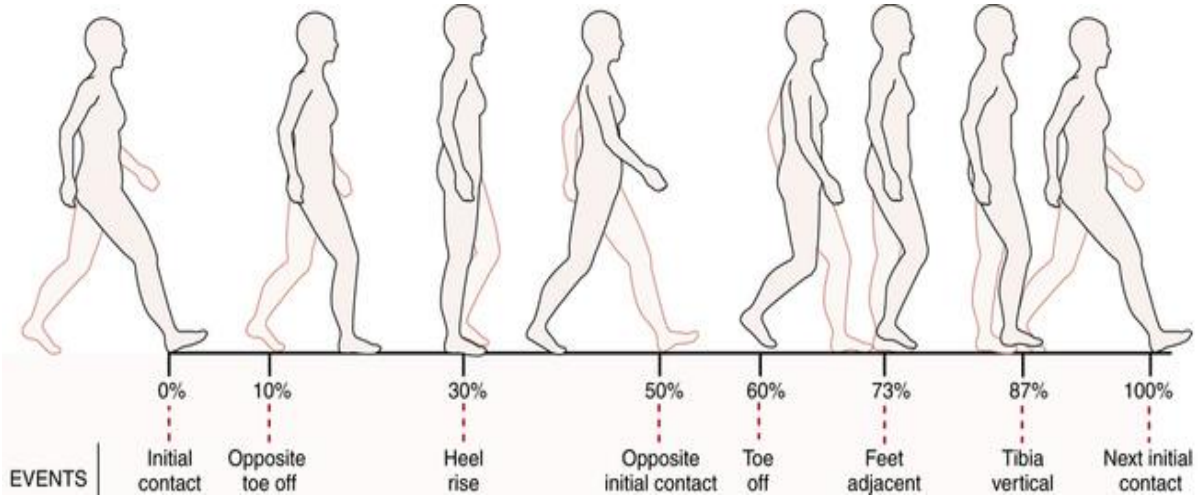

Figure 1.3 Visual representation of a gait cycle in human walking[6]

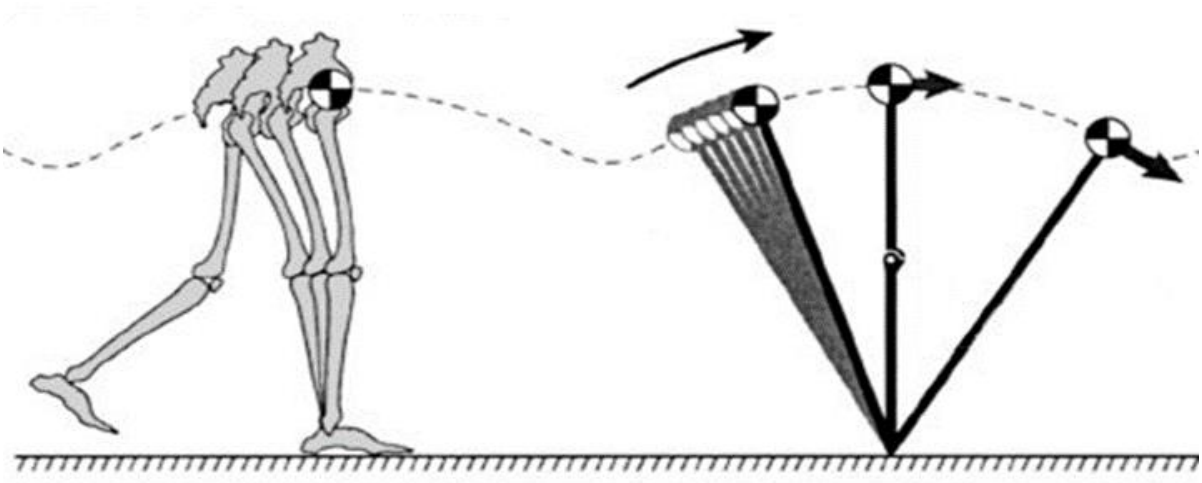

Figure 1.4 Visual representation of the inverted pendulum model[7]

[6] Modified version of [54].
[7] Source [55].

1.4.2 Gait Analysis Methods

Gait analysis is commonly used to determine walking status and several assessment methods have been developed over the years [56, 57] . The present thesis will provide only a brief overview of three key methods, which is observational gait analysis, OMCS and use of IMUs, with main focus on the latter.

Observational Gait Analysis

An easy and fast method to capture human posture and movement is by observational gait analysis (OGA) [58, 59]. OGA is genuinely a qualitative method which identifies alterations of normal gait cycle by visual observation [58]. It is very often combined with the use of a stopwatch, thus adding semi-quantitative elements of human movement, when people are asked to walk over a predefined area. It is a low cost method that is widely used in clinical settings to achieve a rapid function assessment [58, 59]. In spite of being broadly used, OGA is highly dependent on judgements made by the observer, thus lowering validity and reliability of the measurements. Moreover, OGA does not provide analysis of the causal implications of abnormal gait [59].

Optical Motion Capture Systems

The reference method in gait analysis is the OMCS which uses three-dimensional body movement analysis [48]. In this approach, gait of an individual is analysed by capturing standardized markers using cameras of high sampling rate, while participants walk down a predefined walkway. OMCS are of major importance as they provide objective data on all kinematics (joint motions) including spatio-temporal parameters [48, 60]. Indeed, OMCS are considered as the “gold standard’ for gait analysis due to their efficiency in determining functional status and pathological conditions [61]. However, despite OMCS being of superior validity compared to other methods, its clinical applications are limited due to genuine limitations. These include complex set-up, time-consuming operation procedure, enormous

amounts of data to analyse and challenging interpretation [61, 62]. Hence, given clinical decisions are made on the basis of interpretation of gait data, OMCS should be used with caution in clinical settings.

Inertial Measurement Units

The need for an objective assessment method which can accurately distinct between health outcomes and is concurrently easily used in real-life conditions resulted in the development of small, light, relatively affordable, portable sensors, known as "inertial sensors" [56, 61, 63]. The combination of such sensors in particular three-axis accelerometers, three-axis gyroscopes and magnetometers is called an "inertial measurement unit" (IMU) [61], which is to be used hereafter to describe all inertial sensors, for simplicity. The basic principle of IMUs relies on their ability to measure the inertia (or absence of it) of a mass in suspension. This is done via capacitive accelerometers which translate the displacement of the CoM into electric signals. Gyroscopes provide data on the angular displacement (rotation) of the IMU by integrating the angular velocity [61]. Magnetometers re-calibrate IMUs to correct for bias associated with measurement error[8] which accumulates over time [61].

To date, there is no general consensus with regard to the optimal algorithm, analysis software, body site to place IMU or a standard operating procedure [61]. Nonetheless, IMUs are the most commonly used devices in gait analysis, because they provide a reliable and extensive battery of temporal and spatial gait parameters and can be used in both laboratory and clinical settings [48, 61]. Indeed, a recent meta-analysis has concluded that despite differences in modelling, reference systems and test procedures, IMUs are in good agreement with reference gait analysis of OMCS for basic gait parameters, with satisfactory reliability in clinical settings [61]. Finally, an additional major feature of IMUs is that they have been used and validated in

[8] Defined as "*the difference between a measured quantity and its true value*" [64]. See 7.3 Methodological Considerations.

numerous populations including people with neurological conditions [65-68], stroke [69], multiple sclerosis [70] and those in rehabilitation [71].

1.4.3 Gait Control

Gait is normally regulated by the central nervous system via a combination of automatic and non-automatic procedures [72]. In general, under “undisturbed” conditions when no additional stimuli is present (e.g. obstacles), walking is regulated by subcortical brain regions, mainly basal ganglia, and is considered an automatic and rhythmic procedure [72]. Despite being automatic, normal gait may also activate other brain regions such as the primary motor cortex and spinal cord as well as the prefrontal cortex and premotor areas via an unconscious locomotion pathway, as recent research suggests [73].

However, when multiple tasks are required concurrently with walking, there is an increased activation of this indirect locomotion pathway, which mainly involves functions of the prefrontal cortex area [74]. This brain area regulates executive functions, working memory and attentional resources, which are vital for multi-tasking. This pattern is observed even among healthy young people, but it is much more prevalent in older people [75]. This is mainly because of detrimental brain structural changes and loss of executive functions, which naturally occur with ageing. With ageing, resources of the brain get limited to smoothly integrate all concurrent tasks into normal walking and despite the partial neural compensation, the central nervous system becomes unable to manage the two tasks concurrently [76]. In such cases, which are much more highlighted in cognitively declined older adults, who have an increased deterioration of higher cognitive systems, walking is no more an “automatic” procedure but becomes a “conscious” procedure [77]. This transition in gait control, which often reflects impaired gait ability, has been largely investigated in cognitive-motor interference paradigms, which are described below.

1.5 Cognitive-Motor Interference

In everyday life, walking is not a process performed in isolation. It is rather the manifestation of a complex interplay of various body systems and functions, performed in multiple environments under challenging and shifting conditions [77]. For example, it is very usual for individuals to walk and concurrently perform a cognitive task such as recalling directions or having verbal communication. In such cases, this challenging interplay of managing available cognitive resources while controlling gait is defined as “cognitive-motor interference” (CMI) [78].

The concept suggests that when individuals walk in “real-life” conditions, they tend to alter performance of either the cognitive or motor task or both, which designates the level of cognitive workload spent [79]. In particular, for older people, motor performance tends to be less of an automatic process and more a higher-order cognitive system function [72]. Cognitive-targeted strategies may compensate for age-related declines in locomotion to a certain extent; however these resources are limited and when exceeding individual capacity, people are unable to combine multiple activities while walking [75]. This is largely detectable in older people with cognitive decline when walking performance also declines, because the compensatory mechanism is insufficient compared to healthier or younger people [80]. This may be a precautionary mechanism to avoid falls and ensure safe locomotion [81].

1.5.1 Cognitive-Motor Interference Strategies

Despite the general perception of the concept, there is no established consensus on which task people tend to prioritize, with nine possible scenarios: (1) motor task prioritization-no cognitive change, (2) cognitive task prioritization-no motor change, (3) mutual facilitation, (4) motor-related cognitive interference, (5) cognitive-related motor interference, (6) cognitive priority-motor worsening, (7) motor priority-cognitive worsening, (8) mutual interference, and (9) no interference [82]. In any of these scenarios, the difference in walking and/or cognitive

parameters between undisturbed walking and when walking and performing a cognitive task is defined as “CMI cost” [79]. For example, if an individual prioritizes the cognitive task and drops motor performance (cognitive-related motor interference or cognitive priority-motor worsening), CMI cost will capture the reduction in walking parameters between undisturbed versus walking and performing a cognitive task.

There are various theories regarding magnitude and direction of CMI. Most theories hypothesize that when walking and cognitive tasks are performed concurrently, there is a competition for attentional resources or/and neural pathways that process information [83]. The “*central capacity sharing*” model suggests that when people perform two tasks simultaneously such as walking and recalling directions, available resources are re-distributed between tasks [83]. The “*bottleneck*” model proposes that two tasks that share similar neural processing, like the cortical region in walking and executive functions of older people, can be performed only sequentially and not concurrently [83]. On the contrary, the “*cross-talk*” model suggests that when two tasks share similar neural domains, they do not disturb each other and therefore can be performed facilitating each other, because they use similar pathways [83]. In this latter theory, there is no interference.

1.6 Walking Speed

Abnormal gait, due to age-related physical decline, is present in more than 30% of people aged over 70 [84]. Evidence supports an interaction in the decline rates of gait-motor-cognitive axis [7], in particular regarding age-related cognitive disorders such as mild cognitive impairment and dementia; yet a causal relationship is still unclear [85]. Gait metrics have been found to distinguish neurological groups such as Parkinson’s disease [67], Huntington’s disease [66], mild cognitive impairment [85] and dementia [86] and evidence is emerging for multiple sclerosis [87] and diabetic peripheral neuropathy [65]. However, overall, there is no established level of evidence for other gait parameters and their relationship with age-related overall decline and frailty, with the exception of walking speed [88].

Gait analysis provides a broad range of walking parameters including temporalspatial, symmetry and walking efficiency. Walking speed is a parameter defined as the distance covered divided by the time taken to cover the distance and its standard unit is m/s. It can be assessed by time-limited tests such as the 10-m or 20-m walking test, with time and distance frame varying across walking tests. Irrespective of the assessment method, walking speed is the end product of a complex interaction of numerous body systems and functions, from muscle strength and aerobic capacity to balance ability, cognitive status and postural control [89].

1.6.1 Normative Values for Walking Speed

Depending on the protocol and test used to perform gait analysis, reference values of normal walking speed vary across age groups and sex. *Chambers and Sutherland (2002)* [49] have found a mean walking speed of 1.14 m/s for seven-year old children and 1.23 m/s for adults aged over 40. An emerging volume of evidence has been published to describe reference values of walking speed, at usual or maximum pace, for healthy community-dwelling older people [90-96]. Reference values have also been proposed for those at risk of frailty [97]. A key systematic review of 41 studies of various designs, has recently provided median values of walking speed at self-selected pace [90]. Walking speed was consistently higher in men at all ages, from 20 to 80, and increased with age for both sexes, with its peak at ages 30-40 for men (1.46 m/s) and at 40-50 for women (1.38 m/s).

1.6.2 Walking Speed and Overall Health

According to the International Academy on Nutrition and Ageing Task Force [98], walking speed should be considered a "*single-item autonomous community-dwelling indicator*" for older people at high risk of health decline. Values of walking speed above 1 m/s are related to lower likelihood of age-related adverse outcomes [99], hospitalization, and disability [100]. In addition, walking speed has been shown to be highly predictive of adverse health conditions [101],

mortality [93] and survival rates in older people [28, 100, 102]. Indeed, improvements in usual walking speed, have been associated with 60% longer survival for older people over an eight-year period [102]. It is important that even marginal improvements as minor as 0.1 m/s, may lead to significant higher survival rates [28]. Furthermore, values lower than 0.6 m/s have been associated with a two to three fold higher risk of falls in older people [100]. In hospitalized patients aged over 65, a cut-off point as low as 0.2 m/s has been suggested to identify those at high risk of adverse health outcomes [103]. Finally, walking speed is also predictive of frailty [104], in particular when combined with a measure of physical performance such as grip strength [105]. An overview of walking speed in relation to health outcomes is presented in Figure 1.5.

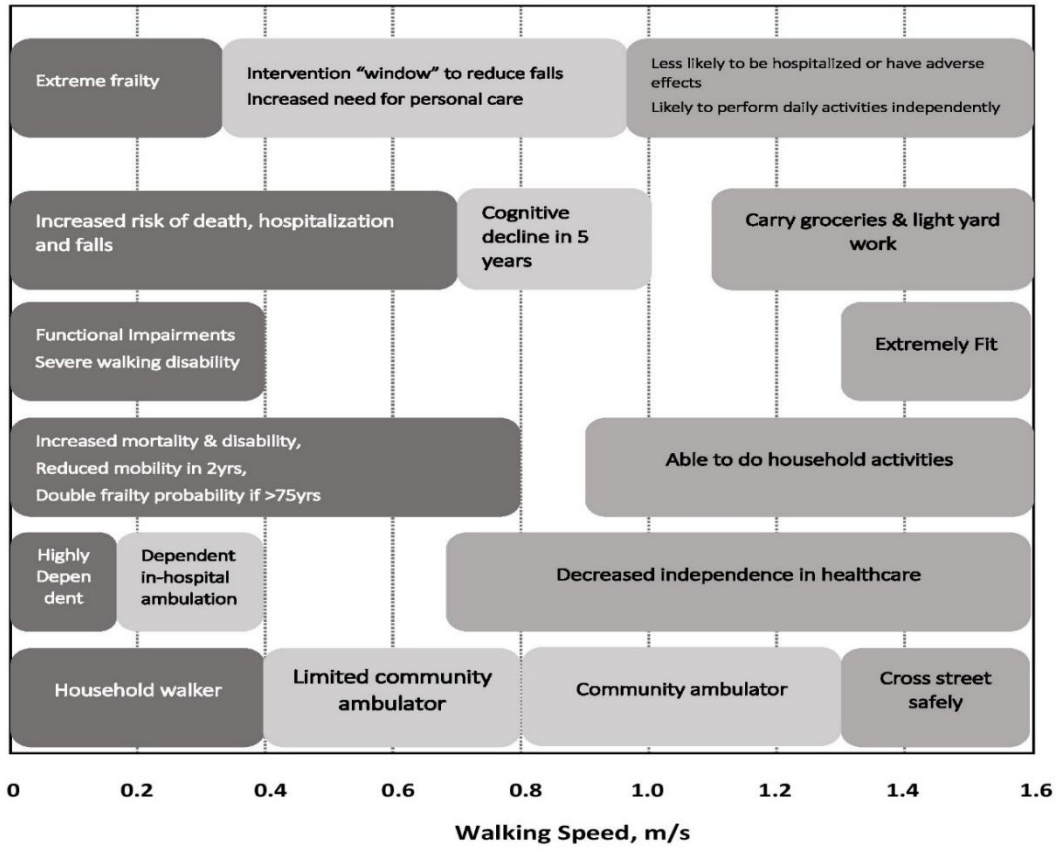

Figure 1.5 Description of walking speed and associated health outcomes[9]

[9] Modified version of [89].

Walking Speed and Physical Decline

To date, there is no consensus regarding valid diagnostic measures of age-related physical decline, but physical performance tests have been suggested to be useful tools [106]. In older people, walking speed is a strong correlate of muscle mass and strength and thus reflects musculoskeletal changes [107]. Indeed, decreases in walking speed are often the clinical manifestation of loss in muscle mass and strength, which are apparent with ageing [108]. More importantly, although measures of skeletal mass may suggest a moderate decline in older people, a decrease in walking speed is likely to be much steeper and rapid [109].

Walking speed has been consistently associated with age-related physical decline and frailty [100, 110-112]. A cut-off point of <0.8 m/s in walking speed has been suggested to diagnose physical frailty in primary care settings [113], and walking speeds over 0.9 m/s rule out this risk [98]. In addition, a recent cohort study of 1,400 community-dwelling older people in Korea found a strong inverse association between walking speed (mean speed: 0.85 m/s) and physical frailty status [114]. Among community-dwelling older women in the Women's Health and Ageing (WHA) Study, walking speeds <0.4 m/s were associated with physical decline one year later [112]. In line with this, a longitudinal study of older Japanese women showed that loss of bone mineral density, which is major element of the musculoskeletal system, was expressed as slower walking speed over a two-year period [111]. Finally, among hospitalized older people, walking speeds <0.6 m/s were associated with limited mobility in a prospective study in the United States (the US) [110]. It is therefore, plausible to consider walking speed as an early and reliable reflector of physical decline with ageing, well in advance of biological physical decline.

Walking Speed and Cognitive Decline

Walking speed has been shown to be predictive of cognitive decline in healthy older people [115, 116] and among those with dementia [86]. Recent meta-analyses on walking speed and cognition status have established the association of slower walking speed and cognitive decline in older people [115, 117]. Utilizing data from 26 cross-sectional studies, *Demnitz et al.*

(2016) [117] found significant although small associations between gait as mobility measure and global cognition, processing speed, executive function and memory among 26,355 healthy older adults. In the Mayo Clinic Study of Ageing, faster walking speed among healthy and demented people at age 70-89, reflected better global cognition and was also associated with lower cognitive decline over a four-year follow-up period [118]. Moreover, evidence from the WHA Study showed an inverse association between cognitive decline and baseline walking speeds >0.75 m/s over a three-year follow-up period, among 560 community-dwelling older women [112].

In particular for neurological populations, even slight improvements in walking speed reflect better cognitive status [115, 119]. For example, using data from cross-sectional and longitudinal studies of 29,520 participants, *Peel et al. (2019)* [115] showed that changes in walking speed by 0.11 m/s in patients with cognitive impairment, 0.2 m/s for those with mild dementia, and 0.41 m/s for moderate dementia, were associated with clinically meaningful protective effects on cognition. Confirming these findings, a systematic review of various neurological populations further suggested that walking speed changes of 0.1-0.2 m/s might be of major importance for cognitive function in these groups [119].

1.6.3 Walking Speed and Cognitive-Motor Interference

It is sensible to assume that walking speed will likely decrease when a cognitive task is performed, which will be expressed as an increase in CMI cost for engaging cortical higher-order processes. This increase usually derives from limited attentional capacity, inability to divide the existing capacity and/or declined integrity of executive functions [76, 120]. Indeed, several studies on CMI paradigms have proposed age-related declines in walking speed with increased cognitive workload, in older populations [77, 121-124]. Nonetheless, the magnitude of the effect on walking speed may vary in older people depending on cognitive task type and complexity [73].

A recent meta-analysis, of 27 cross-sectional studies, showed a significant decrease in walking speed due to CMI, on average by 0.19 m/s, when verbal-fluency tests were performed while walking, among healthy older people with walking speed >1 m/s [122]. In agreement with this, another meta-analysis showed significant reductions in walking speed of older people, when tasks required high executive function, such as verbal fluency [77]. The CMI cost was present in healthy (-0.12 m/s, 95% CI: -0.16, -0.08) and neurological (-0.16 m/s, 95% CI: -0.23, -0.08) people, but was not significant for simple tasks such as reaction time or discrimination tasks. More importantly, it was stronger for older people because of age-related structural and biological changes in cognitive and motor systems. However, performance of verbal fluency tests was not affected by increasing age, thus revealing higher efficiency of older people in concurrent walking and speech [77]. The decrease in walking performance of older people under CMI conditions has also been shown in a systematic review of 69 studies [123]. In general, CMI has been shown to affect walking performance more than performance of cognitive task and magnitude is often stronger with ageing [121]. Overall, despite heterogeneity in methodological designs and CMI strategies, decline in walking speed is expected in most cases when older people concurrently perform a cognitive task.

Chapter 2 - Literature Summary

2.1 Summary

This chapter discusses available literature on the relationship between diet and healthy ageing and physical and cognitive function. It also provides insights on the effect of diet (quality, foods, and nutrients) and of dietary patterns on walking speed. Finally, it reflects on the rationale for this thesis, the aims and the specific objectives.

2.2 Diet and Health

Intake of essential nutrients often declines with ageing, in particular among older people, due to eating issues, loss of taste receptors, alterations in metabolism and food absorption and overall physical and mental health deterioration [125]. In addition, malnutrition both as undernutrition and as obesity may indirectly increase the burden of frailty and disability in both community and inpatient older populations [126]. Therefore, to prevent or counteract the above mentioned nutritional imbalance, action at earlier life stages may be of major importance. Of particular interest, lifestyle changes such as improvements in dietary habits over adulthood contribute significantly to healthier ageing and improving overall health and shall be feasible to incorporate into everyday practice in older people [127].

According to the WHO, adherence to "*presumably healthy and balanced dietary patterns*" [128], contributes to better health state and lower incidence of age-related chronic diseases. It has been suggested that around eight out of 10 cases of CVD, including stroke and type 2 diabetes (T2D) could have been prevented with modification of lifestyle risk factors, including diet [129]. Importantly, healthy dietary habits have been shown to increase life expectancy [130, 131]. In addition, a recent systematic review highlights the importance of healthy diets, such as the MedDiet, to preserve self-perceived quality of life in older people [132]. Independent of quantity, diet quality has been consistently and strongly associated with reduced risk of all-cause

mortality, CVD, cancer and T2D, all of which are often prevalent with physical frailty [133]. For example, healthy dietary patterns that are high in antioxidants and anti-inflammatory components, such as the Mediterranean Diet (MedDiet), have been found to be inversely associated with risk of all-cause mortality [134] and frailty [135, 136] in older, mainly Western populations.

2.2.1 Diet and Physical Functioning

To date, energy and protein intake [137, 138] and specific micronutrients such as vitamin D [139], fatty acids [140, 141] and those rich in antioxidants [142-146] have been the main focus of research, when investigating the relationship of nutrition and physical decline. They are all perceived as beneficial to tackle the physical frailty and sarcopenia related symptoms [126, 147, 148].

Of various nutrients, vitamin D is widely investigated and it has been shown to improve muscle strength, muscle mass and physical performance, in particular in older people [139, 149-153]. It has also been associated with reduced risk of falls [154] and frailty prevalence [139] Findings from the National Survey of Health and Development (NSHD) in the UK suggest that composition of diet in energy and protein may be of importance in terms of muscle weakness and physical capability [155]. In particular in men, low protein intake has also been shown to reflect low physical performance [156]. Evidence is accruing on nutrients with antioxidant properties; for example low intake of vitamin E has been associated with steeper decline in physical function in older people in the BACH Survey (the US) [143] and the InCHIANTI Study (Italy) [157]. Vitamin C and beta-carotene (vitamin A) have been correlated positively with physical strength and performance in Italians aged over 65 [146]. Furthermore, low carotenoid intake from fruit and vegetables has been associated with higher six-year risk of decline in skeletal muscle strength in the same study [145]. Evidence from the TwinsUK study has recently confirmed these associations between higher intakes of antioxidants, predominantly of vitamin C, and higher skeletal muscle mass and power in women [142]. With regard to less investigated

nutrients, findings from a cohort in Australia showed positive associations between intakes of magnesium, phosphorus, and zinc and appendicular lean mass but not strength in community-dwelling older people [144]. In particular for magnesium, evidence has been emerging, with findings from the EPIC UK-Norfolk study [158] and the UK Biobank [159], both proposing a protective effect on bone and skeletal muscle mass in older people. Overall, it can be concluded that there is potential for multiple dietary components rather than single nutrients to slow down physical decline.

A key element of physical decline, sarcopenia, which is age-related muscle loss, has been linked to malnutrition (both under and over nutrition) [126]. There is emerging evidence that a lifelong healthy diet, with main focus on protein and vitamin D intake, prevention of obesity and healthy food choices such as fruit and vegetables, is likely to revert or reduce rates of sarcopenia [126, 127, 148, 160]. The importance of a healthy diet to tackle sarcopenia and thus age-related physical decline has also been highlighted in a recent overview, where the authors concluded that older people need to "*ensure sufficient intakes of protein, vitamin D, antioxidant nutrients and long-chain poly-unsaturated fatty acids (PUFAs)*" [161]. Independently of total amount of protein, a dietary pattern that includes equal bouts of high quality protein per meal of 25-30 g has been recommended to maximize muscle protein synthesis in older people and thus limit the risk of sarcopenia [138].

Of emerging research interest is the exploration of dietary patterns against age-related physical decline. A key review summarized four systematic reviews of epidemiological studies on the role of dietary patterns on muscle mass retention and delay of sarcopenia [160]. The authors concluded that to date there is sufficient evidence to support "*a positive association between healthier dietary patterns and muscle function, physical performance and less mobility decline in older people*" [160]. Diets rich in these components, such as the MedDiet diet and the Baltic Sea diet have been associated with less loss of skeletal muscle mass, better muscle quality and lean mass and better performance in older women in the OSTPRE-

FPS Study (Finland) [162]. Similarly, evidence from the Nurses' Health Study showed an association between better diet quality in midlife, as defined by high MedDiet scores, and 46% better odds of healthy ageing 15 years later, in particular with regard to physical function [163]. Finally, findings from the TwinsUK further revealed a protective effect of high MedDiet scores on age-related skeletal muscle in non-Mediterranean healthy older women [164].

Given frailty is a common age-related syndrome, often accompanied by sarcopenia and physical decline, research has also focused on its nutritional determinants. A recent review has proposed the potential of healthy dietary patterns with regard to prevention or postponing frailty prognosis [165]. A typical MedDiet pattern, with main focus on its content of olive oil, vegetables and protein intake, even above the dietary guidelines, has been found to have a protective effect against risk of frailty [166]. Similarly, findings from the Osteoporotic Fractures in Men Study aged over 65, showed an inverse association of overall diet quality and both prevalence and incidence of frailty [167]. Finally, higher fruit and vegetable consumption, indicating nutrient-rich eating choices, has been found to contribute to lower risk of physical frailty [168]. Overall, despite the need for long-term randomized controlled trials (RCTs) on diet and frailty, the importance of healthy diet against physical frailty is well-established.

2.2.2 Diet and Cognitive Functioning

Although 60% of overall cognitive ability is genetically predisposed, maintaining an active lifestyle even in later life may facilitate a smoother slope in age-related cognitive decline [169, 170]. In general, older people who take part in community activities and are more active, tend to have higher cognitive function than those who do not [14]. Evidence from the Whitehall II Study has revealed a protective effect of modifiable factors such as smoking, alcohol, fruit and vegetable consumption and physical exercise on the relationship between cognition and mortality, thus highlighting the mediating role of healthy lifestyle [171]. Furthermore, an independent inverse association between healthy dietary patterns and physical activity in early

and middle life and incidence of cognitive decline 20 years later, has been shown in the NSHD [172]. Therefore, diet as part of a healthy lifestyle may contribute significantly against age-related cognitive decline [173].

The National Institute on Ageing-Alzheimer's Association has suggested a direct relationship between diet and brain structural and activity changes [174]. Healthy dietary patterns, rich in antioxidants and anti-inflammatory properties, have been consistently found to be associated with better global and domain-specific cognitive health [175-177] and lower risk of cognitive impairment, Alzheimer's disease and dementia [178, 179]. Indeed, a systematic review has concluded on a protective effect of MedDiet on cognitive performance using data from 25 cohorts [177]. In agreement with this, a key meta-analysis on cognitive health in older people, confirmed the positive association between MedDiet and global cognition [176]. However, there was no effect on processing speed or verbal fluency, which are important cognitive domains in CMI paradigms. Interestingly, findings from the key PREDIMED-NAVARRA randomized trial in Spain suggested a positive impact of an intervention with MedDiet with extra-virgin olive oil or mixed nuts on cognition among older people over a six-year period [180].

Findings were similar with regard to cognitive decline, with an observed 20% lower risk of cognitive disorders among middle aged people who follow a MedDiet, according to a key meta-analysis of prospective cohorts [178]. Other dietary patterns, originally designed to target CVD risk factors, such as the dietary approach to systolic hypertension (DASH) and the combined MedDiet-DASH diet intervention for neurodegenerative delay (MIND), have also been associated with a lower risk of cognitive impairment in healthy older adults [179]. Finally, data supporting the beneficial impact of healthy dietary patterns against cognitive decline is also evident, albeit limited, for dietary indices of different ethnic groups, such as the Healthy Eating Index (HEI) [181] and the Nordic Diet [182].

2.3 Diet and Walking Speed

Adverse changes in physiology due to ageing are present well in advance before clinical functional decline is observed [183], and diet quality as a modifiable lifestyle factor may affect those changes [125, 165]. Considering walking speed indicates survival rates and overall health status in older people, it may be suggested that a healthy diet will also possibly reflect faster walking speeds.

2.3.1 Diet, Lifestyle and Walking Speed

As part of a healthy lifestyle including no smoking, regular leisure physical activity, moderate alcohol consumption (if any) and normal body weight, a healthy diet can also contribute in maintaining high overall life quality and physical performance, of which walking speed is a major determinant [89]. Results from the cross-sectional Hertfordshire Cohort Study (HCS) in the UK [184] showed a positive association of healthy dietary patterns, as part of midlife lifestyle, with better physical function, as indicated by faster walking speed among people aged over 60. In addition, findings from the Health ABC in the US showed that non-obese people aged over 70 who maintained an unhealthy lifestyle including poor diet, had a 57% higher risk of mobility limitation in later life, reflecting slower walking speed [185]. In line with this, *Sabia et al. (2014)* [186] found a cumulative detrimental effect of unhealthy lifestyle habits on walking speed 20 years later, among middle aged individuals in the Whitehall II Study. Interestingly, out of all unhealthy behaviours, accumulation of 10 years of low diet quality as per <2 servings of fruit and vegetable per day, was a major predictor of slow walking speed at age 65. This underlines the importance of duration of unhealthy lifestyle, including poor diet, in relation to physical function. Finally, a recent prospective study of 1,800 midlife women from the SWAN Study in the US, showed a positive association between exposure to a nine-year period healthy lifestyle (no smoking, physical activity and healthy diet) and better physical performance, as reflected by faster speeds over a 4-m walk [187].

2.3.2 Nutrients and Walking Speed

Overall, several studies on specific nutrients have shown an association of higher diet quality and better physical performance including walking speed in older people [149-151, 153, 155, 188, 189]. Furthermore, differences in dietary intake have been observed in relation to gait ability of older people. Among 350 independently living men and women aged over 60 in the NMAPS Study, the US, slow walking speed was associated with low energy, protein and carbohydrates intakes [190].

In older people, a protective effect of high (>1 g/kg/day) versus low protein intake (<0.8 g/kg/day) on physical function, as expressed by walking speed, has been suggested by a recent meta-analysis of observational studies [137]. However, another key recent meta-analysis of RCTs on protein supplementation among non-frail older adults did not show any relationship of high protein intake and walking speed [191]. Finally, an RCT of older people in China also reported null associations between an exercise and supplementation intervention and walking speed over a three and six-month period [192]. Therefore, it is likely that among well-functioning older people with habitual protein intake, the protein type might be of more importance than the amount.

Regarding quality of fat intake, findings from the MAPT Trial of men and women aged over 75, suggested a faster walking speed decline among people with low omega-3 (ω-3) fatty acids levels in red cells over a three-year period [193]. In agreement with this, a notable meta-analysis of four RCTs on ω-3 fatty acid supplementation, found a significant improvement of walking speed among 236 medically stable older people, highlighting the major anti-inflammatory role of ω-3 fatty acids [140].

In the NMAPS Study, low intakes of micronutrients and vitamins such as zinc, calcium and vitamin C were associated with slower walking speed in adults aged over 60 [190]. A recent meta-analysis of 22 observational studies, concluded that slow walking speed at usual pace

is positively associated with deficiency of vitamin D in older adults [194]. A great volume of evidence has been published for the relationship of antioxidants and anti-inflammatory nutrients and walking speed, most of which support the protective effect of these nutrients on maintenance of physical performance [140, 146, 193, 195-199]. In the WHAS Study, low intakes of antioxidants were associated with high oxidative stress and walking speed decline among disabled women aged over 65 [199]. Supporting those findings, serum carotenoid and selenium levels, both of which are major antioxidants and reflect fruit and vegetable intake, have been associated with maintenance of walking speed over a three-year period in older disabled women [197]. Higher total plasma carotenoid levels were related to lower risk of severe walking disability and lower decline of walking speed in older people in Italy, over a six-year period in the InCHIANTI Study [198]. Finally, the same trend for antioxidants has been shown among healthy community-dwelling older women in the HCS Study, with vitamin C and beta-carotene being indicative of faster walking speed [195].

2.3.3 Dietary Patterns and Walking Speed

There is an increasing trend in nutritional research to examine dietary patterns rather than single nutrients, as people consume foods in combination [200]. Table 2.1 shows an overview of key studies on the relationship of diet quality and walking speed. Presumably healthy dietary patterns, such as the MedDiet, all of which are of high quality, have been associated with better physical performance and physical function, as indicated by faster walking speed [162, 184, 196, 201-211]. Adherence to a MedDiet has been related to faster walking speed in older people, as shown in the US/Israeli National Health and Nutrition Survey (NHANES) [207]. Furthermore, recent findings from the Seniors-ENRICA longitudinal cohort, suggested a positive relationship between high MedDiet scores and physical function including walking ability, over a 3.5-year period among older people [202]. Findings from the prospective InCHIANTI Study in Italy showed that high adherence to MedDiet was associated with a smoother decline of physical performance, of which walking speed is a major element, three,

six and nine years later [196]. Interestingly, compared to those with lower diet quality, high adherence to MedDiet was related to 30% lower risk of new mobility issues in later life in that study.

Evidence is also supportive, although not universal, in non-Western populations where dietary patterns of high quality, such as the Nordic diet [204], a Japanese diet [212], a Korean diet [213] or those aligning with dietary guidelines [210], have been associated with better functional status of which walking speed is a key element. For example, data from insurance databases has revealed a lower five-year incidence of functional disability among Japanese people aged over 65 with high adherence to a healthy Japanese dietary pattern [212]. On the contrary, a null association between high recommended food scores and walking speed was found among older Korean women in the National Fitness Award project [213].

2.4 Sex-Specific Associations of Diet and Functional Status

As discussed in page 6, there are well-established differences between men and women regarding biological ageing, both in terms of physical [27, 30] as well as cognitive trajectories [33]. In general, men are benefited from higher absolute values of muscle mass and strength alongside higher bone volumes than women [26], despite much steeper rates of decline with ageing. In addition, women show overall better cognitive status at midlife and also have the advantage of declining more smoothly cognition-wise as compared with men [33]. However, because women start with lower absolute levels of musculoskeletal function, they are also more prone to age-related functional disability [214].

Furthermore, it has been consistently reported that women adhere to healthy lifestyles, including healthy diets, more often than men [188, 215-220]. Adding to this, women have in general stronger health beliefs and knowledge about the importance of healthy diets, greater likelihood of dieting and they are overall more health conscious [221]. This partially explains

why nutritional interventions promoting healthy diets may be more effective among men versus women, who already have strong perceptions about healthy eating [222].

Hence, considering the above described sex differences both of lifestyle behaviours and ageing trajectories, an important question is raised of whether diet may yield its benefit differently among men and women against age-related functional decline. Surprisingly, this relationship is largely under-explored with regard to physical and cognitive function due to number of reasons. A common mis-practice highly used in studies including both sexes is to split analysis by sex. This approach reduces sample size per analysis and most importantly it does not allow for interactions and inter-correlations of covariates between men and women. In order to maximize sample size and to ensure statistical power, observational studies mainly analyse men and women jointly by adjusting for sex [196, 201, 202, 207, 209, 210]. Despite this approach minimizing the probability of wrongfully accept a null hypothesis, when not true (type II error), it does not allow to detect potential interactions between sex and diet-health relationships. Other studies investigate diet-ageing relationship either only in women [162, 163, 223, 224] or men [225] and thus fail to account for sex differences.

To date, only few studies have assessed the relationship of diet and age-related physical function considering effect modification by sex [195, 203, 204, 217, 226, 227]. Among 25,500 people from Eastern Europe (the longitudinal HAPIEE study), higher adherence to a MedDiet at midlife reflected significantly better self-reported physical function by the 36-Short-Form Health Survey cross-sectionally in both men and women; yet there were null associations among men and women regarding the 10-year subsequent slope of physical decline [226]. Despite its longitudinal nature with multiple measures of physical function, there was only one assessment of diet at midlife, diet quality was modelled using a region-specific index and physical function was self-reported. These limitations may have hindered any substantial effect of diet quality on sex-specific trajectories of physical function. Using data from the Hertfordshire Cohort Study in the UK, *Martin et al. (2011)* [195] showed positive associations

between higher intakes of antioxidant nutrients (vitamin C, β-carotene, selenium) and vitamin D and faster 3 minute walk times among women at midlife but not among men. However, this study was cross-sectional and investigated only specific nutrients rather than diet quality; hence it did not reflect on the synergistic and holistic effect of diet. Finally, recent evidence from the NSHD in the UK revealed a longitudinal cumulative sex-specific effect of dietary patterns over 30 years in adulthood, which were rich in nutrients important for bone health, on bone mineral density in late midlife [217]. The associations between diets rich in Ca, K and protein were positive and significant for women but null for men. This study added valuable evidence on potential sex-specific associations of diet and age-related bone mass; yet dietary patterns were a posteriori and bone mineral density represents only a single domain of the musculoskeletal system rather than overall functional status with ageing.

With regard to walking speed, a recent cross-sectional study of 380 middle to older aged men and women in Spain, showed a positive significant association between a posteriori “healthy” dietary patterns and walking speed in men but not women [203]. Furthermore, they also found a detrimental effect of a posteriori “unhealthy” dietary patterns on walking speed, lower limb strength, agility and aerobic ability in both men and women. Although sex-specific associations were revealed in this study, the cross-sectional design and diet being assessed a posteriori largely limit the impact of these findings. The most relevant evidence on sex-specific associations between diet quality and physical and muscle function comes from the Helsinki Birth Cohort Study in Finland, where among ~1,100 well-functioning men and women, higher diet quality by Nordic diet score at late midlife was associated with greater grip and leg strength 10 years later, only in women but not men [227]. Findings were very similar and sex-specific for physical performance as measured by the Senior Fitness Test in the same study, in which higher Nordic diet scores at midlife reflected 15-20% better results in walk tests, chair rise stands and arm curls 10 years later only in women [204]. These studies reinforced the concept of potential sex-specific effect of diet over the lifespan on physical function with ageing; still a Nordic diet is region-specific and dietary assessment was done only at late midlife. Deriving

from this evidence, it would be therefore very important to expand these sex-specific relationships to non-regional dietary indices over adulthood and objective measures of later life physical function and according to this literature summary, there is a great potential in this area.

2.5 Summary/Research Gap

The relationship between diet and physical function with ageing is an important research topic. To date, understanding about this relationship is derived from evidence from observational studies and interventions on measures of ageing, physical performance or physical capability. Some studies focus on important systems and functions of mobility with ageing such as muscle, bone and fat mass. Some other use measures of physical function like performance and functional tests, while other explore the impact of cognitive status on healthy ageing. Regarding diet, some research focuses on specific nutrients or food groups, whereas others highlight the importance of diet as a whole. As a general conclusion, the hypothesis of a beneficial effect of diet on healthier physical and cognitive function with ageing is supported. However, to fully understand the relationship, there are many specific research questions that need to be addressed.

This summary of literature supports a protective effect of diet quality against physical and cognitive decline by self-perceived indices of quality of life and self-reported questionnaires [132, 228, 229], muscle mass and strength changes [139, 141, 142, 144, 145, 159, 160, 164, 191, 227, 230-232], diagnosis of frailty and sarcopenia [126, 138, 147, 160-162, 233-235] and objective measures such as grip strength, timed up and go test, balance tests and chair rise test [146, 150, 151, 153, 155, 156, 188, 195]. However, evidence is scarce for objective measures of walking speed, which reflects both physical and cognitive decline and is tightly linked to daily activities in older people, with only a few studies exploring this relationship (Table 2.1). The impact of diet quality on walking speed is of vital relevance for older people because walking is involved in most everyday actions and therefore this thesis will explore this relationship.

This review also showed that studies on diet and walking speed to date focus on specific nutrients [152, 193, 197, 199, 236], on dietary patterns applicable to ethnic populations [162, 204, 207, 209] or on *a posteriori* patterns [203, 205, 206]. Most studies found a protective effect of diet against slow walking speed; yet investigating single nutrients explains only a single dimension of the relationship, foods are consumed in combination and *a posteriori* approaches are sample-specific and are not derived from evidence-based knowledge. Moreover, regional dietary patterns, despite valuable, may be limited to specific ethnic populations and thus not generalizable. To date, investigation of the relationship between diet quality in line with dietary recommendations and objective measures of walking speed in older adults is scarce, if any. Therefore, there is a significant gap in exploration of this relationship.

This summary of literature has also found a gap in the knowledge regarding the link between diet quality and walking speed as an indicator of cognitive decline in older age. To date, a large volume of studies has shown a protective effect of diet directly on cognition and age-related cognitive decline [176, 179, 181, 182, 237]. However, there is no evidence for the impact of diet on walking speed in CMI paradigms, which has been shown to be a good indicator of the overall function with ageing [89]. Hence, this will be the first thesis to originally investigate this relationship.

Maintenance of a healthy diet at early older age has been shown to be of great importance for healthier ageing [188] and this thesis intends to add evidence to this hypothesis. This literature summary also revealed that most studies explored dietary intake at one time point at early older age [162, 204, 207, 208, 210], with the exception of some evidence for a cumulative effect of diet on physical function, but not directly on walking speed [184, 186, 188]. Ageing is a complex procedure, deriving from accumulation of impairment over time. Furthermore, physiological and functional changes across the lifespan are present well in advance before actual functional decline is observed. Hence, it is very important to extend current understanding on

the relationship between the cumulative effect of diet over longer periods in life and walking speed in later life considering the lack of evidence.

As described in page 32, the present literature summary has revealed a significant lack of evidence on exploration of potential sex differences in the relationship between diet and physical function. This thesis will further contribute to knowledge by assessing potential modification effect by sex, considering these well-established sex differences. In addition, the age of the participants in most studies varied and in most cases a threshold of age 60 was set to reflect the “early older age”. However, in terms of walking speed, no study was conducted on a sample where all participants were of same age and historical period (generation). Hence, this thesis will provide novel evidence on the topic by including people from a birth cohort and thus being more homogenous with regard to dietary exposure. Finally, it is expected that older people will suffer higher rates of age-related functional decline compared to younger ones. This results in most studies including mainly already declined older individuals when assessing diet in relation to physical function. Therefore, this thesis will originally contribute to knowledge by including a population of generally well-functioning older adults, albeit ageing. Overall, the present thesis intends to bridge all scientific gaps described above.

Table 2.1 Summary of key studies on the relationship between dietary patterns and walking speed.

Authors	Description of study	Results
Hengeveld et al., (2019) [201]	Prospective (4 years follow-up) N=2,154, age 70-81, the US Measures: Healthy Eating Index (HEI, 0-100), poor: <51, medium: 51-80, high: >80 Outcome: 20-m WS with cut-off 1.0 m/s (frailty main endpoint)	WS (<1.0 m/s): n=390 (18.2% of N) A null association between HEI and slowness but lower plant protein was associated with higher incidence of slowness.
Isanejad et al., (2018) [162]	Cross-sectional/prospective (3 years follow-up) N=554 women, age 65-72, Finland Measures: MedDiet (MED, 0-8), Baltic Sea diet (BSD, 0-25), Q4 (7-8 and 16-25) vs Ref (0-3 and 0-9) and continuous Outcome: 10-m WS at maximum pace	WS (sd), m/s, Ref-1.59 (0.33) – Q4-1.81 (0.31) 1 point increase in BSD was associated with 0.13 [0.01] m/s mean difference in WS at baseline (multivariable). 1 point increase in MED was associated with 0.09 [0.01] m/s mean difference in WS at baseline (multivariable). No significant association over 3 years. WS for any diet, although women in Q4 MED had less decline in WS -0.18 [0.03] m/s than Ref -0.44 [0.03] m/s.
Bibiloni et al., (2017) [203]	Cross-sectional N=380, age 55-80, Spain Measures: “MedDiet” (MED) and “Westernized” (WD), CAT4 vs Ref Outcome: 30-m WS at usual pace	WS [95% CI], m/s (women), Ref- 2.38 [2.21, 2.56], WDCAT4- 2.07 [1.99, 2.17], Ref- 1.81 [1.73,1.89], MEDCAT4- 1.94 [1.85, 2.04] (men), Ref- 2.38 [2.21, 2.56], WDCAT4- 2.07 [1.99, 2.17], Ref- 2.22 [2.11, 2.36] MEDCAT4- 2.44 [2.31, 2.61] WDCAT4 vs Ref was associated with slower WS in men and women ($p<0.001$, multivariable). MEDCAT4 vs MEDCAT3 was associated with faster WS in men but not women ($p<0.05$), multivariable).[208]
Perala et al., (2016) [204]	Prospective (10 years follow-up) N=1,072, age 61, Finland Measures: Nordic diet (NDS, 0-25), Q4 (14-25) vs Ref (0-10) and continuous Outcome: 6-min WS	WS [SE], m/s, (women), Ref-0.88 [0.04], Q4-1.18 [0.05], (men), Ref-1.08 [0.04], Q4-1.25 [0.06], $p<0.05$ 1 point increase in NDS was associated with 0.015 m/s (95% CI 0.002, 0.028) faster WS in men, controlled for age. 1 point increase in NDS was associated with 0.015 m/s (95% CI 0.006, 0.025) faster WS in women (multivariable).

WS: walking speed, MedDiet: Mediterranean diet, Q: quartile, Ref: reference, CAT: category

Continued Table 2.1

Authors	Description of study	Results
Zbeida et al., (2014) [207]	Cross-sectional N=2,791, age 71, the US Measures: MedDiet (MED, 0-9), CAT3 (6-9) vs Ref (0-2) and continuous Outcome: 6-m WS	WS (sd), m/s, Ref-0.75 (1.38), CAT3: 1.39 (2.16) MED (CAT3 vs. Ref) was associated with 29% (95% CI 0.51-0.97) higher odds of having faster WS (p=0.03, multivariable), but attenuated by cognitive status. 1 MED point increase was associated with 6% (95% CI 0.88-0.99) lower risk of slower WS (p=0.03, multivariable).
Leon-Munoz et al., (2014) [206] (2015) [205]	Prospective (3.5 years follow-up) N=1,872, age 68-70, Spain Measures: MedDiet (MEDAS, 0-14, MED, 0-9), "prudent" (PD) and "Westernized" (WD) diets, CAT3 vs Ref Outcome: slow or fast WS at usual pace (4.57-m walk)	Slow WS, (women): Height ≤1.59 m and WS ≤0.65 m/s or Height ≥1.59 m and WS ≤0.76 m/s, (men) Height ≤1.73 m and WS ≤0.65 m/s or Height ≥1.73 m and WS ≤0.76 m/s High WD (CAT3 vs Ref) was associated with 1.85 fold higher risk (95% CI: 1.19-2.87) of slow WS over 3.5 years (multivariable). High MEDAS (CAT3: 9.1 vs Ref: 5.2) was associated with 47% lower risk (95% CI: 0.35-0.79) of slow WS over 3.5 years (multivariable). A null association for PD or MED.
Bollwein et al., (2013) [208]	Cross-sectional N=192, age 83, Germany Measures: MedDiet (MED, 0-9), Q4 (6-9) vs Ref (0-3) Outcome: slow or fast WS at usual pace (4.57-m walk)	Slow WS, (women): Height ≤1.59 m and WS ≤0.65 m/s or Height ≥1.59 m and WS ≤0.76 m/s, (men) Height ≤1.73 m and WS ≤0.65 m/s or Height ≥1.73 m and WS ≤0.76 m/s prevalence: 22% High MED (Q4) was associated with 71% lower odds (95% CI: 0.09 -1.00) of having low walking speed vs low MED (Ref) (p=0.043, multivariable).

WS: walking speed, MedDiet: Mediterranean diet, Q: quartile, Ref: reference, CAT: category

Continued Table 2.1

Authors	Description of study	Results
Xu et al., (2012) [210]	Cross-sectional N=2,132, age 70, the US Measures: Healthy Eating Index (HEI-2005, 0-100), Q4 (72, 66-91) vs Ref (37, 15-46) and continuous Outcome: 6-m WS at usual pace	WS [SE], m/s, Ref 0.95 [0.02], Q4-1.00 [0.01] High HEI-2005 (Q4 and Q3 vs Ref) was associated with 0.03 [0.02] m/s mean difference in WS (p=0.03, multivariable), but attenuated by physical activity levels.
Shahar et al., (2012) [209]	Cross-sectional/prospective (8 years follow-up) N=2,225, age 74, the US Measures: MedDiet (MED, 0-9), CAT3 (6-9) vs Ref (0-2) Outcome: 20-m WS at usual/rapid pace	Usual WS (sd), m/s: Ref-1.15 (0.19), CAT3: 1.19 (0.19) Rapid WS (sd), m/s: Ref-1.55 (0.31), CAT3: 1.65 (0.30) Faster walking speed was more likely within the high MED category for both usual and rapid speed at baseline (p=0.02, multivariable). Over 8 years, both usual and rapid 20-m walking speed declined in all MED groups. Higher MED (CAT3 vs ref) predicted less decline in usual WS (p=0.049, multivariable), but attenuated by body fat but not in rapid WS (p=0.134, multivariable).
Talegawkar et al., (2012) [211]	Prospective (6 years follow-up) N=690, age 73, Italy Measures: MedDiet (MED, 0-9), CAT3 (6-9) vs Ref (0-3) Outcome: slow or fast WS at usual pace (4.57-m walk)	Slow WS, (women): Height ≤1.59 m and WS ≤0.65 m/s or Height ≥1.59 m and WS ≤0.76 m/s, (men) Height ≤1.73 m and WS ≤0.65 m/s or Height ≥1.73 m and WS ≤0.76 m/s High MED (CAT3 vs Ref) was associated with 52% lower risk of slow WS (95% CI: 0.27, 0.86, multivariable).
Milaneschi et al., (2010) [196]	Prospective (follow-up: 3, 6 and 9 years) N=935, age 74, Italy Measures: MedDiet (MED, 0-9), CAT3 (6-9) vs Ref (0-3) Outcome: 4-m WS at usual pace	WS: 1 if ≤0.42 m/s, 2 if 0.43-0.58 m/s, 3 if 0.59-0.75 m/s, 4 if ≥0.76 m/s High MED (CAT3 vs Ref) was associated with better lower body performance including WS at baseline and less decline at year 3, 6 and 9 (p<0.05, multivariable).

WS: walking speed, MedDiet: Mediterranean diet, Q: quartile, Ref: reference, CAT: category

2.6 Aims and Objectives

Aim

The main aim of this thesis was to investigate the relationship between diet quality in late midlife and over adulthood and walking speed in later life, indicating age-related overall, physical and cognitive function. Hereafter, the term “late midlife” refers to age 60-64, the term “adulthood” refers to the period from age 36 to 64 and the term “later life” refers to age over 70.

Hypothesis

The thesis was designed to test the following: first, it was hypothesized that people who had a presumably high diet quality in late midlife compared to those with low diet quality, would have a better profile of physical function, as indicated by faster walking speed in later life. Second, it was hypothesized that high diet quality in late midlife would also reflect faster walking speed and reduced CMI cost in older life, when a cognitive task was performed concurrently with walking, thus additionally indicating cognitive function in older life. Finally, it was hypothesized that the magnitude of this relationship would be greater when investigating the cumulative effect of high diet quality over longer periods in adulthood.

Objectives

The general objectives of the thesis are presented in this section. Specific objectives of each study are described in the relevant chapters. Overall objectives were:

1. The extent to which diet quality in late midlife and over longer periods in adulthood, in line with dietary guidelines, was associated with walking speed in later life, reflecting age-related physical function.

2. The extent to which diet quality in late midlife and over longer periods in adulthood, in line with dietary guidelines, was associated with walking speed and CMI cost when walking and concurrently performing a cognitive task in later life.
3. The extent to which there was a relationship when modified by sex.
4. The extent to which there was a relationship with increasing complexity of the cognitive task while walking.
5. The extent to which individual dietary components were associated with walking speed and CMI cost in later life.

Chapter 3 - Methodology

3.1 Summary

This chapter provides an extensive overview of the methodology used across this thesis. The study population is introduced and the data used including all diet, walking speed and descriptive characteristics are presented. The statistical methods applied are also discussed and the maximum sample size for this thesis is described.

3.2 Study Population

The thesis will utilize data from participants in Insight 46 (n=502), initiated in 2014, which is a sub-study of the Medical Research Council (MRC) National Survey of Health and Development (NSHD), a British birth cohort that initially comprised 5,362 men and women, born in 1946.

3.2.1 National Survey of Health and Development

The MRC 1946 NSHD is a longitudinal study of a nationally representative cohort of 5,362 registered single births within marriage (2,547 males and 2,815 females) in Britain. All births occurred during the first week of March 1946 across mainland Britain (England, Wales, and Scotland) [238].The cohort is stratified by social class and geographical distribution.

Initially, between 3rd and 9th of March 1946, all legitimate births were recorded (N=16,695). Health visitors contacted local authorities, of which 92% responded, listing 15,130 new mothers, eight weeks after birth. After checking the clinic notes, health visitors successfully interviewed 13,687 of them (1.9% refused, 7% untraceable), which accounted for 82% of total births in that week (Figure 3.1). Out of those interviewed (via their mothers) in 1946, *Douglas et al. (1958)* [239] randomly selected a follow-up sample of all legitimate single births from non-manual and agricultural married couples and one out of four single births from manual married

couples. This resulted in a sample of 5,362 children which were representative of the social and geographical distribution of the post-war national native born population and which comprise the original population in the NSHD.

The cohort has been followed up prospectively 24 times, with the follow-up period covering all life stages including birth, toddler/infant (ages 2 and 4), schoolchild (ages 6, 7, 8, 9 and 10), adolescence (ages 11, 13, 15 and 16), early adulthood (ages 18, 19, 20, 22, 23, 25 and 26), mature adulthood (ages 31, 36, 43 and 53) and late adulthood (ages 60-64 and 68-73) (Table 3.1). Despite the long duration of the cohort, response rates and adherence have been maintained high across all ages, limiting attrition rates[10] and loss to follow-ups to minimum levels [240-242] (Table 3.1). During the latest follow-up (24th, 2014, age 68), 2,816 study members were still alive in mainland Britain [243].

[10] Occurs when "participants drop out during a study. A typical example in longitudinal studies is attrition due to multiple follow-ups" [64]. See 7.3 Methodological Considerations.

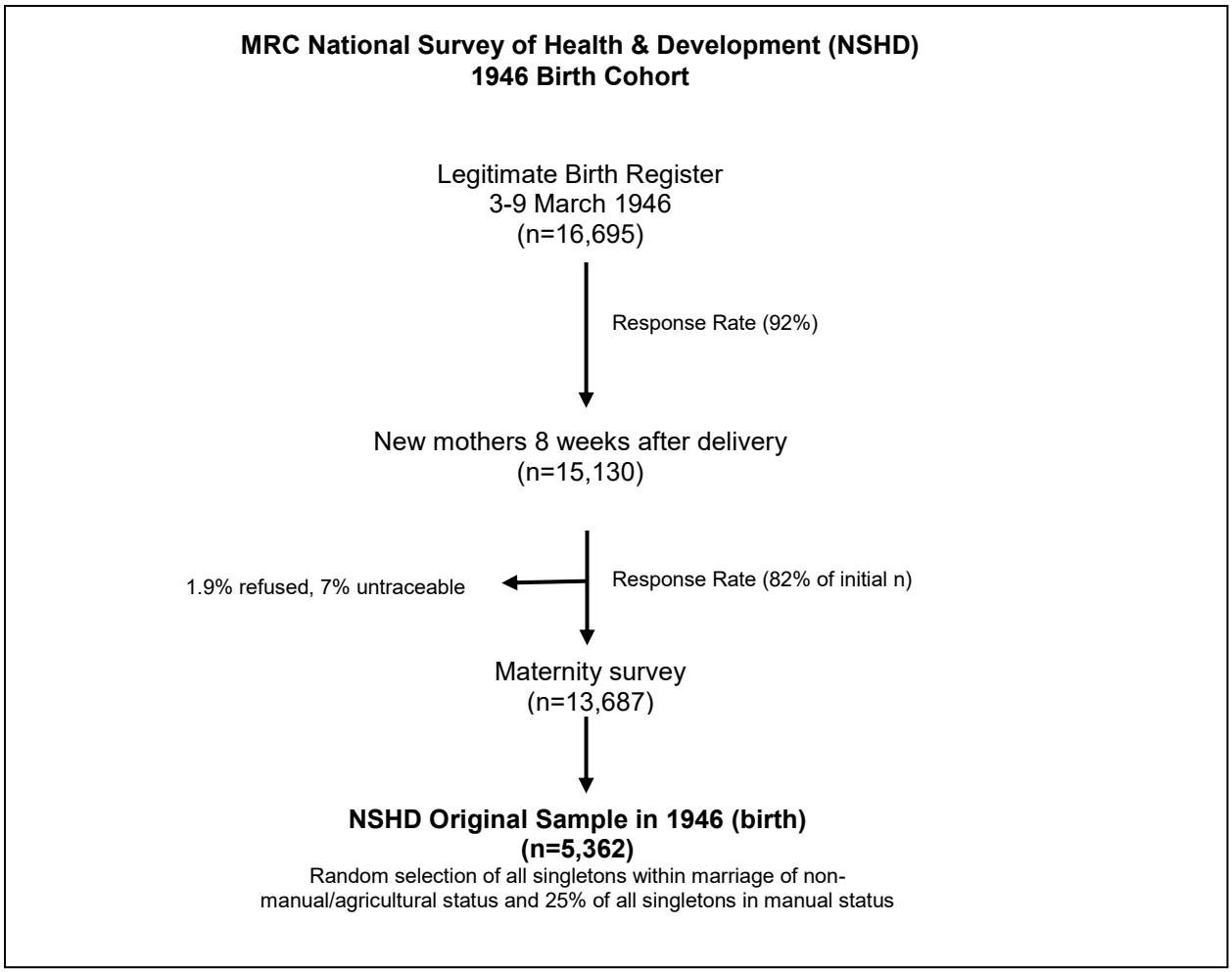

Figure 3.1 The 1946 sample collection procedure and the original sample of the NSHD[11]

[11] Modified version of [239].

Table 3.1 Available population within the NSHD at each age of data collection [12]

		Population not available				Population contacted	
		Cumulative Total		Abroad in Period			
Year	**Age in years (no. of assessments)**	**Deaths**	**Refusal**	**Living abroad /Emigrated**	**Unable to contact**	**Successfully contacted**	**% of previous period**
Means (each age period)					(cumulative)		
1946-50	0-4 (2)	230	1	190	452	4,695	88%
1951-61	5-15 (8)	253	1	305	516	4,307	92%
1962-81	16-35 (9)	321	158	460	953	3,538	82%
Total (each contact year)					(cumulative)		
1982 [1]	36 (1)	323	520	644	553	3,322	94%
1989 [1]	43 (1)	365	540	618	588	3,262	98%
1999 [1]	53 (1)	469	640	580	638	3,053	93%
					(>10y)		
2006-2010 [1]	60-64 (1)	718	594	567	320	2,662	87%
2014-2017 [2]	68-71 (1)	957	620	574	395	2,648	99%

[1] Ages of interest: Dietary data was collected at ages 36, 43, 53 and 60-64 and screening of dietary choices at age 69-71.
[2] Ages of interest: Gait data was collected only in the sample of the sub-study Insight 46 at age 69-71.

[12] Modified version of [241].

Research questions were formed according to public health hazards at each follow-up resulting in available data to vary at each age (Appendix 1). The rationale to establish the cohort in 1946 was that fertility was falling and the scope was to "*to explore the cost of and care in pregnancy and child birth*" [241]. An extensive summary of data collected at each age and the specific method and measurement type used has been published by *Wadsworth et al. (2003, 2006)* [241, 244]. Among the data collected during the 70-year period (1946-2017), the most common methods used were postal questionnaires, physical examination and interviews by research nurses and health visitors [241]. During the follow-ups all lifestyle, including dietary data, socioeconomical, educational, medical, anthropometric, musculoskeletal, cognitive, mental and health data were collected (Table 3.2).

The study was conducted in agreement with ethical guidelines of the Declaration of Helsinki at all ages and all actions involving human participants were approved by various ethical centres including all: the Bristol and Weston Health District (age 36), the Joint UCL/UCLH Committee on the Ethics of Human Research (age 43), the North/Central Thames Multi-Centre Research Ethics Committee (age 53), the Greater Manchester Local Research Ethics Committee, the Scotland A Research Ethics Committee (age 60-64), and the Queen Square Research Ethics Committee (age 68-71). Written informed consent was obtained from all study members (or their mothers) at all ages of data collection. A detailed summary of history of consent and ethical approval is attached as Appendix 2.

Table 3.2 Overview of life course data available for the NSHD study participants[13]

	Age of Assessment (years)						
	Birth (1946)	**(1-4)**	**(5-15)**	**(16-31)**	**(32-53)**	**(60-64)**	**(68-71)**
No of data collections	1	2	8	8	3	1	1
Measures							
Socioeconomic status	✓	✓	✓	✓	✓	✓	✓
Social status	-	-	-	-	✓	✓	✓
Occupation	-	-	-	✓	✓	✓	✓
Behaviour and mental health	-	✓	✓	✓	✓	✓	✓
Comorbidity	✓	✓	✓	✓	✓	✓	✓
Anthropometric measures	✓	✓	✓	✓	✓	✓	✓
Smoking status	n/a	n/a	n/a	✓	✓	✓	✓
Exercise and physical health	n/a	n/a	✓	-	✓	✓	✓
Diet [1]	-	✓	-	-	✓ **(3 times) (36, 43, 53)**	✓ **(1 time) (60-64)**	-

n/a: non-applicable

[1] Measure of interest for this thesis.

[13] Modified version of [245].

Continued Table 3.2

	Age of assessment (years)						
	Birth (1946)	**(1-4)**	**(5-15)**	**(16-31)**	**(32-53)**	**(60-64)**	**(68-71)**
No of data collections	1	2	8	8	3	1	1
Respiratory function	-	-	-	-	✓ (3 times) (36, 43, 53)	✓	✓
Cardiovascular function	-	-	-	-	✓ (3 times) (36, 43, 53)	✓	✓
Musculoskeletal measures/Mobility	-	-	-	-	✓ (53)	✓	✓
Blood samples	-	-	-	-	✓ (53)	✓	✓
Urine sample	-	-	-	-	-	✓	-
Cognitive function (verbal/non-verbal)	-	-	✓ (8, 11, 15)	✓ (26)	✓ (43, 53)	✓	✓

3.2.2 Insight 46

For this thesis, a sub-sample of 502 randomly recruited participants from the original NSHD was used, who comprise the Insight 46. An extensive study protocol paper with detailed overview of sampling eligibility and data collection procedure has been published by *Lane et al. (2017)* [245]; a modified version of the consort chart of the study as described and published by *James et al. (2018)* [246] is presented in Figure 3.2.

Insight 46 is a prospective two time-point neuroscience sub-study of the NSHD which was initiated during the latest follow-up among 2,689 original NSHD study members who were aged 69, lived in Britain and were in active follow-up. The rationale for Insight 46 was to explore functional measures, in particular age-related cognitive decline, considering that 30% of adults of this age group are likely to be in preclinical stages of chronic neurodegenerative diseases [245]. They were old enough to be considered at high risk of pre-dementia pathology but young enough to be considered at high risk of incident dementia. Inclusion criteria were set on the basis of maximizing the life course data collected during previous follow-ups (Table 3.3). To eliminate the possibility of biasing sampling collection procedure in terms of who might be at risk of cognitive decline or not, original NSHD study members were invited to participate in Insight 46 if meeting the following: (1) availability of prior life course data in NSHD, (2) participation in the clinic assessment at age 60-64 and (3) willingness to attend a London-based clinic [245, 246].

All participants who were eligible and gave written consent (n=841), attended a clinic visit twice (ages 69-71 and 71-73) and went through an extensive battery of clinical, neurological and cognitive assessments (Table 3.2). They were also asked to perform a gait assessment [245]. Ethical approval for Insight 46 was obtained from the Queen Square Research Ethics Committee (14/LO/1173) (Appendix 2).

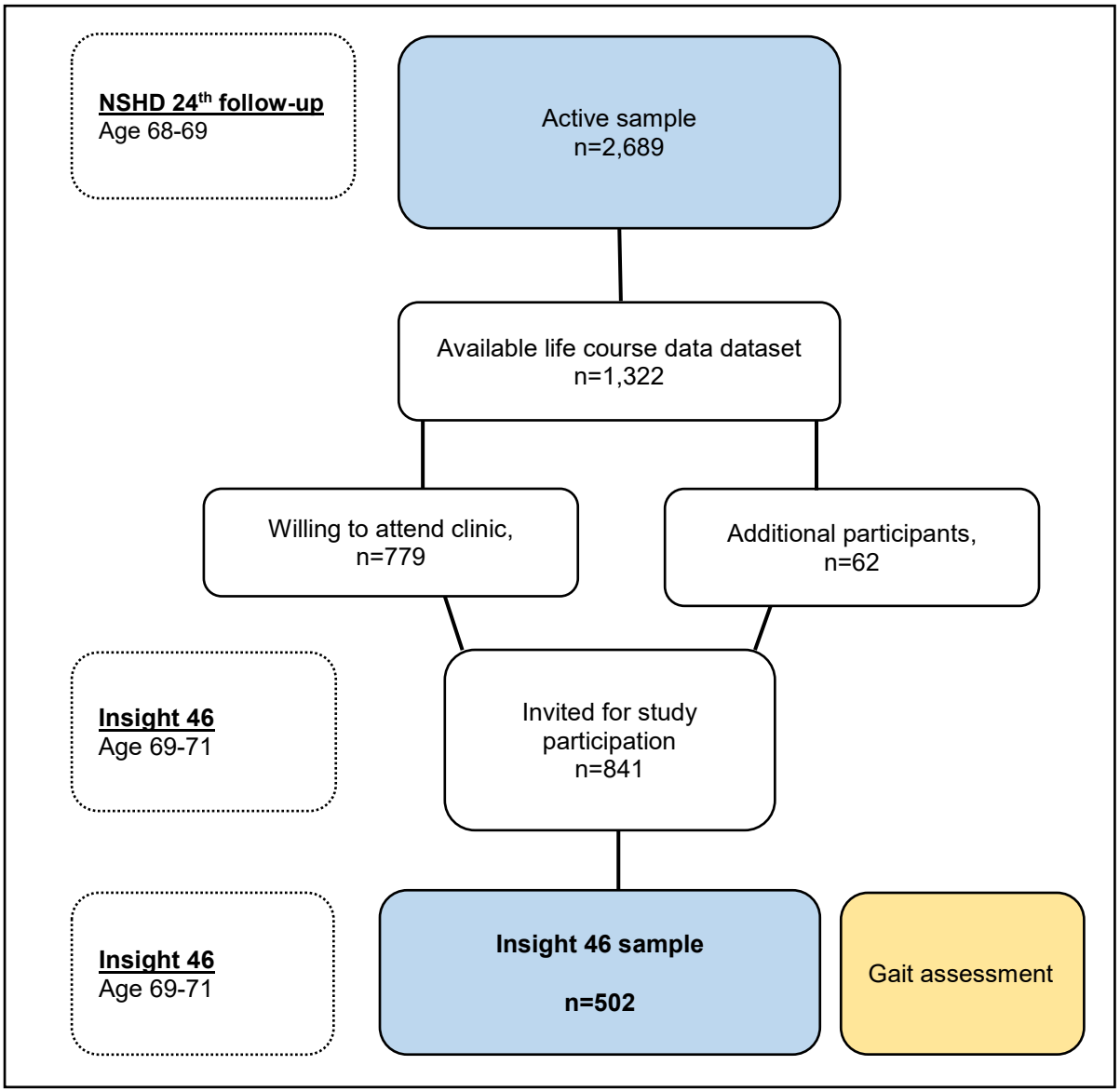

Figure 3.2 Consort chart of the Insight 46[14]

[14] To reach sample of 500, participants without full set of life course data were also included.

Table 3.3 Inclusion criteria for Insight 46[15]

- Participation at a clinic visit at age 60-64.
- At least one indicator of parental occupational social class or education.
- Highest education qualification by age 26.
- Health behaviours: at least one measure of smoking and physical activity at age 36, 43, 53 or 60-64.
- Memory and processing speed at age 60-64 **AND** at least one set of measures at either age 8, 11 or 15.
- Blood pressure, lung function, adult height and weight: at least one measure of each at age 36, 43, 53 or 60-64.
- Teacher ratings of behaviour and temperament at age 13 or 15, **AND** at least one measure of affective symptoms at age 36, 43, 53 or 60-64.
- Birth weight and at least one measure of height and weight at age 4-15.
- Blood sample either at age 53 or 60-64.

[15] Modified version of [245].

3.2.3 Representativeness

Due to its methodological design, the NSHD sample is not completely representative of the general adult UK population in terms of the following: sampling procedure did not include multiple births and those out of marriage; hence there is no representation of these sub-groups [241]. Since recruitment, there has been a dynamic change in the migration rates from and to the UK, resulting in an increased variation of ethnic groups. The initial sample consisted of wholly white natives, therefore it is not representative of the current UK population [240]. Moreover, loss to follow-up since baseline has revealed an overall pattern of mainly less representation of people with lower educational attainment and lower social class [244]. To date, there have been multiple studies on the representativeness and response rates of the NSHD [238, 240, 241, 247]. At age 68-69, participation rates were still very high (Table 3.1). In general there has been a consistent continuous participation with more than two-thirds of participants having missed only a maximum of two out of 23 previous follow-ups, with distribution by sex still being fairly equal [243]. Participants at age 60-64 with lower childhood cognition, lower educational attainment and higher lifetime smoking habits were less represented in the study [247]. At ages 43 and 53, there was an over representation of people who had a professional or intermediate job, were home owners and of widows, whereas educated men and single people were somewhat underrepresented [241]. However, indication of mis-representativeness was small in most cases and when compared with the 2001 England Census reference population, occupational social class and unemployment status were not significantly different [241, 247]. Finally, it is important to mention that at age 60-64, the NSHD sample was more advantaged in terms of limiting illness and thus reflected an overall healthier sub-population [247]. As expected, at age 69, presence of multi-morbidity and severe ill-health was a significant reason of loss to follow-up [243]. Overall, it can be claimed that the NSHD is still fairly well representative of the white post-war UK population.

Regarding Insight 46, given it is a sub-cohort of the original NSHD, its representativeness is within the same limitations. Participants were randomly selected from the original NSHD, no

selection bias[16] towards higher risk of cognitive decline were made and inclusion criteria were based only on capitalizing life course data from previous follow-ups. However, survivors at age 69 were generally healthier and more likely to be more health conscious as they had provided life course data at previous ages, as compared to non-participants [245]. Indeed, people with better cognition, smoke-free life and better self-perception of overall health were over represented in Insight 46, and additionally individuals with lower educational attainment and lower socio-economic position were under presented [246]. Regarding gait assessment, only individuals who could complete the walks independently were included and therefore people with mobility issues and severe cognitive decline are not represented in this study. Therefore, it is highly likely that Insight 46 underestimates the life course hazards and rates of health outcomes of the general population [246], but such underestimation is not expected to influence internal validity of findings in this thesis.

3.3 Data Used in This Thesis

Data in this thesis was from participants in Insight 46, who underwent gait assessment at age 69-71 (2015-2017) and also participated in as many as possible of the following dietary assessments of the NSHD: age 36 (1982), age 43 (1989), age 53 (1999), age 60-64 (2006-2010). Hereafter, all assessment points will be referred as age at assessment and a visual representation is provided in Figure 3.3. Details of all variables used are described in the next sections. In general, some variables were unavailable at some ages due to data collection being modified or not performed (Table 3.2 and Table 3.5).

[16] Occurs when "*there is distortion in a measure of association between exposure and health outcome due to a sample selection in which those who complete a study do not accurately reflect the target population"* [64]. See7.3 Methodological Considerations

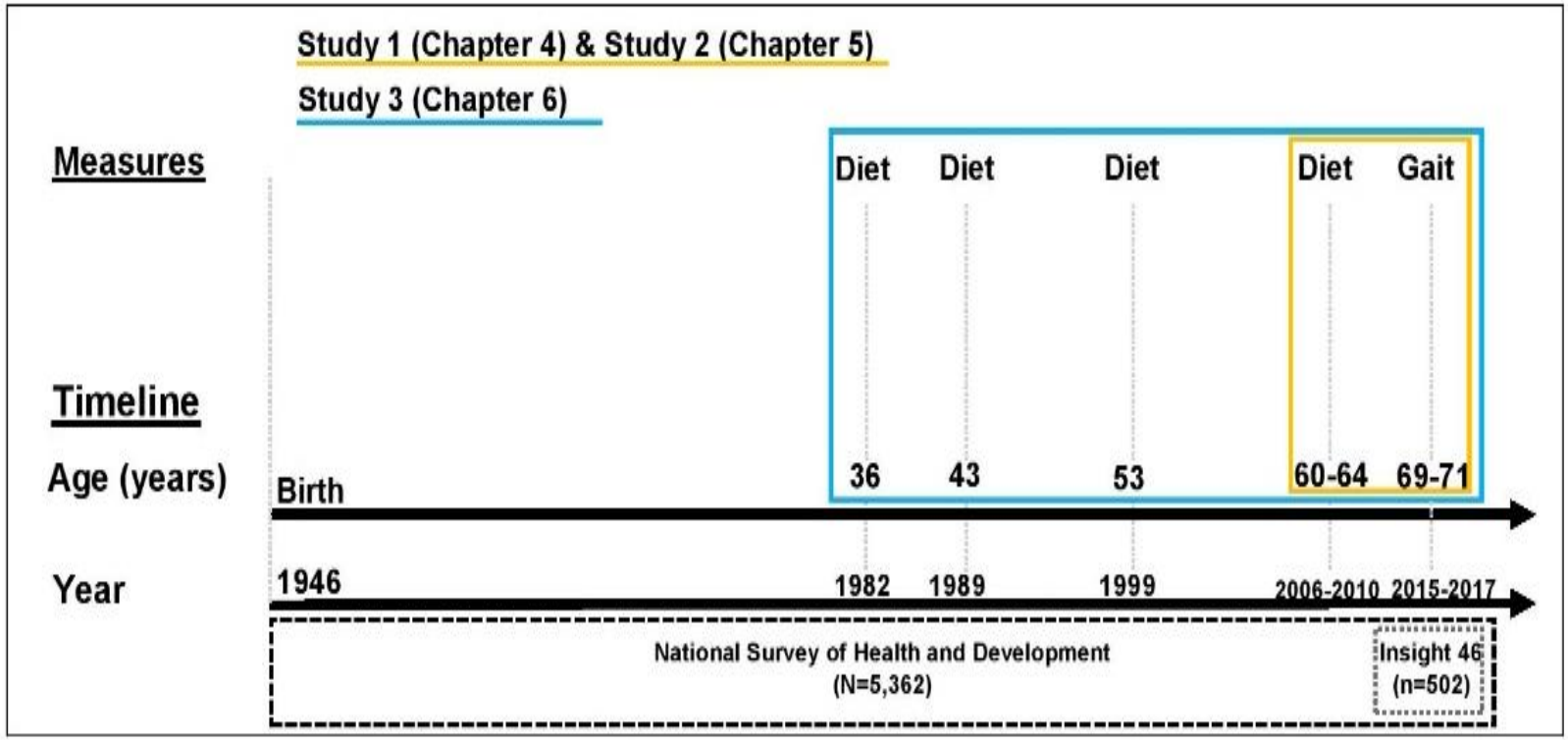

Figure 3.3 Visual representation of availability of dietary and gait data used in the thesis, by assessment age

3.3.1 Dietary Assessment

Food Diaries in NSHD

Dietary data for NSHD was collected when participants were aged 36, 43, 53, and 60-64 (Figure 3.3). A brief screening tool of dietary habits was also administered at age 68-71, but will not be used in this thesis, because comparability with dietary data at earlier ages would not be direct. At ages 36 (NSHD Bristol) and 43 (Dunn Nutrition Unit, Cambridge), two 24HRs and five-day estimated food diaries were used, while at ages 53 (Dunn Nutrition Unit, Cambridge) and 60-64 (MRC Human Nutrition Research, Cambridge) only the five-day diaries were applied.

Dietary assessment was introduced by research nurses during home or clinic visits at each assessment age. The two 24HRs were filled during the interviews with assistance by the nurses. The exact assessment procedure has been described in detail previously [248]. After receiving detailed guidelines and a demonstration, participants were asked to fill in diaries of all foods and drinks consumed anytime in any occasion (home or away) over five days within a week, including three weekdays and two weekend days if possible. They were also asked to record the type and estimated portion sizes based on household measures, food labels and brand names of products and also report recipes and preparation methods. Further guidance was provided by portion size photographs and notes. The diaries were similar in all four occasions with slight differences in supplement use sections. Food diaries were completed between spring and autumn (April to September at age 36, June to October at age 43, and May to November at age 53), whereas dietary assessment was conducted throughout all seasons at age 60-64.

After quality control, dietary information was converted into food codes and weights, using a computerized data-entry program [249]. Using an in-house software with more than 2,000 registered food items (Diet In, Data Out at ages 36-53 - Diet In, Nutrients Out at age 60-64)

[250] all diary entries were then categorized into food groups, sub-groups and food items corresponding to portions and weights. These were converted into average daily nutrient intakes, based on the UK standard portion size reference food tables by McCance and Widdowson's "The Composition of Foods Series" [251]. When nutritional values were missing, data from the Food Standards Agency portion sizes [252], from recipes as described by participants or from manufacturers were used. Due to differences in food availability and dietary recommendations, food groups and single items might differ between assessment ages. For this reason they have been all recoded using the latest software at age 60-64 to allow for direct comparisons and dietary tracking over time. In total, 98 food sub-groups and food items, including beverages were obtained. Food groups and sub-groups were formed by aggregation of food items based on type and nutritional content similarity, using identical methodology as in the National Diet and Nutrition Survey (NDNS) in the UK [253]. Finally, intakes for each day were aggregated at each assessment age to produce mean daily intakes of foods, energy, macro and micronutrients.

In this thesis, only those who completed at least three days of food diaries at each age were included. Data from two 24HRs were not used in any analysis, for consistency with previous evidence from the NSHD [248]. The food diaries have been validated [254] and recommended energy cut-off points (<500 kcal, >3,500 kcal for women, <800 kcal, >4,000 kcal for men) were applied to account for misreporting of dietary intake [44]. Intakes of dietary supplements were not included in main analyses due to differences in availability and coding between assessment points. For secondary analyses, participants who reported at least one supplement (vitamins, minerals, bioactive compounds) at any day of food diaries at age 60-64, were considered as users.

Rationale for Use of Food Diaries

Five-day estimated food diaries were used on the basis of prior evidence on method validation and because of their overall advantages over other methods, when used in long-range

epidemiological studies. First, food diaries provided detailed and accurate information on all food and beverage types over the years and thus allowed for unlimited food items to be included and analysed [42]. In addition, changes in food habits, food availability and food industry and updates on health recommendations were taken into account [42]. This would not be possible if FFQs were used because reporting only consumption frequency of pre-defined food items, would not capture actual dietary changes over the years. Second, five-day diaries were chosen to account for daily variation in diet including weekdays and weekends; seasonality was also taken into account, in particular during assessment at age 60-64 when diaries were completed throughout all seasons [248]. This approach also allowed sporadically consumed food items to be captured. Furthermore, this method limited reliance on participants' memory, gathered additional information on eating occasions and achieved accuracy of diet coding by using concurrent food databases to estimate portion sizes. Selection bias is always a case when administering methods which require high literacy and respondent burden [42, 45]; yet all participants received detailed training and response rates of at least three days of diaries were 84% of those participated in clinic or home visit at age 60-64, out of which 98% adhered for all five days [248].

Measurement error, which is present to some extent in all dietary assessment methods, has been suggested to be of less importance when describing overall dietary patterns [188]. Well-trained researchers demonstrated successful completion of food diaries to participants, reviewed diaries after completion and performed quality control at all stages of dietary assessment, which has been shown to improve data quality [42, 248]. Using similar four-day estimated diaries on consecutive days, the NDNS conducted a feasibility study in 2007 among 1,067 people aged over four, to compare its potential versus four 24HRs on non-consecutive days [254]. They found that response rates were similar for the two methods (50%) and additionally diaries were more flexible and an easier tool to adapt in the study [254]. When compared against doubly-labelled water method, data from the NDNS showed energy

expenditure being underestimated when using food diaries, but it is assumed this was consistent throughout all ages of dietary assessment (from age 36 to 64) [254].

To limit the magnitude of respondent burden while achieving highest data quality, five-day estimated food diaries were used. Data from the EPIC UK revealed that seven-day estimated diaries, as compared with an FFQ and 24HRs, were in best agreement to 16-day weighed diaries, considered to be the 'gold standard', and also achieved high correlation with nutritional biomarkers [255-257]. In addition, seven-day diaries attenuated associations of regression models to lower extent than an FFQ and correlated higher with protein, potassium and sodium intakes from 24-hour urine samples [258]. Similarly, in the Cancer UK Norfolk cohort, seven-day diaries provided more accurate estimates of nutritional intakes of potassium and protein as compared to two FFQs among 145 healthy middle-aged people [259]. In recent validation studies, four-day food diaries were found to better reflect energy and protein intakes versus FFQs and three 24HRs among 450 postmenopausal women in the Women's Health Initiative, when tested against nutritional biomarkers [260]. Finally, evidence from the UK Women's Cohort Study further supported validity of four-day food diaries to capture intakes of major micronutrients, that was vitamin C and vitamin A, when tested against plasma levels of those nutrients [261].

3.3.2 The Healthy Eating Index

Background of the Healthy Eating Index

Research on nutrition has been traditionally conducted on single food items and nutrients; yet this approach does not consider the complex nature of diet as a lifestyle behaviour and the synergistic effect of food items and interactions of nutrients [200, 262]. Furthermore, people consume food in combination rather than nutrients in isolation, a concept which can be captured by analysis of dietary patterns.

Dietary pattern analysis has attracted growing interest recently by researchers because it expresses a wider and more holistic image of diet. It is also often used to form dietary recommendations which are more comprehensible to the general public than single nutrients [200]. Overall, dietary indices/scores are determined by evidence-based research and are powerful tools to assess quality and aspects of quantity of diet [262].

The Healthy Eating Index (HEI) is a useful measure of overall diet quality and of specific dietary components, independent of quantity, which was originally designed and described in 1994-1996 [263]. Since then, it has been revised three times, every five years (2005, 2010, and 2015) [264-266]. Since the original HEI-1995, the index has been re-developed in terms of composition and scoring system and has been tested in various occasions to assess associations with overall mortality [215], health outcomes [267] and biomarkers [268] and conformance to population dietary intakes [269]. The HEI-2015 has been updated to comply with and assess adherence to current evidence-based Dietary Guidelines for Americans (DGAs) [270]. In general, the HEI has been widely used worldwide and is considered a valid and reliable indicator of diet quality [215, 264, 271].

Profile of HEI-2015

HEI-2015 consists of 13 dietary components, ranges from 0 to 100 and puts emphasis on wide selection of food groups and nutrient density within caloric limits. Table 3.4 presents all HEI-2015 components alongside the scoring criteria for minimum and maximum score for each component. HEI-2015 consists of two categories; that is components to be consumed in “adequacy” (total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins and PUFA plus mono-unsaturated (MUFA) to saturated fatty acids ratio) and components in “moderation” (refined grains, sodium, added sugars and saturated fats). Most components are expressed per 1,000 kcal to account for variation in energy intake and its effect on health outcomes. Intakes between the minimum and maximum standards are scored proportionally. Two of the newly added components

(added sugars and saturated fat) are expressed as percentage of total energy intake to account for excessive “empty” caloric intake.

The main improvements made in HEI-2015 in comparison to previous versions are discussed in detail elsewhere [264]. In summary, legumes (pulses) contribute in four groups: total protein foods, seafood and plant proteins, total vegetables and greens and beans. Because legumes are not frequently consumed in non-Mediterranean populations, potential overestimation of those scores is possible only for specific sub-groups such as vegetarians or vegans, when legumes and nuts are likely to contribute significantly to total protein intake. Another improvement is the addition of saturated fat and added sugars as components in “moderation” instead of “empty calories” component in HEI-2010. This is in line with current DGAs to restrict energy intake from added sugars and saturated fat to 10% and 10% respectively [270]. Added sugars are all sugars that are not naturally present in food as sugars in milk and fruit and are added during manufacturing process or as an additive in foods [272]. Finally, alcohol is considered as contributing to total energy intake rather than a component of “empty calories” and considering most components are dense per 1,000 kcal, alcohol is included in the denominator when calculating scores [264].

Table 3.4 Original HEI-2015 components and scoring system[17]

Component	Minimum Points	Maximum Points	Standard for max score	Standard for min score (zero)
Adequacy				
Total Fruits [2]	0	5	≥0.8 cup [9] (~170g) equiv. per 1,000 kcal	No Fruit
Whole Fruits [3]	0	5	≥0.4 cup (~150g) equiv. per 1,000 kcal	No Whole Fruit
Total Vegetables [4]	0	5	≥1.1 cup (~160g) equiv. per 1,000 kcal	No Vegetables
Greens and Beans [4]	0	5	≥0.2 cup (~125g) equiv. per 1,000 kcal	No Dark Green Vegetables or Legumes
Whole Grains	0	10	≥1.5 oz [9] (~45g) equiv. per 1,000 kcal	No Whole Grains
Dairy [5]	0	10	≥1.3 cup (~320g) equiv. per 1,000 kcal	No Dairy
Total Protein Foods [6]	0	5	≥2.5 oz (~75g) equiv. per 1,000 kcal	No Protein Foods
Seafood and Plant Proteins [6,7]	0	5	≥0.8 oz (~25g) equiv. per 1,000 kcal	No Seafood or Plant Proteins
Fatty Acids [8]	0	10	(PUFAs + MUFAs)/SFAs ≥2.5	(PUFAs + MUFAs)/SFAs ≤1.2
Moderation				
Refined Grains	0	10	≤1.8 oz (~55g) equiv. per 1,000 kcal	≥4.3 oz (~130g) equiv. per 1,000 kcal
Sodium	0	10	≤1.1 gram per 1,000 kcal	≥2.0 grams per 1,000 kcal
Added Sugars	0	10	≤6.5% of energy intake	≥26% of energy intake
Saturated Fat	0	10	≤8% of energy intake	≥16% of energy intake

[1] Intakes between the minimum and maximum standards are scored proportionately [2] Includes 100% fruit juice [3] Includes all forms except juice [4] Includes legumes (beans and peas) [5] Includes all milk products, such as fluid milk, yogurt, and cheese, and fortified soy beverages [6] Includes legumes (beans and peas) [7] Includes seafood, nuts, seeds, soy products (other than beverages), and legumes (beans and peas) [8] Ratio of poly- and mono-unsaturated fatty acids (PUFAs and MUFAs) to saturated fatty acids (SFAs) [9] Cups correspond to 240-245 ml, 1ounce (oz) ~28-28.5 grams (g).

[17] Modified version of [264].

Rationale for Use of HEI-2015

HEI-2015 was selected to assess overall diet quality in this thesis given the absence of a national evidence-based dietary index for the UK. The DGAs 2015-2020 in the US [270], in line with which HEI has been designed, are similar and comparable to current UK dietary recommendations [273] and the "Eatwell Guide UK" [274], in terms of both food choices, energy and nutrients for all age groups. Both highlight the importance of optimal ratios of fatty acids (less saturated fat and more MUFAs and PUFAs), higher consumption of vegetables, fruit and whole grains, lower consumption of processed red meat and refined grains (including added sugars), all of which are reflected in the HEI. All recommendations and refinements in guidelines reflect current evidence for diet and disease, which is of major public health importance. For example, high intake of added sugars which substitute sugars from fruit and vegetables have been recently found to be associated with increased risk of obesity [275] and CVD [276]. In addition, both the DGAs 2015-2020 in the US and the "Eatwell Guide" in the UK focus on eating patterns and thus reflect on diet quality rather than quantity.

HEI-2015 has applied energy density scores, which means it captures quality independent of quantity and thus incorporates changes in energy intake which are apparent to ageing [264]. Furthermore, HEI-2015 has been updated based on changes in food availability and evidence-based dietary recommendations at each age of assessment; yet the scoring criteria and composition of the index do not substantially differ over the years [264]. In combination with the longitudinal nature of NSHD with diet being susceptible to changes over time for the same reasons, HEI-2015 is very likely to be a reliable indicator of diet quality at each age of assessment. It is also a valid tool to track relative changes in dietary patterns over time. Indeed, the use of HEI-2015 has been recommended in prospective studies, to reflect refinements related to current dietary guidelines and new evidence of diet and disease [277]. Using different versions of HEI at each age would result in different total scores between similar levels of diet quality. Another reason for choosing HEI-2015 is that it is non-region specific and allows for multiple dietary combinations to achieve good diet quality in contrast to

other valid dietary indexes such as the MedDiet or the Nordic diet [264, 277]. Finally, exploring and tracking diet quality using dietary patterns over time provides more comprehensive public health implications than single nutrient analysis.

A major advantage of HEI over other dietary quality indices is that it has been thoroughly tested for its predictive ability, construct and content validity and reliability in numerous studies and against exemplary menus [215, 265, 271, 278]. Furthermore, the HEI has been consistently associated with lower risk of all CVD, cancer, T2D and neurodegenerative disease and with lower mortality, as shown by recent meta-analyses [133, 279]. In particular for the HEI-2015, its psychometric properties have been evaluated extensively including five forms of construct validity, two of reliability and one of criterion validity [278]. Findings demonstrated encouraging evidence of all properties, concluding that high HEI-2015 scores as compared to low, were associated with a 13-23% lower risk of all-cause and cause-specific mortality in the AARP Study in the US [278]. In line with these findings, the Multi-ethnic Cohort (MEC) among 215,000 people of all ethnicity backgrounds, confirmed this association which was found to be of similar strength [215]. Therefore, HEI-2015 can be considered a valid index of overall diet quality with high clinical relevance.

Calculation of HEI-2015

Calculation of total HEI scores included five steps: (1) identifying dietary constituents for each HEI component; (2) deriving sums for each HEI component; (3) constructing ratios for each HEI component; (4) scoring each HEI component according to standards and (5) calculating scores of component and total HEI scores.

First, for each of 13 HEI components, dietary constituents were identified by comparison with the US Food Patterns Equivalent Database (FPED) [280], the Food and Nutrient Database for Dietary Studies (FNDDS) [281] and MyPyramid Equivalent Database [282]. All dietary constituents, included in each HEI component, are described in detail in Appendix 3. For

example, the “whole fruits” component included: citrus and melon fruits, berries and other intact fruits. After identification of all constituents, all 98 single food items and food sub-groups, which were available in the NSHD database, were disaggregated and matched against constituents in the original database of the NDNS, with focus on item similarity and nutritional content [253].

Second, after all dietary constituents in the NSHD were identified for each HEI component, quantity units were converted from cups and ounces equivalents, which are common units in the US, to grams equivalents, which is a common unit in the UK and European Food Composition Databases. After cross-check of conversion equivalents for each constituent of each HEI component using the “What's In The Foods You Eat Search Tool, 2013-2014” [283] and the UK Composition of Foods Tables [251], all constituents in grams equivalents were then summed to comprise each HEI component. Appendix 3 provides detailed information about conversion equivalents for all constituents used. A cup is a unit of volume equal to approx. 240-245 ml and one ounce is equal to ~28-28.5 g. For example, for “total vegetables” component, 1 cup equivalent was equal 225 g of potatoes and 180 g of raw tomatoes. For constituents consisting of various items, the average weight in grams of all items corresponding to 1 cup equivalent, was calculated (Appendix 3). For example, for “total fruits” component, 1 cup equivalent was equal: 170g of fresh fruit, 130g of dried fruit, 250g of canned/cooked fruit and 215g of fruit smoothie. The end product of this process was the generation of all 13 HEI components including all dietary constituents, expressed in grams equivalents.

Third, the appropriate ratios for each HEI component for each individual were constructed. For most HEI components, these were the ratios of grams equivalents per 1,000 kcal of energy intake, except “fatty acids”, which used the ratio of the sum of MUFA + PUFA to saturated fatty acids and “added sugars” and “saturated fat” components which were expressed as percentage of total caloric intake (Table 3.4). Then, the ratios were scored according to the

HEI scoring standards for each component as seen in Table 3.4. A perfect score per HEI component (5 or 10 depending the component) would be given if the participant met the scoring standard for maximum score. Similarly, a score of 0 would be given per HEI component if the participant met the scoring standard for minimum score. Ratios that ranged between minimum (0 for all components) and maximum (5 or 10) of the scorings standard, were scored proportionally.

For example, for “total fruits”, the minimum score would be 0 points for participants who had 0 grams equivalents of fruits per 1,000 kcal daily, whereas a perfect score of 5 would be assigned for participants who consumed ≥ 170 grams equivalents of fruits per 1,000 kcal daily. For anyone scoring e.g. 120 grams equivalents of fruits per 1,000 kcal daily, a score of 3.5 out of 5 would be assigned, proportionally. The same process was followed to calculate scores for all 13 HEI components. Finally, all 13 component scores were summed per participant to calculate total HEI-2015 scores, ranging from 0 – low diet quality to 100 – high diet quality.

To date, there is no national food composition database to include values for added sugars. To approximate intake of added sugars in this sample, data from the United States Department of Agriculture (USDA) “Database for the Added Sugars, Release 1” [284], the USDA FPED 2011 [280] and relevant published work [285] were used. First, intakes of natural existing sugars primarily in fruit (and juices), dairy products and secondary in vegetables (pulses included) were estimated. Then, values of natural existing sugars were extracted from total sugars to approximate intake of added sugars, which were then converted to energy intake from added sugars. Saturated fat, MUFAs and PUFAs were available at ages 43, 53 and 60-64 and were estimated from the UK Composition of Foods Tables at age 36 [251]. Saturated fat was converted into energy intake from saturated fat. Finally, sodium only from food sources contributed to sodium intake component and values did not include added salt while cooking or on table (Appendix 3).

3.3.3 Gait Assessment

Gait Assessment Procedure

Gait was assessed during participants' visit at the clinical centre (University College London, UCL) between May 2015 and January 2018 (age 69-71, Insight 46) [245]. First, a trained study clinician provided detailed information on the protocol and upon confirmation by the participant, a consent to proceed was granted. An IMU device (LPMS-B, Life Performance Research, Japan) was attached over the projected CoM over the lumbar area level 4/5 [63]. This IMU has previously been shown to be an objective measure of movement in both healthy [286] and diseased populations [66, 67, 287].

Participants were asked to perform three gait tasks, all of which involved walking twice for a set of 10-m walk (standard operating procedure in Appendix 4) across a pre-marked straight line at self-selected pace. Task 1 involved undisturbed walking, Task 2 involved walking under CMI conditions by concurrent performance of a cognitive task - single letter cued (phonemic) fluency - and similarly Task 3 involved walking under CMI conditions by concurrent performance of a more complex cognitive task - alternate letter cued (phonemic) fluency -, (hereafter to be called "Task 1", "Task 2", "Task 3").

Prior to each visit, the sequence of the order to perform each walking task was randomized for each participant by the study coordinator using a random number generator (Microsoft Excel) in order to minimize practice effects. The sequence was uploaded to an imaging informatics software platform (XNAT), was written on a checklist and was disseminated to the clinicians on the day of each visit. Randomization of walking tasks' sequence may also be beneficial against motor fatigue affecting gait performance. Motor fatigue during multiple walking tasks has been shown to reduce neuromuscular performance and may also affect motor control due to reduced reaction time, distorted coordination and proprioception [288]. In particular for gait, participants tend to use adaptive strategies against leg muscle fatigue and walk in more considerate ways as expressed by lower walking speed, so as to ensure stability.

In CMI paradigms, this effect might be stronger because when motor fatigue is reached and the CMI capability reaches its limit, this may further reinforce detrimental effects on motor performance not related to the complexity of CMI paradigm per se, as shown by recent evidence [288]. Therefore, randomization of sequence of walking tasks has contributed towards mitigating the effects of motor fatigue due to multiples walks in this study.

Prior to testing, participants undertook a practice attempt of undisturbed walking 10-m on a corridor free of obstacles and walked back another 10-m to the starting point, where the practice was completed (not recorded). Following that, participants performed all three tasks. Each task was repeated two times and all walks were recorded. At the end of the assessment, each participant had performed a maximum of twelve 10-m recorded walks (three tasks x two times x two 10-m walks).

Walking Speed

Gait analysis was performed for all three tasks using data from the IMU via a bespoke software coded in LabVIEW2015 (National Instruments). The exact methods and models used to estimate all gait parameters have been described in detail by *Esser et al. (2009)* [47]. Acceleration as recorded by the IMU was rotated from the reference of the object to the ground and the relative vertical position (excursion) of CoM was then accurately estimated by double integration, assuming inverted pendulum models [47, 63]. Mean walking speed of all four walks per task was estimated in m/s, based on the vertical acceleration of trunk movements, as step length (corrected for double stance by a correction factor: 80% of foot size) divided by mean step duration [289].

Rationale for IMU-Walking Speed

For the ageing population of the Insight 46, gait analysis via IMUs, in combination with other clinical examination, may facilitate diagnosis of mobility and cognitive decline and neurodegenerative disease. Abnormal gait patterns, indicated by validated IMUs, such as the

one used in this thesis, have been associated with numerous age-related conditions such as diabetic peripheral neuropathy [65], Huntington's disease [66] and Parkinson's disease [67]. In this thesis, walking speed was selected as a non-specific, valid, reliable and sensitive measure of age-related overall functioning [89]. It is of high prognostic value of mobility [103] and cognitive status [115], of adverse health outcomes [98-101, 290], mortality [93] and survival of older people [28, 102] and it is characterized as "the sixth functional vital sign" [89]. Therefore, selection of walking speed as a measure of age-related well-functioning is of major clinical relevance, of important public health implications and is highly relevant for the ageing population [89]. Finally, it is easy to measure in all settings.

A walking protocol of four 10-m walks per task at self-selected pace over a straight obstacle-free pre-marked area was used. First, this approach is popular among clinicians because it is "*more clinically feasible*" than longer walkways [89]. Second, a large volume of evidence supports 10-m to be the "gold standard" distance [291] that combines both "*psychometric properties*" and clinical "*clinical feasibility*", as compared to distances less than five metres and distances over 20 metres [292, 293]. Four walks were performed so as to limit variability and compare walking speed values across the walks. Walks were performed at self-selected pace rather than maximum pace based on previous evidence, which shows *that usual walking pace* is more effective in estimating physical function, health outcomes and overall health with ageing, as compared to maximum speed [113, 294].

Walking in a straight line was used with a turn at 10-m and walking back another 10-m. There is evidence that this may complicate estimation of walking speed due to accelerating de-accelerating phases and inter and intra test re-test accuracy [295]; however data was analysed manually for each 10-m walk which reduced the magnitude of the above complication. On the basis that no established cut-off points of acceleration de-acceleration distances have been set, a static approach was selected at gait assessment and values of walking speed are expected to be slower than those of dynamic start protocols [89]. Therefore, total distance (0-

10 and 10-20 metres) was analysed because exclusion of acceleration de-acceleration phases would introduce additional variability in walking speed measures, as previously shown [296].

3.3.4 Descriptive Characteristics

Table 3.2 shows an overview of all data available at each age. Data availability of descriptive characteristics to be used in this thesis is presented in Table 3.5. Unless otherwise stated, all characteristics were measured or reported at each age of assessment (Chapter 4 and Chapter 5: age 60-64, Chapter 6: ages 36, 43, 53, 60-64 and 69-71). Most information was collected by trained research nurses via interviews, unless otherwise stated. Age at each dietary assessment was calculated as the date of clinical assessment minus birthdate (March 1946) in years. Follow-up period was calculated as the date of gait assessment at age 69-71 minus the date of first day of food diary completion at each age of assessment.

Rationale for Use of Descriptive Characteristics

Inclusion of descriptive characteristics as confounders in the multivariable models was based on: (a) availability of data at each age of assessment (ages 36, 43, 53, 60-64 and 69-71); (b) previous evidence in the NSHD/Insight 46 and (c) plausible biological mechanisms linking them to diet and age-related function, indicated by walking speed/CMI.

***Age/Follow-up Period**:* It is well established that differences in age and subsequently in follow-up period have a great influence on dietary intake [219], the musculoskeletal [126] and cognitive system [33]; However this study included participants from a birth cohort who had the same age at each assessment and therefore age and follow-up were not strong confounders, as tested in all models.

Socioeconomic Status: It has been well reported that socioeconomic status across lifespan, including education, adult occupation and marital status, greatly impact physical [297] and

cognitive [298] status in later life and therefore the ageing process. A history of manual vs non manual work has been independently associated with low physical function and muscle strength in older people [299]. Higher level of education has been widely reported to favour better cognitive function with ageing, despite a recent meta-analysis questioning this concept [300]. In addition, being married or living with a partner has been associated with better physical capability in UK and US populations [301] as well as lower odds of cognitive impairment with ageing [302]. Finally, socioeconomic factors significantly influence diet quality in a way that better educated and more affluent people tend to have higher diet quality [303]. Therefore, multivariable analyses in this project were adjusted for occupation, education and marital status, as discussed in Table 3.5.

Number of Comorbidities: The number of diseases tend to increase with ageing and also correlate strongly with age-related physical and cognitive decline in older people [304]. Overall, increasing number of comorbidity and disability with ageing is likely accompanied by faster age-related decline in functional status [305] and often reflects abnormal walking status [306]. In addition, increasing counts of chronic disease with ageing reflect overall a lower diet quality and are more frequent among people who adhere to unhealthier lifestyles [128]. Hence, all multivariable models assessing the relationship between diet quality and walking speed/CMI cost, reflecting functional status, were controlled for prevalence of major age-related comorbidities up to late midlife, as shown in Table 3.5.

Physical Activity: Adherence to leisure physical activity, both of aerobic and resistance training, has been associated with improved muscle mass and strength, lower rate of fat accumulation, improvements of fat free mass, lower incidence of physical disability and frailty and better cognitive function with ageing [5, 172, 305]. In the NSHD, physical activity over midlife was the strongest predictor of slower cognitive decline over 20 years [172] and across adulthood cumulative exposure to physical activity reflected better physical performance in midlife. In addition, leisure activity as a major lifestyle behaviour is also associated with diet in

so more health conscious people tend to be more physically active and follow healthier diets [184]. Finally, despite important implications discussed in 6.5 Discussion and 7.3 Methodological Considerations, physical activity was considered as a behavioral factor and thus was controlled for in all multivariable models as shown in Table 3.5.

Smoking Status: Lifetime smoking habits are strongly related to physical performance at midlife and may thus lead to decreased physiological reserve, as shown by evidence in the NSHD [307]. Furthermore, as part of an overall lifestyle, high exposure to smoking has been associated with poor physical function [184], lower health-related quality of life [308] and higher incident mobility decline with ageing [185]. Finally, likewise most lifestyle factors, smoking clusters strongly with dietary habits, in so more health conscious people tend to smoke less and also follow healthier diets and vice versa [309]. Therefore, smoking status was used as confounder in all multivariable models as shown in Table 3.5.

Supplement Use: Despite evidence being inconclusive [191] it has been suggested that supplement use may be beneficial against physical [154] and cognitive [310] decline with ageing. In the NSHD, supplement use was not thoroughly assessed and methods of supplement intake were inconsistent over the time points. Because dosage and type of supplements were not exclusively assessed, except if captured in the 5-d diaries, supplement use was mainly modelled as a binary confounder of use vs no use at age 64 to reflect on overall health consciousness of participants. It is widely reported that supplement use clusters with other healthy lifestyle behaviours including diet [311].

Body Mass Index / Waist to Hip Ratio: Body size as often assessed by body mass index and waist to hip ratio in adulthood, has been consistently associated with poorer physical performance including walking speed as well as muscle strength as measured by grip strength [312]. This relationship has been shown to be very strong in particular for those who have high body mass index and low muscle strength in midlife. In addition, body size is largely affected

by composition of diet, both in terms of quantity (energy intake) and quality (nutrient dense vs nutrient poor food items) and tends to cluster significantly with healthy and unhealthy lifestyle behaviours [309]. Therefore all multivariable models were adjusted for either body mass index or waist to hip ratio, according to available data, as explained in Table 3.5.

***Mini Mental State Examination (MMSE)*:** Cognitive status is a major determinant of daily activities including multi-tasking, in particular for older people [13]. When walking undisturbed and especially in CMI paradigms, better cognitive status has been associated with faster walking speed and overall better performance when walking and concurrently performing a secondary task [74, 115, 116]. Despite a causal pathway is not yet established, cognition is perceived as an important confounder in the relationship between diet and walking speed, as better cognition is also linked to healthier diet, as shown by consistent evidence [237]. Given the absence of cognitive status up to age 64 and because cognitive performance was not measured during the CMI paradigm at age 71, all multivariable models were adjusted for MMSE score measured at age 71 as described in Table 3.5.

Chair Rise Stand Time / Grip Strength: Both measures are widely used as valid predictors of lower limb and overall muscle strength, respectively, across adulthood and also correlate with walking speed, as measures of physical and cognitive decline [313]. Chair rise stand ability has been also shown to reflect balance performance, which is another crucial element of successful walking, in particular in CMI paradigms [314]. As measures of physical capability, they have been associated with diet quality and overall lifestyle, in so better diet reflects higher measures of these measures [188]. Importantly, considering that walking speed data was unavailable at any age of dietary assessment, multivariable models were adjusted for these measures to account for physical performance/capability of participants at baseline, as described in Table 3.5.

Balance Time Test: Data was available for one leg standing balance tests at midlife, which reflect physical capability and have been shown to predict survival in older people in the NSHD [315]. Balance tests correlate with gait speed and when combined, they both reflect on performance in CMI paradigms, considering balance is also predictive of cognitive decline and subsequent health [316]. Finally, as a measure of physical capability, balance tests have been associated with lifestyle factors including diet quality at midlife, in so better dietary habits reflect better physical capability. Hence, multivariable models were adjusted for balance test performance as shown in Table 3.5.

Table 3.5 Data availability of descriptive characteristics by age of assessment

			Age (years)				
Characteristics	**Categories**	**Comments**	**36**	**43**	**53**	**60-64**	**69-71**
Demographics							
Occupation	• I - Professional • II - Intermediate • IIINM - Skilled Non-Manual • IIIM - Skilled Manual • IV - Partly skilled • V - Unskilled	Overall social class up to age 15-53 * by National Statistics Socio-economic classification- assumed constant up to age 64. • Categorized as “Professional/Skilled Non-Manual” vs “Skilled Manual/Semi-Skilled/Unskilled”, with the latter being the reference category in main analysis.	*	*	✓	*	*
Education	• None • Formal • Secondary	Self-reported education level up to age 26 *, assumed constant up to age 64. • Categorized as “None”, “Formal”, “Secondary” or ≥ “Secondary Education” (up to age 16), with “None” being the reference category in main analysis.	✓	*	*	*	*
Marital status	• Married • Living with Partner • Single • Widowed • Separated • Divorced	Self-reported marital status at each age of assessment. • Categorized as “Married/Partner” vs all other categories in main analysis.	✓	✓	✓	✓	✓
Health							
Number of Comorbidities	0-5	Generated as diagnosis, self-report or medication for any of the following conditions at each age of assessment: 1. CVD including angina, heart failure, myocardial infarction, stroke or coronary artery bypass graft; 2. Diabetes type I or II; 3. Hyperlipidaemia; 4. Hypertension; 5. Cancer • Categorized as “Number of Comorbidities” or n≥ 2 comorbidities up to age 64 in main analysis, as the optimal cut-off point with the most observations in Insight 46.	✓	✓	✓	✓	✓

Continued Table 3.5

Characteristics	Categories	Comments	Age (years) 36	43	53	60-64	69-71
Lifestyle							
Leisure time physical activity	• None • 1 to 4 times/week • ≥ 5 times/week	Self-reported leisure time physical activity in last four weeks at each age of assessment. • Categorized as "≥ 5 times/week", "1 to 4 times/week" and "None", with the latter being the reference category at age 64 in main analysis in Chapters 4 and 5. • Modelled as a continuous variable to reflect cumulative exposure from age 36 to 71 in Chapter 6, as thoroughly discussed in p.139.	✓	✓	✓	✓	✓
Smoking status	• Current • Former • Never	Self-reported smoking habits at each age of assessment. • Categorized as "Current", "Former", "Never", with the latter being the reference category at age 64 in main analysis in Chapters 4 and 5. • Modelled as a continuous variable to reflect cumulative exposure from age 36 to 71 in Chapter 6, as discussed in page139.	✓	✓	✓	✓	✓
Supplement use	• Yes • No	Self-reported at age 60-64. For other assessments, available from food diaries †. • Due to inconsistency in assessment methods over adulthood, only a binary variable "Yes" vs "No" of supplement use at age 64 is used in main analysis in Chapters 4 and 5.	✓ †	✓ †	✓ †	✓	–
Anthropometrics							
Body mass index, BMI	Continuous variable, kg/m^2	Calculated as body weight in kilograms by height in metres squared (kg/m^2) at each age of assessment. • Used as interval variable at age 64 in main analysis in Chapter 4. The variable had the highest prevalence of missing values and multiple imputation was not optimal; therefore it was replaced by waist to hip ratio to additionally account for sex-specific anthropometric differences.	✓	✓	✓	✓	✓

Continued Table 3.5

Characteristics	Categories	Comments	Age (years) 36	43	53	60-64	69-71
Anthropometrics							
Waist to Hip Ratio (WHR)	Continuous variable, arbitrary unit	Calculated as measurement of waist in centimetres by hip measurement in centimetres. Arbitrary unit. • Used as a measure of sex-specific anthropometric differences at age 64, which are likely to have an impact on walking pattern in Chapters 4 and 5. • Modelled as a continuous variable to reflect cumulative exposure from age 36 to 71 in Chapter 6, as discussed in page 139.	–	✓	✓	✓	✓
Leg length	Continuous variable, metres	Measured only at age 69-71 in Insight 46 during gait assessment. • Used to normalize walking speed for body size differences in all Chapters.	–	–	–	–	✓
Cognition							
Mini Mental State Examination, (MMSE)	0-30	Assessed only at age 69-71. • Used as a measure of cognitive status at age 64 † in Chapters 5 and 6 to account for cognitive ability in the CMI paradigm. • Assumed that at this age it will be at least equal if not higher than at age 69-71.	–	–	–	– †	✓
Physical Performance							
Chair rise stand time	Continuous variable, seconds	Measured as time taken to rise from a sitting to standing position with straight back and legs and then sit down again 10 complete times. • Used as a continuous variable at age 64 in Chapter 5 in main analyses to account for lower limb strength and power as well as balance and coordination, when walking and performing the verbal fluency task. • Also, modelled as a continuous variable to reflect cumulative exposure from age 53 to 71 in Chapter 6, but not used in main analysis due to poor model fit. Available in Appendix 7.	–	–	✓	✓	✓

Continued Table 3.5

Characteristics	Categories	Comments	Age (years) 36	43	53	60-64	69-71
Physical Performance							
Balance time, eyes open	Continuous variable, seconds	Measured as the longest time, to a maximum of 30 seconds, for which participants could maintain a one-legged stance in a standard position with eyes open. • Categorized as ≥30 seconds at age 64 in main analysis in Chapter 4, to assess static postural and balance control, as it provides information regarding risk of falling in the elderly. • Also, modelled as a continuous variable to reflect cumulative exposure from age 53 to 71 in main analysis in Chapter 6.	–	–	✓	✓	✓
Balance time, eyes closed	Continuous variable, seconds	Measured as the longest time, to a maximum of 30 seconds, for which participants could maintain a one-legged stance in a standard position with eyes closed. • Not used in any main analysis due to poor fit. • Modelled as a continuous variable to reflect cumulative exposure from age 53 to 71 in Chapter 6, but not used in main analysis due to poor model fit. Available in Appendix 7.	–	–	✓	✓	✓
Grip strength	Continuous variable, kilograms	Measured in kilograms, isometrically using an electronic handgrip dynamometer. Maximum attempt recorded. • Used to reflect on muscle strength over adulthood. • Modelled as a continuous variable to reflect cumulative exposure from age 53 to 71 in Chapter 6, as discussed in page 139.	–	–	✓	✓	✓

3.4 Overview of Descriptive Data in Insight 46

To facilitate interpretation of the data provided in each chapter and because of multiple dietary assessments and collection of several factors at each age over adulthood, an overview of descriptives is provided hereby for the NSHD/Insight 46, overall and by sex.

Table 3.6 (overall) and Table 3.7 (by sex) provide descriptive data for diet quality by HEI-2015 score at each age. There is a trend towards improvement of diet quality from age 36 to 64 among participants in Insight 46 by total HEI-2015 and component scores ($p<0.05$). In addition, there is an increase in the number of participants who meet the standard for maximum scores in most HEI components from age 36 to 64 ($p<0.05$). With regard to comparison by sex, both men and women improved their diet quality over adulthood ($p<0.05$) and women had higher total and component HEI-2015 scores and they also met the standard for maximum scores in most HEI components more often than men ($p<0.05$). Further comparisons of diet quality by sex and over adulthood are provided in the following chapters.

Table 3.8 shows raw and normalized data on walking speed and cognitive motor interference cost at age 69-71 among participants in Insight 46. Men had faster raw walking speed values than women in all walking tasks ($p<0.05$); however after controlling for body size differences, walking speeds did not differ between men and women at any task ($p>0.05$). Similar, CMI cost was not significantly different in men versus women, neither in Task 2 nor in Task 3. Further discussion on walking speed values by sex is provided in each study, in the following chapters.

Table 3.9 shows descriptives for all variables at each age of assessment, used as confounders in main analyses in the present thesis. Overall, men had higher rates of attending higher education than women up to age 26, they used to work more often in manual jobs up to age 53 and were more likely to be living with partner of being married than women at each age of assessment ($p<0.05$). They also had higher prevalence of comorbidities than women up to age 64 ($p<0.05$). Regarding lifestyle, there were no significant differences in leisure time

physical activity or smoking habits over adulthood between men and women, but women used more often supplements at age 64 than men ($p<0.05$). Body mass index was higher among men versus women up to age 43, but did not differ after that age. Leg length and waist to hip ratio were larger in men compared to women ($p<0.05$). Cognitive status at age 69-71 did not differ by sex and was very high, considering the age group. Finally, men scored consistently higher than women in all physical performance tests over adulthood ($p<0.05$); thus reflecting a better profile in absolute values of muscle mass and strength, on average.

Table 3.6 Total and by component HEI-2015 scores at each age of dietary assessment in NSHD/Insight 46, overall, n=502

Age of assessment, years	**36**		**43**		**53**		**60-64**	
Number of participants	313		369		346		444	
	Mean [sd]							
Age, years	36.3 [0.2]		43.4 [0.2]		53.4 [0.2]		63.3 [1.0]	
HEI-2015, 0-100	47 [11]		49 [12]		56 [13]		62 [13]	
Component scores, range	Mean [sd], n max score [1] (%)							
Adequacy								
Total Fruit, 0-5	1.6 [1.5]	27 (9)	2.0 [1.6]	48 (13)	3.5 [1.6]	155 (45)	**3.6 [1.5] ***	**195 (44)** *
Whole Fruit, 0-5	2.6 [1.8]	81 (26)	2.8 [1.8]	118 (32)	4.2 [1.5]	248 (72)	**4.3 [1.4] ***	**332 (75)** *
Total Vegetables, 0-5	3.2 [1.0]	38 (12)	3.2 [1.1]	61 (17)	3.4 [1.2]	98 (28)	**3.8 [1.1] ***	**172 (39)** *
Greens & Beans, 0-5	3.2 [1.6]	107 (34)	3.5 [1.5]	140 (38)	2.7 [1.8]	96 (28)	**3.5 [1.7] ***	**191 (43)** *
Whole Grains, 0-10	4.7 [3.9]	77 (25)	5.5 [3.8]	107 (29)	5.7 [3.8]	107 (31)	**6.5 [3.5] ***	**164 (37)** *
Dairy, 0-10	4.2 [2.0]	7 (2)	4.5 [2.3]	16 (4)	5.1 [2.4]	23 (7)	**4.8 [2.3] ***	23 (5)
Total Protein Foods, 0-5	4.6 [0.7]	238 (76)	4.3 [1.0]	241 (65)	4.4 [0.9]	237 (69)	4.6 [0.8]	335 (76)
Seafood Protein Foods, 0-5	2.9 [1.9]	107 (34)	3.0 [1.9]	138 (37)	3.2 [1.9]	144 (42)	**3.5 [1.9] ***	**237 (53)** *
Fatty Acids, 0-10	0.5 [1.0]	0 (0)	0.9 [1.5]	1 (0.5)	1.3 [1.9]	3 (1)	**2.2 [2.5] ***	9 (2)
Moderation								
Refined Grains, 0-10	4.6 [3.7]	50 (16)	5.1 [3.5]	70 (19)	4.7 [3.6]	60 (17)	**6.0 [3.5] ***	**120 (27)** *
Sodium, 0-10	7.6 [2.2]	114 (36)	7.1 [2.6]	88 (24)	7.1 [2.5]	71 (21)	7.7 [2.4]	162 (37)
Added Sugars, 0-10	6.2 [2.4]	21 (7)	6.6 [2.3]	46 (13)	7.4 [2.2]	68 (20)	**7.3 [2.1] ***	**68 (15)** *
Saturated Fat, 0-10	0.4 [1.2]	1 (0.5)	1.8 [2.5]	6 (2)	3.9 [3.2]	23 (7)	**4.5 [3.1] ***	**31 (7)** *

* p value ≤ 0.05 per repeated measures analysis of variance or non-parametric equivalent (Friedman's test). Significance levels denote a change from age 36 to 64.
[1] Number of participants who met the dietary recommendation for each component and thus the standard for maximum score in each component.

Table 3.7 Total and by component HEI-2015 scores at each age of dietary assessment in NSHD/Insight 46, by sex, n=502

Age (years)	36				43				53				60-64			
	Women (n=158)		Men (n=155)		Women (n=183)		Men (n=186)		Women (n=177)		Men (n=169)		Women (n=223)		Men (n=221)	
HEI-2015, 0-100																
Median (range)	48 (23-75)		45 (20-74)		53 (23-86)		47 (24-75)		60 (30-86)		52 (22-85)		65 (27-94)		60 (26-92)	
Mean [sd]	48 [11]		46 [11]		53 [11]		47 [12]		59 [12]		54 [13]		64 [13]		61 [13]	
Component scores,	Mean [sd], n max score [1] (%)															
Adequacy																
Total Fruit, 0-5	**2.0***	23	1.2	4	**2.5***	39	1.5	9	**4.0***	106	3.0	49	**3.9***	120	3.2	75
	[1.6]	(3)	[1.1]	(3)	**[1.7]**	(21)	[1.4]	(5)	**[1.4]**	(60)	[1.6]	(29)	**[1.4]**	(54)	[1.6]	(34)
Whole Fruit, 0-5	**3.0***	58	2.2	23	**3.4***	81	2.2	37	**4.5***	148	3.8	100	**4.5***	187	4.0	145
	[1.8]	(15)	[1.7]	(15)	**[1.7]**	(44)	[1.8]	(20)	**[1.1]**	(84)	[1.7]	(59)	**[1.1]**	(84)	[1.6]	(66)
Total Vegetables, 0-5	3.2	24	3.2	14	**3.4***	39	2.9	22	**3.7***	66	3.1	32	**4.0***	104	3.6	68
	[1.0]	(9)	[1.0]	(9)	**[1.1]**	(21)	[1.0]	(12)	**[1.2]**	(37)	[1.2]	(19)	**[1.0]**	(47)	[1.1]	(31)
Greens Beans, 0-5	3.4	60	3.1	47	**3.6***	81	3.3	59	**3.0***	64	2.5	32	**3.7***	109	3.2	82
	[1.6]	(30)	[1.6]	(30)	**[1.5]**	(44	[1.5]	(32)	**[1.8]**	(36)	[1.7]	(19)	**[1.5]***	(49)	[1.7]	(37)
Whole Grains, 0-10	4.9	41	4.5	36	5.8	55	5.1	52	**6.2***	62	5.1	45	6.7	88	6.4	76
	[4.0]	(23)	[3.9]	(23)	[3.7]	(30)	[3.9]	(28)	**[3.6]**	(35)	[3.9]	(27)	[3.4]	(39)	[3.6]	(34)
Dairy, 0-10	**4.7***	5	3.7	2	**5.1***	14	3.8	2	**5.8***	19	4.3	4	**5.3***	18	4.3	5
	[2.1]	(1)	[1.8]	(1)	**[2.5]**	(8)	[1.9]	(1)	**[2.5]**	(11)	[2.0]	(2)	**[2.5]**	(8)	[2.1]	(2)
Total Protein, 0-5	4.6	125	4.6	113	4.4	126	4.3	115	4.4	117	4.5	120	4.5	164	4.6	171
	[0.7]	(72)	[0.8]	(73)	[1.1]	(69)	[1.0]	(62)	[1.0]	(66)	[0.8]	(71)	[0.9]	(74)	[0.8]	(77)
Seafood Protein, 0-5	3.0	58	2.9	49	2.9	68	3.1	70	3.3	79	3.1	65	3.5	121	3.5	116
	[1.9]	(31)	[1.8]	(32)	[3.4]	(37)	[1.8]	(38)	[1.9]	(45)	[1.9]	(38)	[1.8]	(54)	[1.9]	(52)
Fatty Acids, 0-10	0.4	0	**0.7***	0	**1.1***	1	0.8	0	1.3	2	1.4	1	2.1	7	2.2	2
	[0.7]	(0)	**[1.1]**	(0)	**[1.6]**	(1)	[1.3]	(0)	[2.0]	(1)	[1.9]	(1)	[2.7]	(3)	[2.3]	(1)
Moderation																
Refined Grains, 0-10	4.4	23	4.9	23	5.7	40	4.5	30	4.8	31	4.5	29	6.1	66	5.8	54
	[3.6]	(15)	[3.8]	(15)	[3.5]	(22)	[3.5]	(16)	[3.7]	(18)	[3.6]	(17)	[3.4]	(30)	[3.5]	(24)
Sodium, 0-10	7.3	45	**7.9***	69	6.9	44	7.3	44	6.9	34	7.3	37	8.0	93	7.5	69
	[2.2]	(44)	**[2.2]**	(45)	[2.7]	(24)	[2.4]	(24)	[2.7]	(19)	[2.3]	(22)	[2.4]	(42)	[2.4]	(31)
Added Sugars, 0-10	6.3	14	6.0	7	6.7	25	6.5	21	7.5	31	7.3	37	7.2	35	7.3	33
	[2.3]	(4)	[2.4]	(5)	[2.3]	(14)	[2.2]	(11)	[2.0]	(18)	[2.3]	(22)	[2.0]	(16)	[2.1]	(15)
Saturated Fat, 0-10	0.2	0	**0.7***	1	1.8	3	1.8	3	3.9	14	3.8	9	4.3	17	4.7	14
	[0.8]	(1)	**[1.4]**	(1)	[2.6]	(2)	[2.4]	(2)	[3.3]	(8)	[3.1]	(5)	[3.1]	(8)	[3.0]	(6)

* p value ≤ 0.05 per analysis of variance or equivalent non-parametric test (Kruskal–Wallis). Significance levels denote difference between women and men.

[1] Number of participants who met the dietary recommendation for each component and thus the standard for maximum score in each component.

Table 3.8 Descriptive data on walking speed/cognitive-motor interference cost at age 69-71 in NSHD/Insight 46, overall and by sex, n=502

		Overall	Women	Men
Task 1 – Undisturbed Walking	n	471	234	237
Walking speed, m/s	mean [sd]	1.42 [0.18]	1.39 [0.18]	**1.45 [0.19] ***
Normalized walking speed[1], -		0.48 [0.06]	0.48 [0.06]	0.48 [0.06]
Task 2 – Walking & Verbal Fluency	n	469	232	237
Walking speed, m/s	mean [sd]	1.23 [0.21]	1.20 [0.19]	**1.27 [0.22] ***
Normalized walking speed		0.41 [0.07]	0.41 [0.07]	0.42 [0.08]
CMI cost[2], %		-13.4 [9.7]	-13.7 [9.3]	-13.1 [10.1]
Task 3 – Walking & Complex Verbal Fluency	n	465	229	236
Walking speed, m/s	mean [sd]	1.19 [0.22]	1.16 [0.21]	**1.21 [0.23] ***
Normalized walking speed		0.40 [0.07]	0.39 [0.07]	0.40 [0.08]
CMI cost, %		-16.8 [11.1]	-16.4 [11.4]	-17.1 [10.7]

* p value ≤ 0.001, † p value ≤ 0.05

[1] Walking speed values were normalized to body size, to account for anthropometric differences between sexes, as introduced by *Hof (1996) [317].*

[2] CMI cost: Cognitive Motor Interference cost: calculated as percentage difference in walking speed when performing Task 2 or Task 3 as compared to Task 1, as introduced by Kelly et al., (2010) [318].

Table 3.9 Descriptive characteristics at each age of assessment in NSHD/Insight 46, used as covariates in main analyses, overall and by sex, n=502

	Overall (n=502)	Women (n=246)	Men (n=256)
		Mean [sd], n (%)	
Demographics			
Occupation up to age 53			
Professional/Non-manual	426 (85)	214 (87)	212 (83)
Semi-skilled/Manual/Unskilled	76 (15)	32 (13)	**44 (17)** ‡
Education up to age 26			
None	79 (16)	40 (16)	39 (16)
Formal	143 (29)	**82 (34)** ‡	61 (25)
≥ Secondary	265 (55)	120 (50)	**145 (59)** ‡
Married/Living with partner, yes			
Age 36	413 (82)	199 (81)	**214 (84)** ‡
Age 43	405 (81)	194 (79)	**211 (82)** ‡
Age 53	413 (82)	198 (80)	**215 (84)** ‡
Age 64	397 (79)	184 (75)	**213 (83)** ‡
Age 71	397 (79)	176 (72)	**221 (86)** ‡
Health			
No of comorbidities, up to age 64	1.3 [1.0]	1.2 [1.0]	**1.5 [1.0]** ‡
CVD	76 (15)	31 (13)	45 (18)
Diabetes	35 (7)	13 (5)	22 (9)
Hyperlipidaemia	135 (27)	46 (19)	**89 (35)** *
Hypertension	354 (71)	157 (64)	**197 (77)** *
Cancer	57 (11)	**36 (14)** †	21 (8)
Total Comorbidities, n >2	176 (35)	73 (30)	**103 (40)** *
Lifestyle			
Leisure physical activity, times/week			
Age 36			
None	127 (25)	68 (28)	59 (23)
1 to 4	124 (24)	62 (25)	62 (24)
≥ 5	213 (42)	99 (40)	114 (45)
Age 43			
None	187 (37)	98 (40)	89 (35)
1 to 4	132 (26)	70 (28)	62 (24)
≥ 5	166 (33)	69 (28)	**97 (38)** ‡
Age 53			
None	163 (32)	83 (34)	80 (31)
1 to 4	107 (21)	45 (18)	62 (24)
≥ 5	223 (44)	116 (47)	107 (42)
Age 64			
None	255 (51)	120 (49)	135 (53)
1 to 4	95 (19)	50 (20)	45 (18)
≥ 5	146 (29)	73 (31)	73 (29)
Age 71			
None	231 (46)	109 (45)	122 (48)
1 to 4	74 (15)	38 (15)	36 (14)
≥ 5	193 (38)	98 (40)	95 (37)

* p value ≤ 0.001, † p value ≤ 0.05

Continued Table 3.9

	Overall (n=502)	Women (n=246)	Men (n=256)
		Mean [sd], n (%)	
Lifestyle			
Smoking status			
Age 36			
Never	164 (33)	88 (36)	76 (30)
Former	205 (41)	96 (39)	109 (43)
Current	94 (19)	45 (18)	49 (19)
Age 43			
Former	239 (48)	110 (45)	129 (50)
Current	80 (16)	39 (16)	41 (16)
Age 53			
Former	273 (54)	127 (52)	146 (57)
Current	49 (10)	24 (10)	25 (10)
Age 64			
Former	281 (56)	130 (53)	151 (59)
Current	27 (5)	14 (6)	13 (5)
Age 71			
Former	307 (61)	141 (57)	166 (65)
Current	18 (4)	9 (4)	9 (4)
Supplement use at age 64, yes	234 (47)	**140 (57)** *	94 (37)
Anthropometrics			
Body Mass Index, kg/m^2			
Age 36	23.7 [3.1]	22.9 [3.2]	**24.5 [2.8]** *
Age 43	25.1 [3.3]	24.6 [3.7]	**25.4 [2.8]** *
Age 53	27.1 [4.2]	26.9 [4.9]	27.1 [3.4]
Age 64	27.7 [4.4]	27.6 [4.9]	27.8 [3.7]
Age 71	27.8 [4.6]	27.6 [5.2]	27.9 [3.9]
Waist to hip ratio			
Age 43	0.83 [0.09]	0.76 [0.06]	**0.90 [0.05]** *
Age 53	0.86 [0.08]	0.79 [0.05]	**0.92 [0.05]** *
Age 64	0.91 [0.08]	0.86 [0.06]	**0.96 [0.06]** *
Age 71	0.91 [0.08]	0.86 [0.07]	**0.96 [0.06]** *
Leg length, cm	90 [8.5]	85 [8]	**94 [7]** *
Cognition			
Mini Mental State Examination, (MMSE)	29 [1]	29 [1]	29 [1]

* p value ≤ 0.001, † p value ≤ 0.05

Continued Table 3.9

	Overall (n=502)	Women (n=246)	Men (n=256)
		Mean [sd], n (%)	
Physical Performance			
Chair rise stand time, s			
Age 53	20.2 [5.9]	20.5 [5.9]	19.9 [5.9]
Age 64	23.8 [6.4]	24.8 [6.9]	**22.8 [5.7]** *
Age 71	23.1 [6.8]	23.8 [6.3]	**22.4 [7.1]** †
Balance time, eyes open, s			
Age 53	26.9 [7.2]	25.9 [8.0]	**27.7 [6.1]** *
Age 64	22.6 [9.9]	20.9 [10.4]	**24.2 [9.3]** *
Age 71	21.4 [10.8]	20.8 [10.7]	22.1 [10.7]
Balance time, eyes closed, s			
Age 53	8.5 [7.6]	7.0 [6.1]	**9.9 [8.6]** *
Age 64	5.5 [5.4]	4.9 [4.4]	**6.1 [6.3]** *
Age 71	4.5 [4.5]	3.9 [3.8]	**5.1 [5.1]** †
Grip strength, kg			
Age 53	38.6 [13.9]	29.2 [7.9]	**47.9 [12.3]** *
Age 64	36.6 [13.6]	26.6 [7.3]	**46.2 [11.2]** *
Age 71	33.2 [10.9]	24.6 [5.5]	**41.3 [8.2]** *

* p value ≤ 0.001, † p value ≤ 0.05

3.5 Maximum Sample Size

Maximum sample size in this thesis was defined by data availability of walking speed. Different inclusion criteria were set for each study and thus final sample size differed in each chapter. Of 502 participants who underwent gait assessment, gait data was missing completely at random for 14 (accelerometer or equipment failure), missing at random for three (no time, allergies, unwillgness to perform cognitive task) and missing not at random for six (health conditions not allowing subjects to perform the walks).

Maximum percentage of missing data of walking speed was 3.7% (n=479). To ensure sufficient statistical power and optimal data quality, a criterion of completeness of walking speed data has been applied throughout this thesis as following: available walking speed data for at least two out of four walks in each task. Therefore, the maximum sample size for this thesis was n=474 for Task 1, n=469 for Task 2 and n=465 for Task 3. Walking speed data for this thesis was available for 479 people (245 men and 234 women) from the Insight 46, Figure 3.4. An overview of missing data of walking speed per walk per task during gait assessment is presented in Table 3.10.

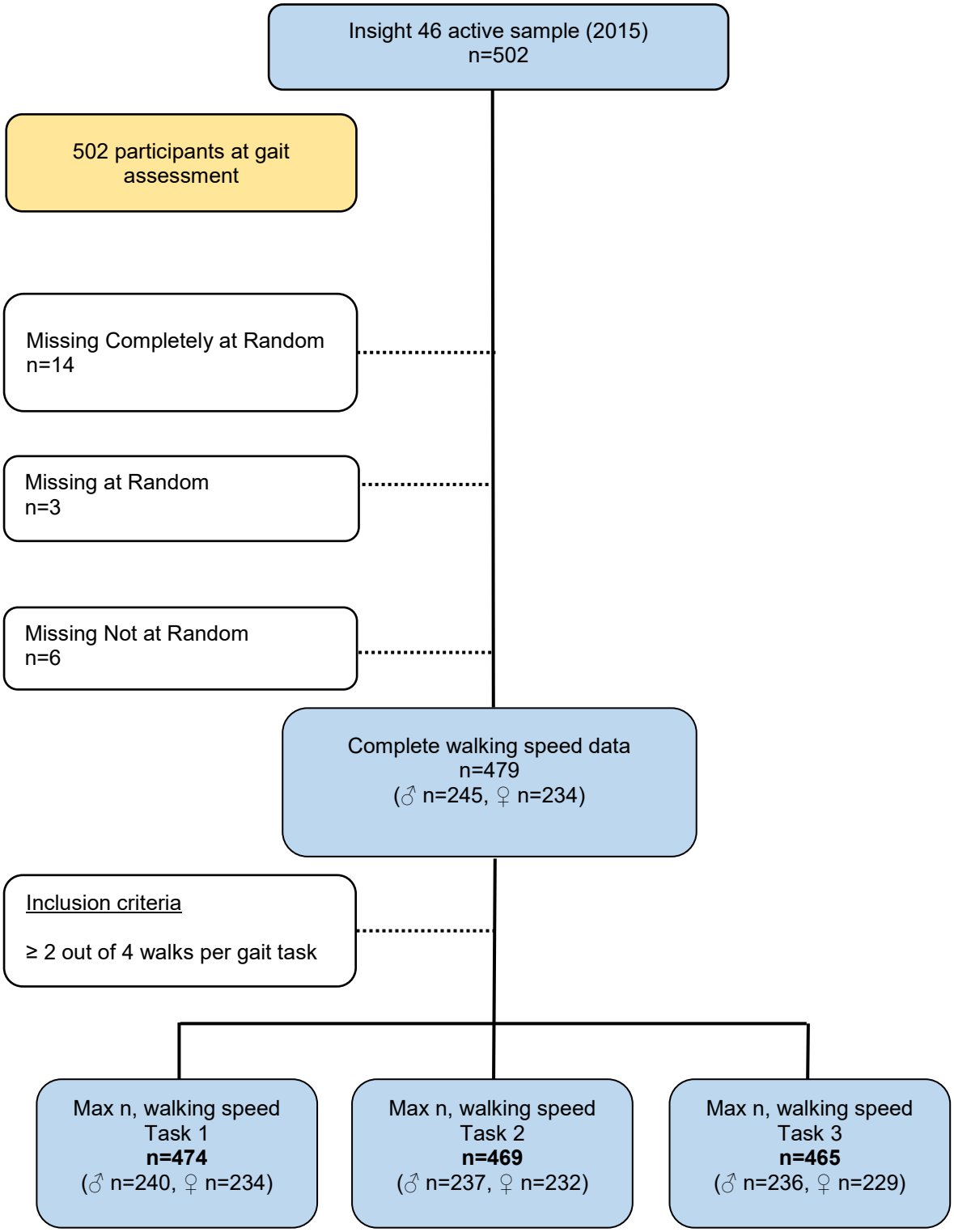

Figure 3.4 Maximum sample in the thesis by data availability of walking speed in Insight 46 at age 69-71

Table 3.10 Missing cases of walking speed per gait task in Insight 46

	Gait data (n=479)	
Walking speed, m/s	**n missing [1]**	**% ***
Task 1 (n=474)		
Walk 1	10	2.1
Walk 2	8	1.7
Walk 3	7	1.5
Walk4	17	3.5
Task 2 (n=469)		
Walk 5	14	2.9
Walk 6	14	2.9
Walk 7	14	2.9
Walk 8	15	3.1
Task 3 (n=465)		
Walk 9	16	3.3
Walk 10	17	3.5
Walk 11	17	3.5
Walk 12	18	3.7

m: metre, s: second

[1] Missing values for each walk are presented as percentage of maximum valid gait data at age 69-71

3.6 Statistical Methods

Specific methods with corresponding statistical analysis are described in each chapter. In general, diet quality was indicated by the HEI-2015 score as continuous variable per 1 or/and 10-point increment at each age (Chapter 4 and 5). Walking speed was modelled as continuous variable in m/s and normalized for leg length (arbitrary unit) at age 69-71 (Chapter 4, 5 and 6). Descriptive characteristics were presented as means ± standard deviations or frequencies at each age, unless otherwise stated. Differences of characteristics and diet quality by sex were explored using chi-square test for categorical variables, independent samples t-tests for continuous variables and Kruskal-Wallis tests for ordinal variables. Finally, repeated measures analysis of variance or non-parametric equivalents (Friedman's test) were used to test for differences in descriptives over dietary assessment ages.

Overall, analyses were carried out to explore the overall and by sex association between diet quality (HEI-2015) in late midlife and over adulthood and walking speed using linear regression models, as shown in Figure 3.5. Results were presented with point estimates of dietary exposure (regression coefficient) alongside corresponding 95% confidence intervals [319]. If an association or a trend were found, further analysis was conducted to assess the independent estimate of diet quality, after controlling for descriptive characteristics.

In Chapter 6, a 3-step approach was followed. First, individual growth curve models (IGC) using exploratory linear mixed models (LMM) [320] with fixed and random factors were tested, to assess individual and average developmental trajectories of HEI-2015 scores in adulthood. IGC expresses patterns of change of diet quality over time based on growth parameters, intercepts and slopes [321]. Considering previous evidence [218-220, 248], sex and occupation status were included as predictors in the models. IGC estimated one set of growth parameters for total sample, allowing for individual deviations from the average-level trajectory. However, it did not allow for exploration of potential sub-groups of different levels of diet quality in relation to the average-level trajectory [322].

Variability around the mean growth parameters was thus further explored to identify whether at least two or more distinct groups (trajectories) with no within-group variation but with large between-group variation existed, using “Group-Based Trajectory Modelling” (GBTM) [323, 324]. GBTM is a semi-parametric approach which estimates finite mixture models of probability distributions as polynomial functions of time, determined by the maximum likelihood estimation using a general quasi-Newton procedure [323, 324]. GBTM distinguishes random vs real variation across cases due to its formal statistical structure [323, 324]. Most importantly, GBTM provides comprehensive information as it simultaneously assesses (a) the number, forms and shapes of trajectories of any distinct groups, (b) the proportion of the sample following each trajectory, (c) the posterior probability of each individual of group membership.

Finally, when individual (IGC) and group (GBTM) trajectories were defined, predicted values conditional on previous ages (IGC) and probabilities of membership for each individual (GBTM) were used to assess the relationship between diet quality trajectories over adulthood and walking speed under different walking conditions in later life, considering potential confounders. The detailed procedure of each step is described in Chapter 6.

No *a priori* calculation was conducted to determine the statistical power needed to detect significant differences, as previous evidence has suggested this procedure might be misleading and not relevant [319]. *A posteriori*, the present thesis used the empirical estimator by *Green (1991)* [325], which revealed that a sample size of 210 people would be sufficient to detect a medium effect size on up to 20 independent predictors, on an alpha level of 0.05 and statistical power of 0.8. Significance level was set at 5% two-sided for all statistical tests throughout the thesis. The analyses were carried out in SPSS 26 (SPSS Inc., Chicago, IL, USA) for all descriptive comparisons, for the main analyses (linear regression models) and for the LMM-IGC analysis (mixed function). GBTM was conducted in SAS/STAT 14.3 (proc traj, SAS Institute, Cary, NC, USA).

Rationale for Use of IGC/GBTM

The longitudinal nature of this project required optimal modelling of diet quality over four ages in adulthood, while concurrently ensuring maximum sample size available for analysis, in order to limit bias related to observational design [44]. Additionally, considering the "life course" approach that assumes developmental origins of ageing, health and disease by environmental influences over the lifespan, trajectory based methods were applied in this thesis [5]. This type of analysis identifies distinctive growth trajectories of a variable of interest - that is diet quality in this project - over time that may influence age-related decline. This is of great importance in cases in which a phenomenon - functional decline in this project - is not considered to be acute but rather a manifestation of progressive accumulation of damage over the lifespan responding to environmental factors, such as diet, physical activity and body weight. To date, there are many proposed approaches to identify developmental trajectories over time and each of them has its own strengths and limitations [326]. In this thesis, the IGC approach as well as the GBTM approach were used based on the following rationale.

First, both methods effectively handle unbalanced sample sizes across ages of dietary assessment as well as inconsistent time intervals between assessment years [322]. On the contrary, more common methods such as repeated measures of analysis of variance, regressions with change in scores, z-scores tracking or conditional analysis (hereafter to be named "conventional methods") fail to incorporate this into the parameter estimation [326]. Importantly, both IGC and GBMT handle missing data under the assumption of missing at random, which was met in this project. Conventional methods use only complete sample size over time and thus (a) inflate the probability of type II error by reducing sample size and (b) restrict analysis only among those who have participated in all follow-ups; thus they strongly endanger generalizability of findings [326]. Third, the combination of IGC and GBTM allows for individual deviations from the average growth curve of a sample and simultaneously identifies groups of participants with similar growth curves in each group but of very distinctive curves

compared to other groups [322]. In other words, the combination of methods used in this thesis considers all inter- and intra-individual variation in diet quality over time. Conventional methods, on the other hand, allow mainly for average growth curves or mean comparisons, which despite being valuable, they do not explore the full potential of longitudinal data. Fourth, an overall advantage of IGC and GBTM versus conventional methods, relies on the fact that findings have a straightforward interpretation which is not dependent on restrictive assumptions, such as multicolinearity, conditional dependence [326]. Although conventional methods are simple and straightforward to implement, findings deriving from them may be misleading and difficult to interpret. For example changes in z-scores or conditional analysis do not assume a continuum of development but rather use one time point as a reference; therefore interpretation of all other time points is dependent on one reference point which may not have plausible rationale [326]. Finally, both methods identify rather than pre-assume developmental trajectories of individuals (IGC) or groups (GBTM) deriving from the best data fit; hence they are not dependent on subjective categorization of a priori assumptions, as in cases of change in scores or z-scores [326].

Despite overall strengths versus conventional methods, IGC and GBTM do not come without limitations. Both methods are computationally very intensive and because they identify trajectories a posteriori, solid levels of background knowledge are required to justify findings are meaningful [326]. Similarly, because they can identify all types of growth curves including non-linear, their use should be thoroughly justified by evidence-based hypotheses to establish plausibility of findings. Regarding GBTM, identified groups should not be treated as literal entities or definite groups from which people can step up to another; they rather represent latent strata of individuals following approximately similar developmental growth for the measure of interest (diet quality in this project). To simplify an already complex model, conditional independence of group-based trajectories is assumed in so that heterogeneity between groups will be so large, that members of each group can be categorized safely into the specific group they are assigned [323]. Finally, a generic limitation of statistical approaches

exploring growth trajectories is that the variable of interest needs to be measured more or less at the same age for all cohort members [326]; yet in this project participants derived from a birth cohort and thus this limitation was not relevant.

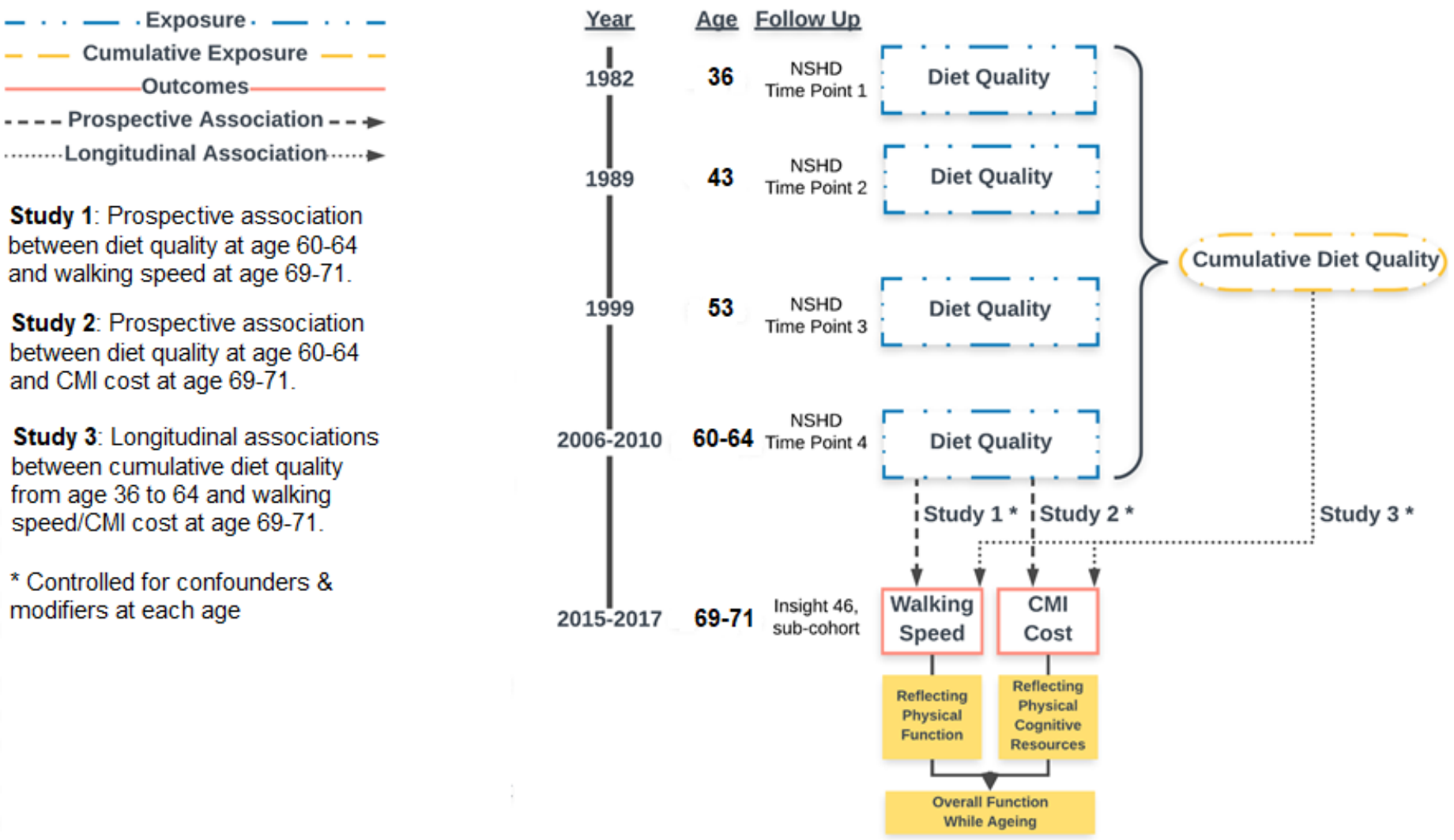

Figure 3.5 Outline of the research project

Chapter 4 - Diet Quality in Late Midlife and Walking Speed in Later Life

This chapter has resulted in a peer-reviewed published paper as well as a peer-reviewed abstract publication, as follows:

Tektonidis TG, Coe S, Esser P, Maddock J, Buchanan S, Mavrommati F, Schott JM, Izadi H, Richards M, Dawes H. Diet quality in late midlife is associated with faster walking speed in later life in women, but not men: findings from a prospective British birth cohort. *The British journal of nutrition*. 2019:1-21. 111.

Tektonidis TG, Esser P, Coe S, Maddock J, Buchanan S, Mavrommati F, Schott J, Izadi H, Richards M, Dawes H. MON-LB692: Diet Quality in Late Midlife is Associated with Faster Walking Speed in Later Life in Women, but Not Men: Findings From a British Birth Cohort. *Clinical Nutrition*. 2019; 38:S316-S317.

4.1 Summary

The aim of this chapter was to explore the prospective association between diet quality of men and women in late midlife and walking speed in later life, reflecting age-related physical function. The results showed there was a null overall association between diet quality in late midlife and walking speed. Sex-specific analysis showed an independent positive association between higher diet quality and faster walking speed in women and a null association for men. Of individual components, greens, beans, whole grains, total, seafood and plant protein were associated with faster walking speed in women. This chapter confirmed that high diet quality as late as midlife is likely to maintain better physical function with sex differences modifying this relationship.

4.2 Introduction

Among lifestyle factors, a healthy diet, as described by the WHO [128], has been shown to slow down the progression of physical decline [165]. An extensive summary of literature on diet, physical function and age-related decline has been presented in Chapter 2. There is accruing evidence for the beneficial effect of single nutrients [151, 153, 193, 195], food groups [184, 186] and regional dietary patterns [163, 196, 202, 204, 209, 210] on physical function; however nutrients are not consumed in isolation and regional dietary patterns may not be appropriate in all contexts due to differences in food preference, availability and accessibility.

The HEI-2015 is a valid overall diet quality index and an extensive overview has been presented in Chapter 3. Evidence for the relationship between the HEI in midlife and physical performance [210] and physical function [163] has been published; yet findings were indicative of cross-sectional associations [163, 210], measures of physical function were self-reported [163] or sample was women only [163]. In addition, findings from the NSHD showed a positive association between *a posteriori* diet quality over a 30-year period in adulthood and objective measures of physical performance in late midlife [188], with current diet in late midlife being of particular importance.

But to further understand the impact of diet quality in late midlife on age-related physical function, it would be useful to assess diet quality according to evidence-based dietary guidelines. Given the already mentioned differences in biological ageing between men and women, it would be also important to assess modification of the association by sex. Moreover, the use of walking speed as an objective measure of physical function, which is also tightly linked to activities of daily living [89] and reflects the musculoskeletal status of older people [8], would add valuable evidence to this research field. Chapter 2 has already discussed available evidence for diet and walking speed and revealed a significant research gap.

Therefore, the aim of this chapter was to explore the prospective association between diet quality of men and women in late midlife and walking speed in later life, reflecting age-related physical function. The specific objectives were:

1. The extent to which overall diet quality at age 60-64, as indicated by an evidence-based diet quality index, the HEI-2015, was prospectively associated with walking speed at age 69-71 in overall well-functioning men and women in a British birth cohort.
2. The extent to which there was a relationship when modified by sex.
3. The extent to which individual dietary components of HEI-2015 were prospectively associated with walking speed at age 69-71.

4.3 Methods

4.3.1 Participants

The data for the analysis were from participants in the Insight 46 with walking speed data at age 69-71 and dietary data in the NSHD at age 60-64 (Figure 4.1). Both cohorts have been described in detail in Chapter 3. Participants with <three days of dietary data (n=54) and <two walks in gait assessment (n=5) were excluded from the analysis to achieve highest data validity. Men with walking speed >1.61 m/s (n=40) and women with >1.52 m/s (n=49) were further excluded, representing non-feasible values, as defined by two standard errors of normative values of walking speed from previous literature [57], and unpublished data. The final sample for this study was 331 people (167 men, 164 women), aged 60-64 at baseline.

4.3.2 Diet Quality at Age 60-64

Dietary assessment at age 60-64 and calculation of the HEI-2015 have been described in Chapter 3. An overview of the components and scoring criteria is shown in Table 3.4 and conversion procedure in Appendix 3. For optimal visualization, radar plots were used to

determine differences in patterns of diet quality between sexes with regard to HEI-2015 component and total scores.

4.3.3 Walking Speed Estimation

Estimation of walking speed has been described on in Chapter 3. For this study, mean walking speed was estimated during four 10-m undisturbed walks. To account for anthropometric differences between sexes, which affect walking pattern, derived walking speed was normalized for leg length at age 69-71, as introduced by *Hof (1996)* *[317]*.

4.3.4 Descriptive Characteristics at Age 64

Identification of descriptive characteristics up to age 64 has been described in detail in Table 3.5. For this study, the following parameters were considered: education attainment up to age 26, occupation at age 53, and the following self-reported characteristics at age 60-64: marital status, leisure time physical activity during past four weeks, smoking status, use of at least one dietary supplement, BMI, total number of comorbidities, balance ability. Missing values of all variables were <4% of study sample, with the exception of 11% for BMI of men (Table 4.1).

Table 4.1 Missing values of descriptive characteristics of participants with dietary data at age 60-64 and walking speed data at age 69-71, overall and by sex, n=331

	Overall (n=331)	**Women (n=164)**	**Men (n=167)**
	n (%)	n (%)	n (%)
Age	0 (0)	0 (0)	0 (0)
Follow-up period	0 (0)	0 (0)	0 (0)
Occupation at age 53	0 (0)	0 (0)	0 (0)
Education at age 26	9 (2.7)	4 (2.4)	5 (3)
Marital status	11 (3.3)	6 (3.7)	5 (3)
Comorbidities	0 (0)	0 (0)	0 (0)
Leisure physical activity	5 (1.5)	2 (1.2)	3 (1.8)
Smoking status	12 (3.6)	6 (3.7)	6 (3.6)
Supplement use	3 (0.9)	2 (1.2)	1 (0.6)
Body mass index	23 (6.9)	3 (0.9)	20 (11.9)
Balance time, eyes open	1 (0.3)	0 (0)	1 (0.6)

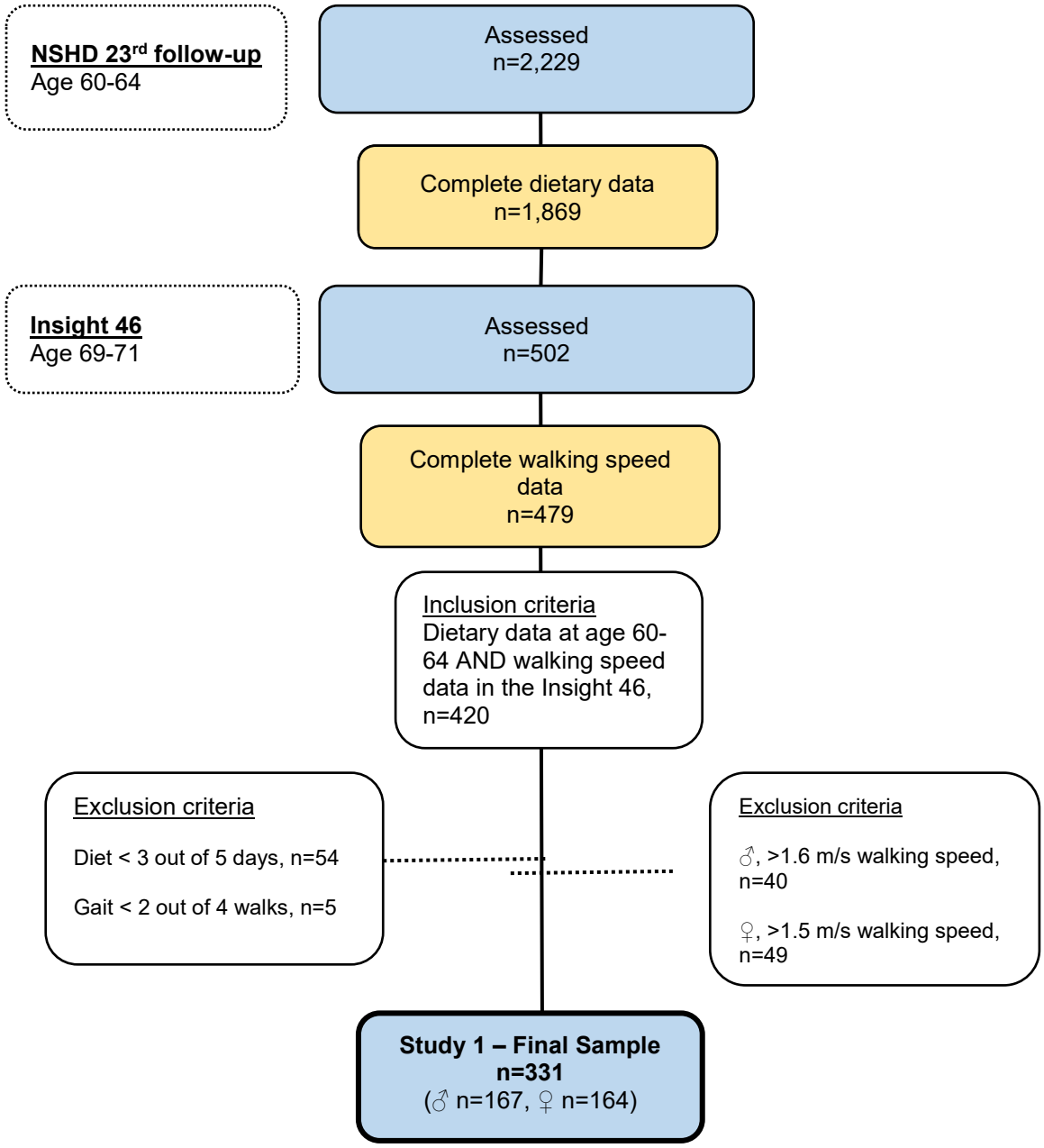

Figure 4.1 Inclusion criteria and sample size for Study 1 (Chapter 4)

4.3.5 Statistical Analysis

Linearity was assessed by a scatterplot of HEI-2015 per 10-point increment against walking speed values. Multicolinearity was assessed against tolerance and variation inflation factor values [327]. Data was assessed for outliers, influential and high leverage observations [327]. Sensitivity analysis was performed by excluding cases with high leverage observations. Homoscedasticity was assessed using visual inspection of the studentized residuals being plotted versus the predicted values of walking speed for women and men. Finally, normality of the studentized residuals was assessed by Shapiro-Wilk test and by graphical methods of normal Q-Q plots [328].

Unadjusted, sex adjusted and multivariable linear regression models were used to determine the association between 10-point increment of HEI-2015 and walking speed. Due to evidence from previous literature [204, 227], a modifying effect of sex was explored and detected and further analysis was stratified by sex. A 10-point increment in the HEI-2015 was selected to reflect more meaningful changes in walking speed. The multivariable models were adjusted for age at dietary assessment, follow-up period, occupation, education, marital status, leisure physical activity, smoking, supplement use, total number of comorbidities, body mass index and balance time with eyes open, all modelled as shown in Table 4.2. In sensitivity analyses, the relationship between the 13 individual HEI-2015 components scores and walking speed was also explored in women using simple and multivariable linear regression models with stepwise function and same covariate adjustments.

4.4 Results

Characteristics of participants up to age 64 are presented in Table 4.2. On average, women were less likely to have a professional occupation, less likely to be married and performed worse in the balance test than men; yet they were more moderately active and used supplements more often (Table 4.2).

Regarding diet quality, participants scored on average 61 HEI-2015 points (Table 4.3), with higher scores in whole fruits and total protein foods. More than 70% of them met the recommendations for these components and they also scored high in sodium and added sugars components; yet only one out of three and less than one out of five met the recommendations of those components, respectively. By sex, women had on average higher total HEI-2015 scores compared to men (Table 4.3). They also had higher scores of individual components such as total fruits, whole fruits, total vegetables, dairy, and sodium and met the recommendations for those components more often, alongside those for greens and beans. Men scored higher only in the total protein food component but there was no indication they met the recommendations more often that women. The same trend can be seen in Figure 4.2, where the percentage of maximum points received for each component on average is presented.

Visual inspection of scatter plots indicated no departure from the assumption of linearity. To correct for multicolinearity, HEI-2015 per 10-point increment was mean centred [327]. Neither studentized deleted residuals nor Cook's distance values showed any influential points or outliers, respectively. After excluding potential high leverage observations, findings did not differ. Finally, homoscedasticity and normality (Shapiro-Wilk's test, $p > 0.05$) were met. There was a statistically significant modifying effect of sex, and the interaction term between diet and sex explained an additional 8.1% of the total variance ($p < 0.01$).

Table 4.4 shows findings of the main analysis. Men had faster walking speed than women, even when controlled for leg length differences. Over a median follow-up period of 7.2 years, a null overall association was observed; yet there was evidence for a modifying effect of sex. In stratified analysis, a 10-point increment in HEI-2015 at age 60-64 was associated with faster non-normalized and normalized walking speed at age 69-71 in women but not men. This association remained following adjustment for various factors. Null associations were found for men in any model. Of the 13 HEI-2015 components, higher scores for greens and beans,

whole grains and seafood and plant proteins were associated with faster walking speed in women in the unadjusted model but only greens and beans and total protein foods in the multivariable model (Table 4.5).

Table 4.2 Descriptive characteristics of participants with dietary data at age 60-64 and walking speed data at age 69-71, overall and by sex, n=331

	Overall (n=331)	**Women (n=164)**	**Men (n=167)**
		Mean [sd], n (%)	
Age, years	63.3 [1.1]	63.3 [1.0]	63.3 [1.1]
Occupation			
Professional/Intermediate	212 (64)	90 (55)	**122 (73)** †
Skilled (non-manual)	72 (22)	**54 (33)** *	18 (11)
Skilled (manual)	29 (8.5)	7 (4)	**22 (13)** †
Semi-Skilled	16 (5)	**13 (8)** ‡	3 (2)
Unskilled	1 (0.5)	0 (0)	2 (1)
≥ Secondary Education,	250 (76)	123 (75)	127 (76)
Married/with Partner	268 (81)	126 (77)	**142 (85)** ‡
Total Comorbidities, n >2	36 (12)	16 (10)	20 (12)
Leisure Physical Activity			
None	173 (52)	79 (48)	94 (56)
1 to 4 times/week	66 (20)	**41 (25)** ‡	25 (15)
≥ 5 time/week	92 (28)	44 (27)	48 (29)
Smoking Status			
Never	119 (36)	64 (39)	55 (33)
Former	198 (60)	93 (57)	105 (63)
Current	14 (4)	7 (4)	7 (4)
Supplement use, yes	159 (48)	**92 (56)** †	67 (40)
Body Mass Index, kg/m	27.1 [3.8]	27.1 (4.2]	27.1 [3.2]
Balance Time, eyes open, ≥ 30s	179 (54)	75 (46)	**104 (62)** †

* p value ≤ 0.001, † p value ≤ 0.01, ‡ p value ≤ 0.05

Table 4.3 The HEI-2015 total and component scores of participants with dietary data at age 60-64 and walking speed data at age 69-71, overall and by sex, n=331

	Overall (n=331)		**Women (n=164)**		**Men (n=167)**	
HEI-2015, 0-100						
Median (range)	61 (27-93)		63 (27-93)		59 (30-92)	
Mean [sd]	61 [12]		63 [12] †		60 [12]	
	Mean [sd], n max score[1] (%)					
Component Scores						
Adequacy						
Total Fruits[2]	3.5 [1.6]	140 (42)	**3.9 [1.4] ***	**85 (52) ***	3.1 [1.7]	55 (33)
Whole Fruits[2]	4.2 [1.4]	243 (73)	**4.5 [1.1] ***	**135 (82) ***	3.9 [1.6]	108 (65)
Total Vegetables[2]	3.7 [1.1]	121 (36)	**4.0 [1.0] ***	**73 (45) ***	3.5 [1.1]	48 (29)
Greens and Beans[2]	3.3 [1.7]	123 (37)	3.5 [1.6]	**67 (41) †**	3.1 [1.7]	56 (34)
Whole Grains	6.5 [3.5]	119 (36)	6.6 [3.4]	63 (38)	6.3 [3.6]	56 (34)
Dairy	4.9 [2.3]	17 (5)	**5.4 [2.5] ***	**14 (9) †**	4.4 [2.0]	3 (2)
Total Protein Foods[2]	4.6 [0.8]	252 (76)	4.5 [0.9]	118 (72)	**4.6 [0.7] †**	134 (80)
Seafood and Plant Proteins[2]	2.8 [1.9]	109 (33)	2.8 [1.9]	56 (34)	2.8 [1.9]	53 (32)
Fatty Acids	2.1 [2.4]	6 (2)	2.1 [2.6]	5 (3)	2.2 [2.2]	1 (1)
Moderation						
Refined Grains	5.9 [3.4]	86 (26)	6.1 [3.3]	47 (29)	5.8 [3.5]	39 (23)
Sodium	7.6 [2.5]	115 (35)	**7.9 [2.5] †**	**68 (42) †**	7.3 [2.5]	47 (28)
Added Sugars	7.4 [2.0]	56 (17)	7.3 [2.0]	29 (18)	7.5 [1.9]	27 (16)
Saturated Fat	4.5 [3.0]	20 (6)	4.2 [3.0]	10 (6)	4.7 [3.0]	10 (6)

[*] p value ≤ 0.001, [†] p value ≤ 0.05

[1] Number of participants who met the dietary recommendation for each component and thus the standard for maximum score in each component, [2] Maximum score is 5; for the rest components is 10.

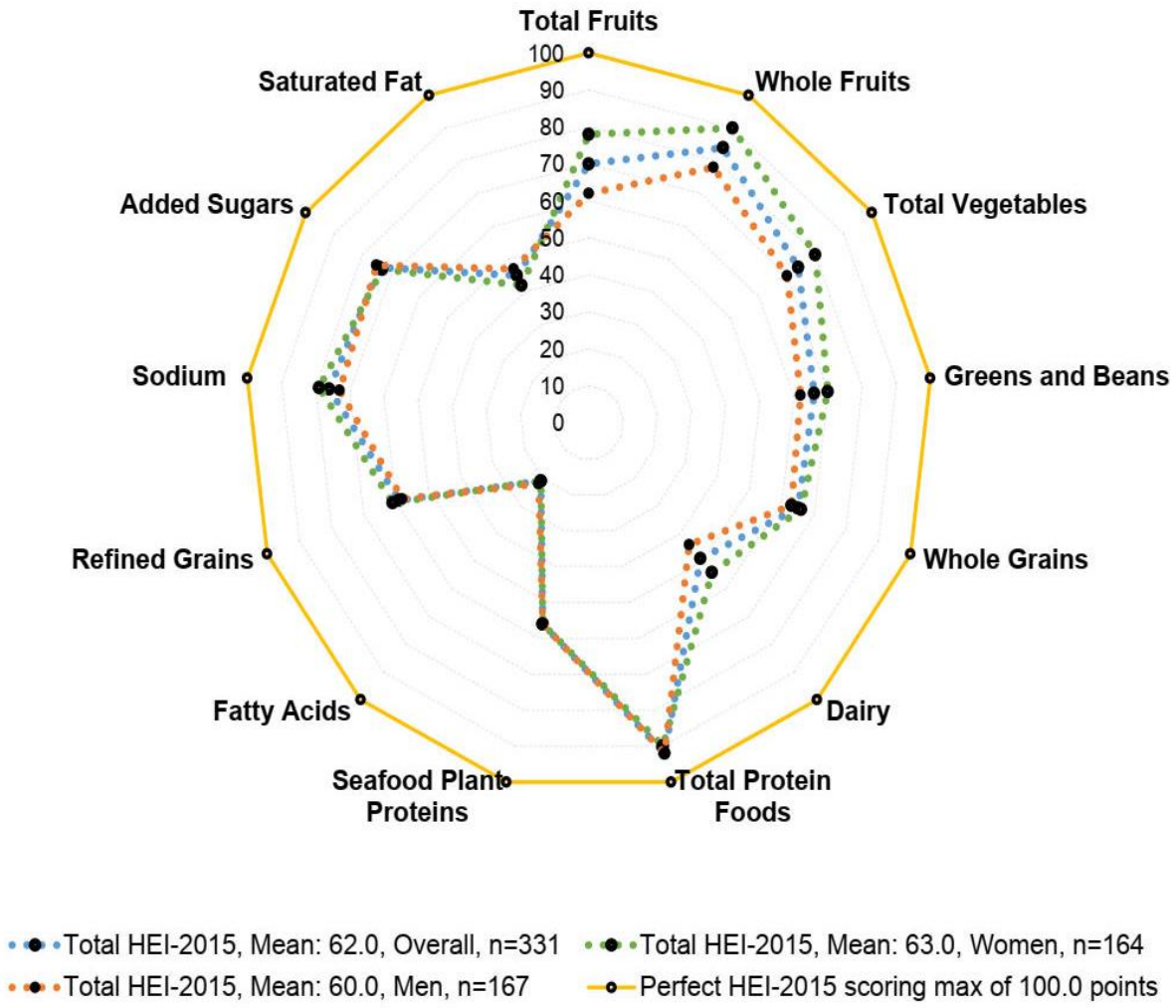

Figure 4.2 Radar plot of the HEI-2015 score at age 60-64 by available data of walking speed at age 69-71, n=331 [18]

[18] The percentage of maximum points received for each component on average is presented, with 0% in the centre and 100% at the outer edge. A perfect HEI-2015 scores a total maximum of 100 points (100% in each component) and is represented by the solid line around the perimetre.

Table 4.4 Unstandardized coefficients (β) and 95% confidence intervals [95% CIs] of walking speed at age 69-71 by 10-point increment of HEI-2015 at age 60-64, overall and by sex, n=331

		HEI-2015, 0-100, per 10-point increment		
		Overall	**Women**	**Men**
	n	331	164	167
Walking speed, m/s	mean [sd]	1.37 (0.15)	1.32 (0.14)	**1.39 (0.15) ***
Sex stratified [1]	β [95% CI]	0.01 [-0.01, 0.02]	**0.03 [0.01, 0.04] ***	-0.01 [-0.03, 0.01]
Multivariable adjusted [2]		0.01 [-0.01, 0.02]	**0.02 [0.01, 0.04] †**	-0.01 [-0.03, 0.01]
Normalized walking speed [3], -	mean [sd]	0.45 (0.05)	0.44 (0.05)	**0.47 (0.05) ***
Sex stratified	β [95% CI]	0.01 [-0.01, 0.01]	**0.01 [0.01, 0.02] †**	-0.01 [-0.01, 0.01]
Multivariable adjusted		0.01 [-0.01, 0.01]	**0.01 [0.01, 0.02] †**	-0.01 [-0.01, 0.01]

[*] p value ≤ 0.001, [†] p value ≤ 0.05

[1] Sex stratified: Overall model was sex adjusted, sex models were stratified by sex due to significant sex interaction, [2] Additionally adjusted for: age (years), time period until gait assessment (years), occupation (reference: unskilled), married/with partner (yes), at least secondary education (yes), smoking status (reference: never), leisure physical activity per month (reference: none), supplement use (yes), number of comorbidities (reference: zero), body mass index (kg/m^2) and balance time (eyes open, seconds), [3] Not adjusted for body mass index because walking speed was already normalized for leg length.

Table 4.5 Unstandardized coefficients (β) and 95% confidence intervals [95% CIs] of walking speed at age 69-71 by HEI-2015 component scores at age 60-64, in women

	Walking speed, m/s		Normalized walking speed, -	
	Unadjusted	**Multivariable adjusted [1]**	**Unadjusted**	**Multivariable adjusted [1]**
Adequacy				
Total Fruits	0.01 [-0.13, .015]	0.01 [-0.16, 0.17]	0.01 [-0.13, 0.15]	0.01 [-0.14, 0.15]
Whole Fruits	0.05 [-0.09, 0.18]	-0.01 [-0.16, 0.14]	0.05 [-0.09, 0.18]	0.02 [-0.13, 0.16]
Total Vegetables	-0.01 [-0.15, 0.14]	0.03 [-0.12, 0.18]	-0.01 [-0.16, 0.15]	-0.01 [-0.15, 0.15]
Greens and Beans	**0.02 [0.01, 0.04]** †	**0.02 [0.01, 0.03]** †	**0.01 [0.001, 0.01]** *	**0.01 [0.001, 0.01]** †
Whole Grains	**0.01 [0.01, 0.02]** †	0.08 [-0.06, 0.22]	**0.01 [0.001, 0.005]** †	0.09 [-0.03, 0.20]
Dairy	-0.04 [-0.17, 0.10]	-0.03 [-0.15, 0.09]	-0.04 [-0.17, 0.01]	-0.03 [-0.17, 0.11]
Total Protein Foods	0.06 [-0.07, 0.20]	**0.03 [0.01, 0.06]** †	0.06 [-0.08, 0.20]	**0.01 [0.001, 0.02]** †
Seafood and Plant Proteins	**0.01 [0.01, 0.03]** †	0.07 [-0.07, 0.21]	**0.01 [0.001, 0.01]** †	0.08 [-0.06, 0.22]
Fatty Acids	-0.02 [-0.15, 0.12]	0.04 [-0.10, 0.18]	-0.02 [-0.15, 0.12]	0.04 [-0.10, 0.18]
Moderation				
Refined Grains	-0.01 [-0.13, 0.13]	0.01 [-0.13, 0.15]	-0.02 [-0.20, 0.17]	0.01 [-0.12, 0.13]
Sodium	0.08 [-0.06, 0.21]	0.06 [-0.08, 0.19]	0.07 [-0.06, 0.21]	0.07 [-0.07, 0.20]
Added Sugars	-0.05 [-0.19, 0.09]	0.02 [-0.12, 0.17]	-0.05 [-0.18, 0.09]	0.01 [-0.14, 0.16]
Saturated Fat	0.03 [-0.11, 0.17]	0.07 [-0.07, 0.20]	0.03 [-0.11, 0.17]	0.07 [-0.06, 0.21]

* p value ≤ 0.01, † p value ≤ 0.05

[1] Adjustments are as per main analysis.

4.5 Discussion

Utilizing data from the longest running British birth cohort, this study showed that diet quality, as indicated by higher HEI-2015 scores at age 60-64, was associated with faster walking speed in women, but not men, seven years later, independently of a wide range of factors. It is novel that this study showed sex differences in the prospective relationship between a valid diet quality index in line with dietary recommendations, in late midlife and better physical function in later life, as indicated by walking speed. This finding further confirms the evidence that healthy dietary choices in late midlife, as those reflected by high HEI-2015 scores, may slow down the rate of age-related physical decline.

A novel finding of this study was that high diet quality was linked to faster walking speed in women but not men. Consistent with this, similar sex differences have been observed in studies investigating associations between diet and physical function [195, 204, 227]. *Perala et al. (2016, 2017*) showed an association between a healthy Nordic diet and better physical performance measured by the Senior Fitness Test [204] and muscle strength [227], only in women. In addition, data from the HCS Study revealed similar sex differences in the association between micronutrients and vitamins and physical performance, with shorter 3-m walk times among older women with higher intakes of antioxidants, beta-carotene, selenium, vitamin D and energy, but not in men [195].

Potential explanations of these findings can be hypothesized. First, women had higher diet quality compared to men in the present study and additionally higher scores in presumably beneficial food groups. Likewise, women of similar age in the MEC Study had higher HEI-2015 scores than men [215]. Several studies have shown sex differences in the general direction of healthier food choices for women than men with regard to both food groups and nutrient intakes [218-220, 248]. Results from the NSHD showed that women in this study have increased intakes of antioxidants over time due to higher consumption of fruit and vegetables and lower consumption of whole milk, butter and red meat, compared to men [218-220, 248]. Additionally,

HEI-2015 is a multidimensional score which allows for different combinations of components to achieve the same total score [264]. Therefore, for a given total HEI-2015 score, different individual component scores might have resulted in differences of the observed association between men and women. Life expectancy of women is longer than men [1] but muscle strength affecting walking ability declines earlier in women [329]. Men who survived to the latest follow-up tend to be more physically robust than women who, despite living longer, have faster muscle strength decline [329], lower initial levels of physical function [155, 330] and slower walking speed than men in the present study. Given the considerable evidence that links healthy diet to muscle mass, strength and physical function of older adults [161], it is likely that women, in whom morbidity rates are higher and musculosketal levels are lower, are more responsive to dietary manipulation in late midlife compared to men with regard to walking speed, which is also predictive of survival rates [28]. The positive association between diet quality and walking speed in women may also indirectly reflect its benefit against age-related disability [331] and sarcopenia [160], resulting in longer survival. Moreover, the possibility of biological sex differences in ageing, with men having more muscle and bone mass than women over the lifespan, despite decline rates being much faster for men in older age, should be considered [30]. Sex hormones are well known to decline much steeper in older women than men, resulting in significant loss of physical function [27]. Finally, sex differences in the observed association may reflect differences in cumulative exposure of high diet quality over the lifespan, which are linked to physical performance in later life, as shown previously [155, 188].

Multiple studies have shown an association between higher diet quality and healthy ageing [163], overall health-related quality of life [228], lower disability rates [332] and better physical performance among older people [210]. A recent analysis from the Nurses' Health Study showed a lower risk of self-reported physical impairment with higher alternative HEI-2010 (aHEI-2010) scores over an 18-year period in older people [224]. In the present study, a 37-unit increase in the HEI-2015 was associated with a clinically meaningful change of 0.1 m/s in walking speed, proposed to be predictive of survival in older people [28], thus suggesting a

small but considerable effect. Similarly, after considering the same kind of factors as in this study, *Xu et al. (2012)* [210] found a cross-sectional association between higher HEI-2005 total scores (median HEI: 55 vs 61 in the present study, range 15-91 vs 27-93 in the present study) and faster walking speed among 2,100 older men and women; yet compared to this study, the sample was older and was less high-functioning, as indicated by slower walking speed, higher prevalence of comorbidities and higher body mass index [210].

Using healthy dietary patterns, albeit cultural and regional specific, evidence supports the findings of this study regarding the relationship of high diet quality in midlife and better physical function in later life [188, 196, 202, 204, 207, 209]. In a prospective study of community-dwelling older adults, walking speed was faster among those with better diet quality as indicated by higher MedDiet scores eight years earlier, suggesting a cumulative effect of diet on mobility performance [209]. Moreover, high diet quality, as reflected by a healthy Nordic diet score, was associated with 20% better physical performance in the 6-min walk test over a 10-year period, among Nordic women aged over 60 [204]. Despite cultural and regional differences in food choice, all these dietary patterns highlight the importance of diet quality over quantity with main focus on intakes of plant foods, whole grains and fish/long-chain ω-3 PUFAs and lower intakes of red and processed meats, added sugars and saturated fat [204, 209]. Therefore, it is likely that overall diet quality, rather than a specific diet, is important for maintaining physical function, as shown in this study.

This study also showed that higher HEI-2015 scores for greens and beans, whole grains, total protein, seafood and plant proteins were associated with faster walking speed in women. Findings are consistent with evidence from prospective studies which showed that lower fruit and vegetable consumption among older people was associated with functional limitations and disability, over an eight-year [333] and a 17-year period [186]. Using data from the NSHD, *Robinson et al. (2018)* [188] assessed the effect diet quality on physical performance over a 30-year period in adulthood, as measured by chair rise, timed-up-and-go and standing balance

tests. The study showed a positive association between early adulthood and early older age dietary patterns, high in fruits, vegetables and wholegrains, and measures of physical performance. It is interesting that using data from the same cohort, the present study confirmed those findings additionally for walking speed, which is another valid measure of physical capability. Regarding protein, the present findings support previous research from the NSHD, which suggested a weak relationship of higher protein intake over middle adulthood with better physical capability in older age [155]; the low strength of the association observed might be due to that study assessing quantity (total protein intake) rather than quality (seafood versus meat protein). Finally, the HCS Study further confirmed the results of the present study for seafood and plant protein foods, by showing a positive association between fatty fish consumption, rich in vitamin D and ω-3 fatty acids, and objective-measures of physical capability among 2,000 older adults [189].

Excessive levels of oxidative stress and inflammation increase with ageing and are involved in loss of skeletal muscle mass and strength leading to sarcopenia [22]. High levels of these are also predictive of declines in physical performance [199] and the onset of disability and frailty [334]. Antioxidants and anti-inflammatory components which fruit, vegetables, nuts, greens and seafood products and a high ratio of unsaturated/saturated fatty acids, have in abundance, counteract oxygen free radicals and downregulate inflammation cytokines [335]. Indeed, a large volume of evidence confirms the beneficial effect of dietary antioxidants and anti-inflammatory components including vitamin D, vitamin C, vitamin E, carotenoids and polyphenols on muscle mass strength [144, 145], physical function and performance [143, 151, 195, 197], frailty [336] and disability [198]. For example, high levels of antioxidants have been associated with high levels of creatine kinase activity, which enhances skeletal muscle repair and with less oxidative damage to genetics, proteins, and lipids in skeletal muscle cells [337]. Thus, they play a major role against atrophy and loss of muscle fibres. Finally, a healthy diet might be also indirectly related to better physical function, as indicated by walking speed, through lower risk of chronic disease such as CVD, obesity or arthritis, all of which are

associated with poor physical ability [338]. Chronic disease, such as CVD, affect multiple body systems, and diets such the ones described by a high HEI score have been shown to reduce its incidence [279].

The study has major strengths including the longest running and in most cases nationally representative British birth cohort of men and women, long follow-up to detect long-term dietary effects, the use of a valid measure of diet quality [264], objective measures of walking speed indicating physical function [89] and detailed information on a broad range of factors at dietary assessment. Diet was measured using food diaries over all seasons, which are still considered the "gold standard" method [42]. Finally, all study participants were within the same age group and there was control for age at dietary assessment, thus limiting this important source of confounding.

Limitations include participants being more likely to have provided dietary information at age 60-64 than those in the original NSHD but not in Insight 46; hence they were possibly more health conscious [246]. Interim health events between baseline and follow-up were not available; however the models were controlled for number of comorbidities at baseline. In addition, participants in Insight 46 were in general healthier than counterparts in the general population [246]. Indeed, walking speed values of men and women in this study were significantly higher than normative values [91], indicating overall healthy ageing. Walking speed was not assessed at baseline; yet the models were controlled for physical activity and balance tests at baseline, both reflecting functional status. Although selection procedure of Insight 46 was thoroughly designed, potential collider bias[19] deriving from selection criteria may be present [339]. Only white British-born people were included in the study; thus generalizability should be made with caution; however, when compared to the NDNS [340], which reflects

[19] Occurs when "*two variables independently influence a third variable, and that third variable is conditioned upon*" [64]. See 7.3 Methodological Considerations.

dietary intake of the British population, the original NSHD sample showed notable agreement in terms of age-matched trends in food [218] and nutrient intake [220]. Finally, despite the prospective design and the thorough adjustment for major confounders, the possibility of residual confounding[20] cannot be excluded.

4.6 Conclusion

In conclusion, this chapter adds evidence to the relationship of high diet quality in late midlife, in particular in women, and better physical function in later life, as indicated by faster walking speed. Despite the point estimate being relatively small, it is important that even slight changes in diet quality in midlife, in line with dietary guidelines, such as increase in consumption of greens, whole grains and whole fruits alongside lower intakes of added sugars and saturated fat from animal sources, are likely to maintain better physical function. Importantly, sex differences are likely to affect this relationship, suggesting that different strategies in lifestyle interventions of ageing people should be further explored.

[20] Defined as "*the distortion that remains after controlling for confounding in the design and/or analysis of a study*" [64]. See 7.3 Methodological Considerations.

Chapter 5 - Diet Quality in Late Midlife and Cognitive-Motor Interference Cost in Later Life

5.1 Summary

The aim of this chapter was to explore the prospective association between diet quality in late midlife and walking speed under CMI conditions in later life. The results showed there was a null overall association, but analysis by sex showed a positive association between higher diet quality and faster walking speed in women and slower speed and increased CMI cost in men, seven year later. Associations for men held after multiple adjustments. Null associations were found with increasing complexity of the cognitive task. Of individual components, higher consumption of greens and beans and of total protein foods and lower saturated fat intake were associated with faster walking speed and lower CMI cost. This chapter expanded the evidence that sex modified the relationship between diet quality in late midlife and walking speed under CMI conditions, reflecting ability to utilize limiting physical and cognitive resources with ageing.

5.2 Introduction

Chapter 4 suggested a protective effect of high diet quality in late midlife on walking speed in later life in women; however it is seldom that people walk in isolation in everyday life. Most actions of movement are performed in combination with another task such as walking and orientating or recalling directions. Cognitive skills play a major role in daily activities and overall well-functioning, in particular of older people who additionally face the challenge of declining physical and cognitive resources. Living independently with ageing is of vital importance and alongside physical function, maintaining optimal cognitive profile is tightly related to quality of life [14, 15]. The rate of cognitive decline with ageing varies and walking ability reflects this interpersonal variability, in particular under CMI conditions, such as walking and performing a cognitive task [77]. Changes in walking speed due to CMI express the overall ability of older

people to combine limiting attentional resources [77, 122]. A detailed overview of potential CMI strategies and its association with walking speed has been described in Chapter 1. Although sex differences in walking performance under CMI conditions are shown to favour women [124], in general, walking speed is expected to slow down (CMI increases) when a cognitive stressor is applied [122].

An active and healthy lifestyle in late midlife is protective against cognitive decline [169, 170]. Healthy dietary patterns are beneficial against detrimental brain alterations [174], cognitive decline [172, 173] and incidence of neurodegenerative conditions [179]. A literature summary on diet and cognition has been discussed in Chapter 2. Research to date has mainly focused on the MedDiet due to its anti-inflammatory and anti-oxidant properties [176, 178]; yet although beneficial, this dietary pattern is regional. In addition, despite accruing evidence for global cognition, findings are not consistent for specific cognitive domains in older people [176]. For example, results from the NSHD showed a longitudinal inverse association of healthy dietary patterns and slower decline in memory and visual search speed [172] whereas a key meta-analysis of RCTs showed no effect of MedDiet on these domains in addition to executive functions [176]. Heterogeneity of findings is partially because cognition is a multidimensional function of various domains, which may or may not be directly affected by dietary exposure.

Considering the importance to maintain walking ability with ageing and the tight link of walking speed with cognitive functioning, it may be preferable to explore the relationship between diet quality and walking speed under CMI conditions. Such exploration would reflect on overall ability to optimally use limiting physical and cognitive resources with ageing. Thus, this approach might be more clinically relevant and likely to carry an important public health message for the ageing population. In addition, despite proposed sex differences in walking performance under CMI conditions, to date there is no research whether those differences may be attributable to lifestyle exposure, in particular diet.

Therefore, hypothesizing that healthier diet may reflect better walking performance under CMI conditions, the aim of this chapter was to explore the prospective association between diet quality of men and women in late midlife and later life walking speed and CMI cost. The specific objectives were:

1. The extent to which overall diet quality at age 60-64, as indicated by an evidence-based diet quality index, the HEI-2015, was prospectively associated with walking speed under CMI conditions at age 69-71 in overall well-functioning men and women in a British birth cohort.
2. The extent to which there was a relationship when modified by sex and with increasing complexity of the cognitive task while walking.
3. The extent to which individual dietary components of HEI-2015 were prospectively associated with walking speed and CMI cost at age 69-71.

5.3 Methods

5.3.1 Participants

The data for the analysis were from participants in the Insight 46 with walking speed data at age 69-71 and dietary data in the NSHD at age 60-64. Inclusion and exclusion criteria are shown in Figure 5.1. The final sample for this study was n=331 (Task 1), n=399 (Task 2) and n=403 (Task 3).

5.3.2 Diet Quality at Age 60-64

Dietary assessment at age 60-64 and calculation of the HEI-2015 have been described in Chapter 3. An overview of the components and scoring criteria is shown in Table 3.4 and conversion procedure in Appendix 3. For optimal visualization, radar plots were used to

determine differences in patterns of diet quality between sexes with regard to HEI-2015 component and total scores.

5.3.3 Walking Speed Estimation/Cognitive-Motor Interference Cost

Estimation of walking speed has been described in Chapter 3 and 4. For this study, mean walking speed in Task 2 (single-letter-cued verbal fluency) and Task 3 (alternate-letter-cued verbal fluency) was estimated over four 10-m walks per task. Normalization for leg length was performed as described in Chapter 4 [317]. CMI cost on walking speed was calculated as:

$$\frac{(Task\ 2 - Task\ 1)}{Task\ 1} \times 100\% \quad [318]$$

Similarly, CMI cost for Task 3 was calculated to reflect negative changes in speed associated with increasing complexity of the cognitive task.

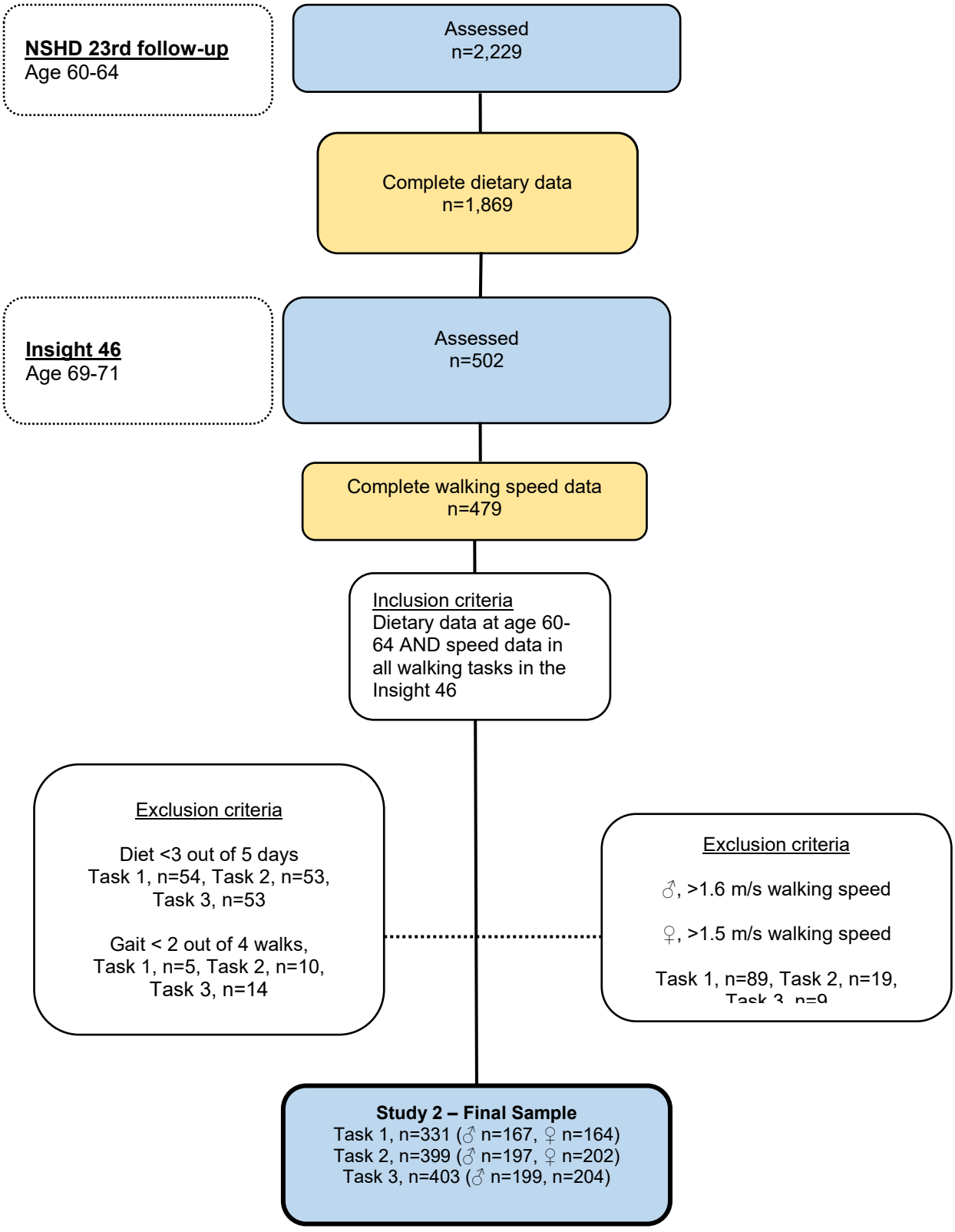

Figure 5.1 Inclusion criteria and sample size for Study 2 (Chapter 5)

5.3.4 Descriptive Characteristics at Age 64

Descriptive characteristics up to age 64 are shown in Table 3.5. For this study, the same parameters as in Chapter 4 were used with the addition of waist to hip ratio, chair rise time at age 60-64 and MMSE score, which was assessed at age 69-71. The addition of the sex-specific waist to hip ratio was based on evidence from Chapter 4 of sex differences modifying the explored relationship and MMSE score and chair rise time were added to control for physical and cognitive performance at dietary assessment age. Missing values of all variables are presented in Table 4.1 and additionally in Table 5.1.

Table 5.1 Missing values of additional descriptive characteristics at age 60-64, n=399

	Overall (n=399)	**Women (n=202)**	**Men (n=197)**
		n (%)	
Waist to hip ratio	0 (0)	0 (0)	0 (0)
Chair rise time	9 (2.2)	4 (2.0)	5 (2.5)
MMSE score	0 (0)	1 (0.5)	0 (0)

5.3.5 Statistical Analysis

Linearity was assessed by a scatterplot of HEI-2015 per 10-point increment against walking speed values and CMI cost in all tasks and diagnostics were explored as in Chapter 4. The multivariable linear regression models were adjusted for age at dietary assessment, follow-up period, occupation, education, marital status, leisure physical activity, smoking, supplement use, total number of comorbidities, waist to hip ratio, MMSE scores and chair rise time, modelled as in Table 4.2 and Table 5.2. Finally, multivariable stepwise regression function was used in sensitivity analyses to explore association between the 13 HEI-2015 component scores and walking speed and CMI cost, when unadjusted results were significant or showed a trend.

5.4 Results

Descriptive characteristics of participants are presented in Table 4.2 and additional characteristics used in this chapter in Table 5.2, overall and by sex. On average, women had lower waist to hip ratio and a better cognitive status score compared to men, although the MMSE scores were close to the maximum score for both. Finally, men were more likely to perform better in the chair rise stand test than women.

Diet quality at age 60-64 has been presented in Table 4.3 and visualized in Figure 4.2. On average women at age 60-64 scored higher in total and most HEI-2015 components than men and also met dietary recommendations more often regarding total and whole fruits, vegetables, greens and beans, dairy products and sodium intake.

Table 5.4 presents results of the main analysis. On average, men had faster walking speed than women even when controlled for leg length differences. In addition, men had a higher CMI cost than women but there was no difference with increasing task complexity. Over a median follow-up period of 7.2 years, null overall association or trend was found for walking speed or CMI cost; however there was strong evidence for a modifying effect of sex. In stratified analysis, a 10-point increment in HEI-2015 at age 60-64 was associated with faster non-and normalized walking speed under CMI conditions at age 69-71 in women and slower walking speed in men (Table 5.4). The point estimate was of the same magnitude for both sexes but of opposite direction. This association remained in all multivariable models for men but not women. Furthermore, an association between higher HEI-2015 scores and increased CMI cost on walking speed was found in men but not women. This association remained in the multivariable model. Finally, a null association was found between diet quality and walking speed or CMI cost with increasing task complexity in either men or women in any model.

Of the 13 HEI-2015 components, higher scores of saturated fat, were associated with faster walking speed under CMI conditions in women in the unadjusted models but associations

were attenuated in the multivariable models (Table 5.5). Furthermore, a trend for higher greens and beans scores was found, which reached statistical significance in the multivariable model. In men, there was a consistent significant inverse association between higher scores of dairy intake and walking speed under CMI conditions in all models and with increased CMI cost only in the unadjusted model (Table 5.6). Higher scores of total protein intake were associated with lower CMI cost in men. Finally, higher scores of fatty acids and whole fruit showed a trend towards increased CMI cost in men; yet results were significant only in the unadjusted (fatty acids) and the multivariable (whole fruit) models, respectively.

Table 5.2 Additional descriptive characteristics of participants with dietary data at age 60-64 and walking speed under cognitive-motor interference conditions at age 69-71, overall and by sex, n=399

	Overall (n=399)	**Women (n=202)**	**Men (n=197)**
	Mean [sd], n (%)		
Waist to hip ratio, cm	90 [8]	**85 [6]** *	96 [5]
Chair rise time, s	24 [6]	25 [7]	**23 [5]** †
MMSE, 0-30 [1]	30 [1]	**30 [1]** ‡	29 [1]

* p value ≤ 0.001, † p value ≤ 0.01, ‡ p value ≤ 0.05

[1] MMSE is treated as ordinal variable and presented as median + interquartile range.

Table 5.3 Descriptive data of walking speed and cognitive-motor interference cost among participants in Insight 46 who performed all walking tasks, overall and by sex (n=403).

	Overall (n=403)	**Women (n=204)**	**Men (n=199)**
		Mean [sd], n (%)	
Task 2			
Walking speed, m/s	1.21 (0.19)	1.18 (0.17)	**1.24 (0.21)** *
Normalized walking speed, -	0.40 (0.06)	0.39 (0.06)	**0.42 (0.07)** *
CMI cost, %	-13.4 (10.0)	-13.2 (8.5)	**-13.5 (11.3)** *
Task 3			
Walking speed, m/s	1.17 (0.20)	1.15 (0.19)	**1.19 (0.21)** *
Normalized walking speed, -	0.39 (0.07)	0.38 (0.06)	**0.40 (0.07)** *
CMI cost, %	-16.8 (10.9)	-16.0 (10.5)	-17.6 (11.1)

* p value ≤ 0.05

Table 5.4 Unstandardized coefficients (β) and 95% confidence intervals [95% CIs] of walking speed under cognitive-motor interference conditions at age 69-71 by 10-point increment of HEI-2015 at age 60-64, overall and by sex, n max=403

		HEI-2015, 0-100, per 10-point increment		
		Overall	**Women**	**Men**
Task 2				
Walking speed, m/s	n	399	202	197
Sex stratified [1]	β [95% CI]	-0.01 [-0.02, 0.02]	**0.03 [0.01, 0.05]** ‡	**-0.03 [-0.05, -0.01]** ‡
Multivariable adjusted [2]		-0.01 [-0.02, 0.01]	0.02 [-0.01, 0.04]	**-0.02 [-0.05. -0.01]** ‡
Normalized walking speed [3], -	n	399	202	197
Sex stratified	β [95% CI]	0.01 [-0.01, 0.01]	**0.01 [0.01, 0.02]** ‡	**-0.01 [-0.02, -0.01]** ‡
Multivariable adjusted		-0.01 [-0.01, 0.01]	0.01 [-0.01, 0.02]	**-0.01 [-0.02,-0.01]** ‡
CMI cost, %	n	326	162	164
Sex stratified	β [95% CI]	-0.8 [-1.7, 0.1]	0.3 [-1.0, 1.5]	**-1.8 [-3.0, -0.6]** †
Multivariable adjusted		-0.5 [-1.5, 0.4]	0.5 [-0.9, 1.9]	**-1.4 [-2.8, -0.1]** ‡

* p value ≤ 0.001, † p value ≤ 0.01, ‡ p value ≤ 0.05

[1] Sex stratified: Overall model was sex adjusted, sex models were stratified by sex due to significant sex interaction, [2] Additionally adjusted for: age (years), time period until gait assessment (years), occupation (reference: unskilled), married/with partner (yes), at least secondary education (yes), smoking status (reference: never), leisure physical activity per month (reference: none), supplement use (yes), number of comorbidities (reference: zero), waist to hip ratio, chair rise time (s) and the MMSE score (0-30), [3] Not adjusted for waist to hip ratio because walking speed was already normalized for leg length.

Continued Table 5.4

		HEI-2015, 0-100, per 10-point increment		
		Overall	**Women**	**Men**
Task 3				
Walking speed, m/s	n	403	204	199
Sex stratified [1]	β [95% CI]	-0.01 [-0.02, 0.02]	0.02 [-0.01, 0.04]	-0.02 [-0.04, 0.01]
Multivariable adjusted [2]		-0.01 [-0.02, 0.01]	0.02 [-0.03, 0.04]	-0.02 [-0.04, 0.01]
Normalized walking speed [3], -	n	403	204	199
Sex stratified	β [95% CI]	-0.01 [-0.01, 0.01]	0.01 [-0.01, 0.01]	-0.01 [-0.01, 0.01]
Multivariable adjusted		-0.01 [-0.01, 0.01]	0.01 [-0.01, 0.01]	-0.01 [-0.01, 0.01]
CMI cost, %	n	323	160	163
Sex stratified	β [95% CI]	-0.6 [-1.6, 0.4]	-0.1 [-1.5, 1.4]	-1.1 [-2.5, 0.3]
Multivariable adjusted		-0.3 [-1.3, 0.8]	0.2 [-1.3, 1.7]	-0.6 [-2.1, 0.8]

[*] p value ≤ 0.001, [†] p value ≤ 0.01, [‡] p value ≤ 0.05

[1] Sex stratified: Overall model was sex adjusted, sex models were stratified by sex due to significant sex interaction, [2] Additionally adjusted for: age (years), time period until gait assessment (years), occupation (reference: unskilled), married/with partner (yes), at least secondary education (yes), smoking status (reference: never), leisure physical activity per month (reference: none), supplement use (yes), number of comorbidities (reference: zero), waist to hip ratio, chair rise time (s) and the MMSE score (0-30), [3] Not adjusted for waist to hip ratio because walking speed was already normalized for leg length.

Table 5.5 Unstandardized coefficients (β) and 95% confidence intervals [95% CIs] of walking speed under cognitive-motor interference conditions at age 69-71 by HEI-2015 component scores at age 60-64, in women, n=202

	Walking speed, m/s		**Normalized walking speed, -**	
	Unadjusted	**Multivariable adjusted [1]**	**Unadjusted**	**Multivariable adjusted [1]**
Adequacy				
Total Fruits	-0.05 [-0.19, 0.09]	-0.06 [-0.21, 0.08]	-0.05 [-0.19, 0.09]	-0.06 [-0.21, 0.09]
Whole Fruits	-0.03 [-0.17, 0.11]	-0.08 [-0.23, 0.06]	-0.03 [-0.17, 0.11]	-0.07 [-0.21, 0.07]
Total Vegetables	0.09 [-0.05, 0.23]	0.07 [-0.09, 0.22]	0.09 [-0.05, 0.23]	0.12 [-0.02, 0.25]
Greens and Beans	0.09 [-0.05, 0.22]	**0.02 [0.01, 0.03] †**	0.08 [-0.05, 0.22]	0.14 [-0.01, 0.28]
Whole Grains	-0.01 [-0.16, 0.14]	0.02 [-0.12, 0.15]	-0.01 [-0.16, 0.13]	0.02 [-0.13, 0.16]
Dairy	0.03 [-0.11, 0.17]	-0.01 [-0.15, 0.14]	0.03 [-0.11, 0.16]	-0.01 [-0.15, 0.13]
Total Protein Foods	0.03 [-0.11, 0.17]	0.02 [-0.12, 0.15]	0.03 [-0.11, 0.16]	0.02 [-0.11, 0.16]
Seafood and Plant Proteins	0.13 [-0.01, 0.26]	0.06 [-0.08, 0.20]	0.13 [-0.01, 0.26]	0.05 [-0.09, 0.19]
Fatty Acids	-0.01 [-0.17, 0.17]	0.07 [-0.07, 0.21]	-0.01 [-0.23, 0.23]	0.08 [-0.06, 0.22]
Moderation				
Refined Grains	0.07 [-0.07, 0.21]	0.03 [-0.11, 0.17]	0.06 [-0.07, 0.20]	0.05 [-0.09, 0.19]
Sodium	0.06 [-0.07, 0.20]	0.06 [-0.08, 0.19]	0.06 [-0.07, 0.20]	0.05 [-0.09, 0.18]
Added Sugars	-0.04 [-0.18, 0.09]	-0.03 [-0.17, 0.11]	-0.04 [-0.18, 0.09]	-0.01 [-0.15, 0.12]
Saturated Fat	**0.01 [0.01, 0.02] †**	0.13 [-0.01, 0.27]	**0.005 [0.001, 0.01] †**	0.14 [–0.01, 0.28]

p value ≤ 0.01, † p value ≤ 0.05

[1] Adjustments are as per main analysis.

Table 5.6 Unstandardized coefficients (β) and 95% confidence intervals [95% CIs] of walking speed under cognitive-motor interference conditions at age 69-71 by HEI-2015 component scores at age 60-64, in men, n=197

	Walking speed, m/s		**Normalized walking speed, -**		**CMI cost, %**	
	Unadjusted	**Multivariable adjusted [1]**	**Unadjusted**	**Multivariable adjusted [1]**	**Unadjusted**	**Multivariable adjusted [1]**
Adequacy						
Total Fruits	-0.09 [-0.23, 0.05]	-0.13 [-0.29, 0.02]	-0.09 [-0.23, 0.05]	-0.14 [-0.29, 0.01]	-0.1 [-0.3, 0.2]	0.1 [-0.3, 0.3]
Whole Fruits	-0.09 [-0.23, 0.04]	-0.14 [-0.29, 0.01]	-0.09 [-0.23, 0.04]	-0.14 [-0.29, 0.01]	-0.9 [-1.9, 0.1]	**-1.3 [-2.5, -0.1]** †
Total Vegetables	-0.07 [-0.21, 0.06]	-0.05 [-0.19, 0.10]	-0.06 [-0.20, 0.07]	-0.04 [-0.19, 0.10]	-0.1 [-0.2, 0.04]	-0.1 [-0.3, 0.1]
Greens and Beans	0.02 [-0.11, 0.16]	0.01 [-0.13, 0.14]	0.02 [-0.11, 0.16]	0.01 [-0.13, 0.15]	0.1 [-0.1, 0.1]	0.1 [-0.1, 0.2]
Whole Grains	-0.01 [-0.11, 0.10]	-0.02 [-0.18, 0.14]	0.01 [-0.09, 0.09]	-0.02 [-0.17, 0.14]	-0.1 [-0.2, 0.1]	-0.1 [-0.3, 0.1]
Dairy	**-0.02 [-0.03, 0.01]**†	**-0.02 [-0.03, -0.01]** †	**-0.01 [-0.01, 0.01]** *	**-0.01 [-0.01, -0.01]** *	**-0.9 [-1.8, -0.1]** †	-0.1 [-0.3, 0.1]
Total Protein Foods	0.07 [-0.06, 0.21]	0.12 [-0.03, 0.26]	0.07 [-0.06, 0.21]	0.11 [-0.03, 0.26]	**3.1 [0.8, 5.4]** *	**2.9 [0.4, 5.4]** †
Seafood Plant Protein	-0.13 [-0.26, 0.01]	-0.10 [-0.25, 0.05]	-0.13 [-0.27, 0.01]	-0.10 [-0.25, 0.05]	-0.1 [-0.2, 0.1]	-0.1 [-0.2, 0.1]
Fatty Acids	-0.09 [-0.23, 0.04]	-0.10 [-0.24, 0.04]	-0.09 [-0.23, 0.04]	-0.10 [-0.24, 0.04]	**-0.7 [-1.5, -0.1]** †	-0.2 [-0.3, 0.1]
Moderation						
Refined Grains	0.01 [-0.12, 0.15]	0.01 [-0.13, 0.15]	0.01 [-0.13, 0.15]	0.01 [-0.14, 0.16]	-0.1 [-0.2, 0.1]	-0.1 [-0.2, 0.1]
Sodium	-0.03 [-0.17, 0.11]	-0.08 [-0.23, 0.06]	-0.03 [-0.17, 0.11]	-0.08 [-0.23, 0.06]	-0.1 [-0.2, 0.1]	-0.1 [-0.2, 0.1]
Added Sugars	-0.08 [-0.22, 0.06]	-0.03 [-0.18, 0.12]	-0.08 [-0.21, 0.06]	-0.03 [-0.18, 0.12]	0.1 [-0.1, 0.2]	0.1 [-0.1, 0.3]
Saturated Fat	-0.06 [-0.20, 0.07]	-0.05 [-0.19, 0.09]	-0.07 [-0.20, 0.07]	-0.05 [-0.19, 0.09]	0.1 [-0.1, 0.2]	-0.1 [-0.2, 0.1]

* p value ≤ 0.01, † p value ≤ 0.05

[1] Adjustments are as per main analysis.

5.5 Discussion

This study provides novel, albeit inconclusive, evidence supporting the hypothesis that diet quality, in particular in women, may have a positive impact on age-related physical and cognitive limiting resources. Findings showed that high overall diet quality in late midlife as indicated by higher HEI-2015 scores was associated with faster walking speed in women seven years later, but slower walking speed and increased CMI cost in men, with the relationship for men being independent of other factors. Null associations were found for speed and CMI cost with increasing complexity of the cognitive task. This is the first prospective study to explore the relationship between diet quality and walking speed and CMI cost in a CMI walking paradigm.

It is interesting in this study that sex was found to modify the above relationship under CMI conditions, in a similar trend as in Chapter 4. Indeed, high HEI-2015 scores reflecting better diet quality were associated with faster walking speed when walking undisturbed and under CMI conditions in women and there was also indication of lower CMI cost, although not statistically significant. In addition, the magnitude of the point estimates was identical for women (0.03 m/s increase in walking speed per 10-point increase in the HEI-2015 score) in both walking tasks. Interestingly, in the present study, the association for men was of the same strength but opposite direction compared to women.

To date, there are no similar studies which directly compare the impact of diet quality on walking speed under CMI conditions. Therefore, discussion will be based on the hypothesis that higher diet quality may likely reflect faster walking speed and lower CMI cost, indicating better ability of older people to optimally combine declining physical and cognitive resources. As described, an emerging volume of evidence has shown favourable effects of a healthy diet on the musculoskeletal system [160] and global cognition [176]. Due to age-related limited executive functions and as a compensatory mechanism to achieve normal movement, older

people show hyper-increased activity of various brain areas when walking under CMI conditions [80]. Importantly, there is consistent evidence for a protective effect of diet on these functions including executive function [341] and processing speed [342] alongside structural integrity [343, 344] and activity [345] of the brain. For example, adherence to the MedDiet, which is very similar in composition as the one described by the HEI-2015, has been associated with lower levels of total brain atrophy in older adults, equivalent to those of people five years younger [343]. The same trend has also been shown for MedDiet in an older UK population over a 3-year period [344]. Despite the estimates size being of low magnitude in this study, the present findings may imply a better total brain activity as a response to higher diet quality, such that older women following healthy dietary habits may be more likely to maintain their walking speed even when a concurrent cognitive task is applied.

Apart from the direct impact of diet on physical function and musculoskeletal system, a faster walking speed under CMI conditions, might be the result of the antioxidant and anti-inflammatory properties of diet on multiple brain areas and functions [346]. For example, increased intakes of ω-3 fatty acids, found predominantly in oily fish, and polyphenols, found in fruits and vegetables, have been shown to protect against damage of white and grey matter, and boost cerebral blood flow, neuroconnectivity and brain cellular signalling [169, 346]. Furthermore, recent evidence suggests a positive association between vitamin B6, found in fish, wholegrain and non-red meat among other foods, and greater activation in dorsolateral prefrontal cortex, which is an important brain area for executive functions and attention, in demented older adults [345]. In addition, resveratrol, a plant-based antioxidant compound found predominantly in berries, grapes and nuts has also shown neuroprotective effects by improving verbal learning and memory performance and enhancing hippocampal activity in older people [169]. There is also indication of a protective effect of vitamin D on brain health [347] and overall cognitive function [348]. Finally, cross-sectional data from cognitively normal older people suggest a protective effect of high diet quality, rich in legumes and fish intake and low in sugars, on cortical thickness [349]. All these components are incorporated in high

HEI scores and may pinpoint the potential of high diet quality to preserve cognitive function and enhance utilization of limiting resources with ageing, as expressed by faster walking speed and reduced CMI cost.

Associations were found between higher HEI-2015 scores and slower walking speed and increased CMI cost in men. This finding is against the initial hypothesis that high diet quality is likely to reflect a faster speed and lower CMI cost in all walking tasks and may be partially explained by sex differences modifying the effect of diet quality on cognitive function. Except those described in Chapter 4, there is also evidence for sex differences in walking speed under CMI conditions, with older men having more difficulties combining the motor and the cognitive task than women [124]. This may be due to differences in: brain neuroanatomy [34] and activity [40], cognitive trajectories with ageing [33], hormonal-induced executive functions [350] and response strategies to stressors [351], all of which seem to favour women. For example, there are well-described differences in cortical thickness [36] and grey matter volume [34] favouring women, both of which are related to better diet quality [349, 352] and are key components of the prefrontal cortex. The latter is a crucial brain region for decision making and planning and although the impact of diet on this brain area is still unclear, a positive effect could be hypothesized, given the overall benefit of healthy diet on brain activity and cognitive status. Therefore, it is likely that achieving high diet quality might be more protective for women when walking under CMI conditions than men, although this would not fully explain the inverse association for men.

Another plausible explanation regarding findings in men might be task prioritization. Women tend to prioritize the two tasks differently than men [353]. In general, men are believed to be less sensitive to task prioritization instructions than women [353] and have less CMI capacity [354], in particular in verbal fluency tasks [355], although recent evidence questions this concept [356]. This may result in inability of men to maintain walking speed because of prioritization of the verbal task, in which they tend to perform worse than women. Therefore given the

hypothesized effect of healthy diet on cognition and brain function, the inverse association may be an artefact, which indirectly reflects a benefit of high diet quality on domains of the concurrent cognitive task rather than a true detrimental effect on walking speed. In other words, it may be that high diet quality is mostly beneficial on sex-specific domains that are more difficult to maintain, such as cognitive performance while walking under CMI conditions in men and walking performance in women. However, some evidence for CMI paradigms opposes to this concept [357]. Within this context, sex differences may also be driven by the fact that men walked already faster than women, which allowed them to pay more attention to the cognitive task and “sacrifice” speed maintenance. In any case, this hypothesis could not be tested in this thesis as performance in the cognitive test was not measured, which is a limitation of study design. What can be safely assumed is that both men and women had a healthy cognitive status as indicated by high later life MMSE scores and hence cognition is unlikely to have driven the findings. Finally, the possibility of the observed associations being due to statistical error cannot be excluded given the marginal confidence intervals and the borderline significance levels for most findings.

This study also showed that higher HEI-2015 scores for greens and beans and saturated fat were associated with faster walking speed in women and total protein scores were associated with lower CMI cost in men. Findings were robust only for total protein foods in the multivariable models. Nevertheless, these findings are in line with the hypothesized beneficial impact of high diet quality on walking performance under CMI conditions. First, adequate total protein intake is recommended to maintain optimal nutritional status in older people towards better lower-limb physical performance and walking ability [137]. In addition, a key systematic review of RCTs showed a protective effect of protein supplementation on specific cognitive domains of healthy older people [175]. Therefore, it is plausible to assume that higher total protein scores will reflect a reduced CMI cost when walking under CMI conditions versus undisturbed walking. Higher scores of saturated fat, which reflect lower intakes, may also be linked to better walking performance under CMI conditions because saturated fat has been

associated with deficiencies in brain domains, neuro signalling, cognitive function [358, 359] and physical performance [360]. In addition, saturated fat often replaces intakes of healthier fatty acids such as PUFAs and thus their beneficial effect on cognitive health is hindered [361]. With regard to greens and beans, evidence supports a protective effect in particular of green leafy vegetables, abundant in vitamin E, carotenoids and folate and of legumes, rich in plant protein and nuts rich in MUFAs and PUFAs, on cognitive health in older people [237]. Besides, all these are key components of the MIND diet, widely believed to be optimal for preservation of cognitive health [362].

Dairy score was associated with slower walking speed and increased CMI cost in men and this finding was the most robust in the sensitivity analysis. Despite the high nutritional value of animal protein contributing to adequate total protein intake in older people, full fat dairy products are also high in saturated and trans-fatty acids. The latter have been found to enhance dysfunction in the blood brain barrier and amyloid beta concentration, predisposing cognitive decline [363] and dementia [364]. Finally, findings for whole fruit and fatty acid ratio scores were only marginal, not consistent and may be due to low statistical power. Moreover, there is no evidence-based mechanism to support these results. Overall, findings for all scores were marginal and of very small clinical magnitude for walking speed and CMI cost. Hence, they need to be treated only as secondary sensitivity analysis which confirms that no individual HEI component has driven the main effects.

Main strengths and limitations in this study are as described in Chapter 4. A weakness specific to this study is the methodology applied in the CMI paradigm, despite the approved standardized operating procedure (Appendix 4). First, performance of the cognitive task (verbal fluency) was not recorded which may have distorted the true associations; yet considering MMSE score at age 69-71 partially accounted for this. Second, although there was randomization of the walking task sequence, there were no instructions regarding task prioritization, which is a key factor to optimize designs of CMI paradigms [365]. Third, magnitude

of CMI depends highly on the task type and in this study only one cognitive task (verbal fluency) was used. For example, there are well-characterized sex differences on cognitive performance such as linguistic tasks favouring women [366] vs spatial tasks favouring men [367]. Nonetheless, decrements in walking speed between tasks were comparable (0.14-0.18 m/s on average) to those observed in most studies [121, 368] and within range of clinically significant change of 0.1 m/s [100].

5.6 Conclusion

In conclusion, findings in this chapter support a positive relationship between adherence to high diet quality in late midlife and faster walking speed in later life in women, under CMI conditions. Opposing to hypothesis, an inverse association between healthy diet and walking performance in men was also found but this may reflect an artefact due to task prioritization rather than actual detrimental effect. This chapter provides novel albeit tentative evidence for potential sex differences modifying the relationship between diet quality and age-related walking performance under CMI conditions, which reflects well-functioning with ageing. This may indicate that healthy diet in midlife might unveil its benefit differently in men and women given that ageing trajectories differ by sex. Nonetheless, with the point estimates being indicative of a relationship but small in both studies, it is important to expand the above relationship into longer periods of dietary exposure over adulthood to reflect on potential cumulative effects.

Chapter 6 - Diet Quality over Adulthood and Walking Speed and Cognitive-Motor Interference Cost in Later Life

This chapter has resulted in a peer-reviewed published abstract and in a virtual oral conference presentation.

Tektonidis TG, Coe S, Esser P, Maddock J, Buchanan S, Mavrommati F, Izadi H, Schott JM, Richards M, Dawes H. Longitudinal Changes in Diet Quality over Adulthood and Physical Function in Older Life: Findings from a British Birth Cohort. Current Developments in Nutrition. 2020;4(Supplement_2):1495-1495.

Tektonidis TG, Coe S, Esser P, Maddock J, Buchanan S, Mavrommati F, Schott JM, Izadi H, Richards M, Dawes H. Longitudinal Changes in Diet Quality over Adulthood and Physical Function in Later Life: Findings from a British Birth Cohort. The American Society for Nutrition – 2020 Nutrition Meeting, Seattle, US, 1 – 4 June 2020.

6.1 Summary

The aim of this chapter was to expand exploration of the observed associations in Chapter 4 and Chapter 5, over a 27-year period of dietary exposure in adulthood, to assess a potential cumulative effect. Women had higher diet quality than men at each age and over adulthood and were more likely to belong to the highest dietary trajectory. There was a null overall association between diet quality and walking speed in all walking tasks, but there was a significant sex-diet interaction modifying the relationship. In women, starting and maintaining high diet quality over adulthood was associated with faster walking speed but not under CMI conditions; yet the association did not hold after adjustment for lifestyle factors. A null association was observed for men in any model. This chapter suggested that achieving and maintaining high diet quality for longer over adulthood is likely to further benefit age-related physical function in women.

6.2 Introduction

Chapters 4 and 5 provided evidence towards sex differences in the relationship between diet quality in late midlife and walking speed, reflecting age-related physical and cognitive function. However, point estimates were very small and direction of the associations was inconsistent between and within sex. Tentative evidence may be partially due to diet being assessed only at one time point. It has been reported that not accounting for changes in dietary behaviours over the life course may result in "*misdetection of diet–disease relationships or attenuation of observed effects*" [44, 369].

Over the life course, dietary intake varies between and within individuals by several factors. Previous chapters provided valuable evidence for the importance of maintaining high diet quality as late as late midlife against functional decline but assuming that diet at single life stages reflects a cumulative intake is likely biased. For example, changes in food habits such as people dining outside home or having holidays abroad more often, increased migration rates resulting in higher ethnic food selection and higher food supply and more evidence-based health claims, have all contributed towards observed changes of dietary intake among British men and women [218, 219]. Finally, if assessed only at one time point, the observed effect of diet may be due to accumulation of exposure over longer periods thus may reflect earlier life dietary habits. Indeed, evidence supports intra-individual tracking of diet over adulthood [188, 217], in particular towards improvements in diet quality with ageing [218-220, 370].

Ageing is a dynamic procedure of accumulated damage over time and despite some known determinants such as sex, it is plausible to hypothesize that timing and duration of exposure to modifiable lifestyle factors is also influential. Knowledge of diet quality patterns over the life course is important because age-related changes in physical function, which is dependent on diet among other factors, may occur years before functional decline is observed [183]. The same trend is observed for cognitive decline, with high diet quality over the lifespan being a determinant of better cognitive trajectories with ageing [172]. The life course approach to age-

related health decline hypothesizes that positive lifestyle habits including high diet quality are more influential from early life to midlife, when people are more likely to be in control of modifiable factors [5, 305].

The cumulative effect of healthy diet as a modifiable behaviour in relation to age-related functional decline has drawn attention recently [171, 172, 186, 188, 217]. For example, lower fruit and vegetable consumption in combination with physical inactivity over a 17-year period in adulthood, increased the risk of physical decline with ageing [186]. In addition, a 30-year period of exposure to high diet quality over adulthood was associated with better physical performance in later life in the NSHD [188]. Healthy dietary choices over a 20-year period in midlife in combination with physical activity have been shown to slow down age-related cognitive decline [172]. Yet, in these studies diet was either considered part of overall lifestyle including physical activity, smoking, body mass index and alcohol intake [172, 186, 371] or was derived *a posteriori* [188]. From a health perspective, it may be preferable to explore evidence-based diet quality indices which capture the synergistic effect of dietary components rather than single nutrients and evidence for their long-term effect on objective measures of ageing, is limited. In addition, well-characterized sex differences in dietary intake over the lifespan and in ageing trajectories, further raise the question whether timing, intensity and duration of dietary exposure modify this relationship.

Therefore, hypothesizing that longer periods of high diet quality exposure over adulthood would yield additional benefits on physical and cognitive function in later life, the aim of this chapter was to explore the longitudinal associations between adulthood trajectories of diet quality in men and women and walking performance in later life, reflecting overall functioning. The specific objectives were:

1. The extent to which cumulative exposure to high diet quality from early to late midlife (from age 36 to 64), as indicated by trajectories of the HEI-2015, was associated with

walking speed and CMI cost at age 69-71 in overall well-functioning men and women in a British birth cohort.

2. The extent to which there was a relationship when modified by sex and with increasing complexity of the cognitive task while walking.

6.3 Methods

6.3.1 Participants

Data was drawn from participants in the Insight 46 with walking speed data at age 69-71 and dietary data in at least one out of four dietary assessments in the NSHD, at ages 36, 43, 53 and 60-64 (Figure 6.1). Inclusion and exclusion criteria are shown in Figure 6.1. Among men and women in Insight 46, dietary data was available as follows: n=313 (age 36), n=369 (age 43), n=346 (age 53), n=444 (age 60-64). The number of participants with at least one valid dietary assessment was n=480, at least two n=423, at least three n=351 and all dietary assessments n=218. The final sample for this study was n=361 (Task 1), n=433 (Task 2) and n=437 (Task 3). Total number of observations for this study were n=1,472 (741 for women and 731 for men) with all ages of dietary assessment combined.

6.3.2 Diet Quality from Age 36 to 64

Dietary assessment at age 60-64 and calculation of the HEI-2015 have been described in Chapter 3. Identical procedures were followed for dietary assessment at ages 36, 43 and 53, from which HEI-2015 component and total scores were calculated. Use of current version of HEI score (HEI-2015) was applied throughout all ages to directly compare trends of diet quality between years and to reflect on current evidence-based dietary guidelines. Finally, radar plots were used to determine differences in patterns of diet quality by age of dietary assessment and by sex with regard to HEI-2015 component and total scores.

6.3.3 Walking Speed Estimation/Cognitive-Motor Interference Cost

The procedures to estimate walking speed, normalize values for leg length and calculate CMI cost, have been described in Chapter 3 and Chapter 5. Identical methodology was followed in this study. In sensitivity analysis, the same cut-off points (Figure 6.1) were used for speed values in all walking tasks to reflect plausible walking patterns. In addition, a looser criterion (1.9 m/s) that reflects the maximum speed before transition to running was also applied [372].

6.3.4 Descriptive Characteristics from Age 36 to 64

Descriptive characteristics collected at each age are shown in Table 3.5. Characteristics were modelled to reflect cumulative exposure over adulthood (from age 36 to 69), based on maximum number of life course data per variable. Prevalence of comorbidities (CVD, cancer, diabetes, hypertension, hyperlipidaemia) was categorized as previously described and total number of diseases up to age 60-64 was calculated, accounting for prevalence at earlier ages. For physical activity and smoking status, a variable of cumulative exposure (from age 36 to 69 - five time points) was calculated as follows: first, points were given at each age (0-none/low exposure, 1-medium exposure, 2-high exposure); these points were summed across the five ages over adulthood; scores ranged from 0 (no or low smoking/physical activity) to 10 (high smoking/physical activity). Similarly, using sex-specific quartiles of max grip strength scores at each age (53 to 69 – three time points), points were allocated to each quartile of the distribution of each participant's ranking; (0=lowest quartile, 1=second quartile, 2=third quartile, 3=highest quartile). Points were summed across all three ages, with 0 reflecting over time low rank in grip strength test and 9 the highest rank. For one leg balance test with eyes open, sex-specific categorization was done as 0=balance less than 30 seconds and 1=balance for 30 seconds at each age due to high proportion of participants achieving maximum score. Sex-specific tertiles of waist-to-hip ratio at each age (43 to 69 – four time points) were created and points were allocated (0=lowest tertile, 1=middle tertile, 2=high

tertile); which were summed across the four ages (0=over time high ratio, 8=over time low ratio). Additional characteristics not included in the analysis are presented in Appendix 5.

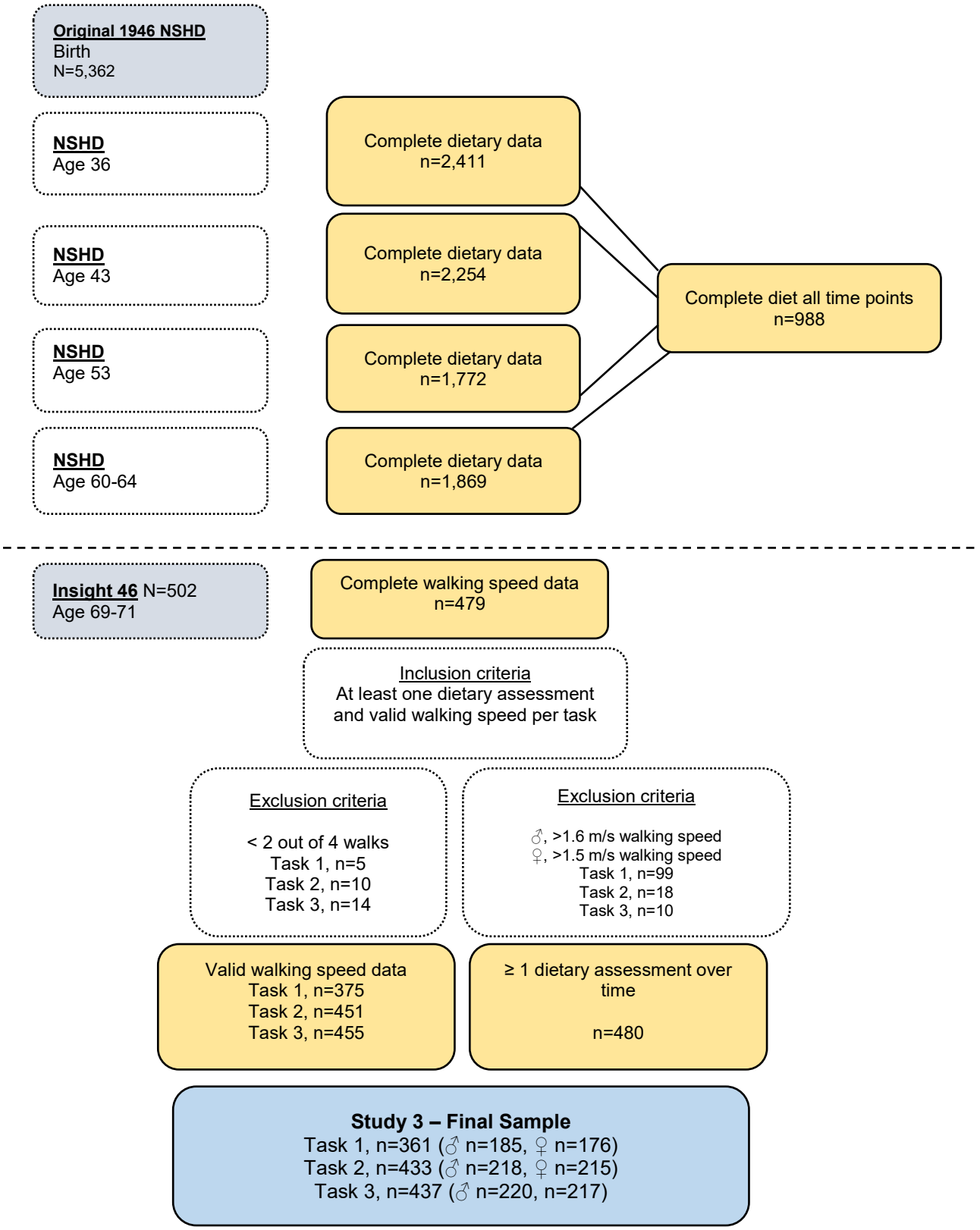

Figure 6.1 Inclusion criteria and sample size for Study 3 (Chapter 6)

6.3.5 Statistical Analysis

Individual Trajectories of HEI-2015 from Age 36 to 64

Pearson's correlation coefficients (r), intraclass correlation coefficients ($ICC_{(3,1)}$, test-retest reliability) and Cronbach's alpha (α, average scores) were used to reflect agreement levels ("tracking") of overall diet over adulthood. To assess changes in diet quality over adulthood while using all available food diaries, trajectories of HEI-2015 were modelled for each participant who provided valid dietary assessment at least at one age (n=480). Diet quality trajectories were estimated by LMM-IGC with maximum likelihood estimator, with HEI-2015 scores at ages 36, 43, 53 and 60-64 as independent variables against time in years from age 36 to 64 (Figure 3.3 and Figure 3.5). To test for inter-individual variability in initial HEI scores and HEI trajectories over time, random effects were allowed for both the intercepts (individuals) and time. Random effects models with various covariance structures were allowed up to quadratic polynomial functions of time (Appendix 6). For each participant, the individual trajectory was modelled as the predicted values of HEI-2015 at age 60-64 conditional on HEI-2015 scores at earlier ages. HEI-2015 predicted values reflected the fixed effect (β) plus the random effect for time by the best linear unbiased predictors. In addition, a conditional model with sex and occupation (manual vs non-manual) at age 36 as predictors (fixed factor) was tested to assess if those factors were related to growth estimates, based on previous evidence [217]. Men and women were modelled together. An interaction term for time by sex was tested.

Group-Based Trajectories of HEI-2015 from Age 36 to 64

GBTM was applied to explore if two or more groups of individuals followed distinct developmental trajectories in terms of diet quality (HEI-2015) over adulthood. An overview of the method has been discussed in Chapter 3. GBTM provides (a) the number, forms and shapes of distinct trajectories (if any), (b) the proportion of the sample following each trajectory, (c) the posterior probability of each individual of group membership. In both LMM-

IGC and GBTM, model selection was based on -2 log likelihood, Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC)) [321, 324] and prior theoretical knowledge from published evidence [217]. In general, the less negative values, the better the model fit to the data. For GBTM, additional criteria as suggested by *Nagin et al. (2010)* [324] were applied (Table 6.1). Final selection of models was made as "*combination of substantive knowledge and statistical inference*" [324]. A generalization of the GBTM was used to incorporate sex in estimating the probability of group membership.

Associations between Adulthood Diet Quality and Walking Speed

Associations between individual and group-based HEI-2015 trajectories over adulthood and walking speed (non-normalized and normalized) in later life, were explored using linear regression models. All diagnostics were assessed as in Chapter 4. The unadjusted models included (a) individual HEI-2015 trajectories (predicted values of HEI-2015 as a function of time from LMM-IGC) as continuous independent variable, with sex as modifier (interaction term HEI/sex), (b) membership in the highest HEI-2015 trajectory (assigned by the GBTM posterior probability) vs all other groups as categorical independent variable, with sex as modifier. Walking speed and CMI cost were treated as continuous dependent variables. If an association or trend was observed, multivariable linear regression models were tested, controlling for education up to age 26, total number of comorbidities up to age 64, scores of adulthood physical activity, smoking, grip strength, balance time (eyes open) and waist to hip ratio. When walking under CMI conditions, models were further adjusted for MMSE scores at age 69.

Table 6.1 Selection criteria for best model fit in group-based HEI-2015 trajectories over adulthood (from age 36 to 64)

1. Preference for the most parsimonious model fitting the data optimally.
2. Difference in the logged Bayes factor between model with k and k-1 parameters >10.
3. Close agreement between each group's estimated probability and actual proportion of participants classified to each group according to the maximum posterior probability assignment rule.
4. Average posterior probability value >0.7 for each group.
5. Adequate sample numbers in each group, >10% of n.
6. Reasonably narrow confidence intervals.
7. Odds of correct classification based on the posterior probabilities of group membership >5 for each group.

6.4 Results

6.4.1 Descriptive Characteristics

Descriptive characteristics over adulthood are presented in Table 6.2, overall and by sex. Descriptives of additional characteristics of not used in the main analysis are presented in Appendix 7. Men had higher rates of high education attainment, higher prevalence of hyperlipidaemia and hypertension and total number of comorbidities than women, who had higher prevalence of cancers and lower waist to hip ratio at each age of dietary assessment ($p<0.05$). An overview of characteristics by group-based HEI-2015 trajectory over adulthood by sex is shown in Appendix 8.

6.4.2 HEI-2015 Component and Total Score by Age of Assessment

HEI-2015 scores by age of assessment are presented visually in Figure 6.2. Overall, there was an increase in all component scores from age 36 to 64, except for total protein foods and sodium, which were comparable at all ages over adulthood (Table 6.3). A visual representation by sex comparison of HEI-2015 component scores over adulthood is shown in Figure 6.3 and a detailed comparison in Appendix 9.

Women had higher HEI-2015 components and total scores at most ages than men, in particular for the following components: total fruit, whole fruit, total vegetables, greens and beans, whole grains and dairy, with men scoring higher than women in sodium and saturated fat components at age 36. Components consumed in moderation showed comparable scores between men and women at most ages. HEI-2015 scores tracked quite similarly over time between men (r: 0.27-0.50, $p<0.001$) and women (r: 0.17-0.49, $p<0.05$) over adulthood. The strength of correlations was weaker the further apart the ages of assessment were. Finally, both men and women showed similar levels of agreement in HEI-2015 scores over adulthood (men, α: 0.72, $ICC_{(3,1)}$: 0.39, $p<0.001$; women, α: 0.76, $ICC_{(3,1)}$: 0.44, $p<0.001$).

Table 6.2 Descriptive characteristics of participants over adulthood (from age 36 to 64), n=502

	Overall (n=502)	Women (n=246)	Men (n=256)
		Mean [sd], n (%)	
Education up to age 26			
None	79 (16)	40 (16)	39 (16)
Formal	143 (29)	**82 (34)** ‡	61 (25)
≥ Secondary	265 (55)	120 (50)	**145 (59)** ‡
No of comorbidities, age 60-64	1.3 [1.0]	1.2 [1.0]	**1.5 [1.0]** ‡
CVD	76 (15)	31 (13)	45 (18)
Diabetes	35 (7)	13 (5)	22 (9)
Hyperlipidaemia	135 (27)	46 (19)	**89 (35)** *
Hypertension	354 (71)	157 (64)	**197 (77)** *
Cancer	57 (11)	**36 (14)** †	21 (8)
Physical activity score, 0-10 [1]	4.9 [2.8]	4.9 [2.9]	4.9 [2.7]
None/Low exposure (0-3)	159 (36)	82 (37)	71 (35)
Medium exposure (4-6)	134 (31)	63 (29)	71 (32)
High exposure (7-10)	147 (33)	75 (34)	72 (33)
Smoking habits score, 0-10 [1]	3.8 [2.9]	3.6 [3.0]	3.9 [2.9]
None/Low exposure (0-4)	165 (36)	88 (39)	77 (34)
Medium exposure (5)	179 (39)	85 (37)	94 (41)
High exposure (6-10)	113 (25)	55 (24)	58 (25)
Max grip strength score, 0-9 [1]	4.5 [2.6]	4.4 [2.6]	4.5 [2.7]
Low (0-3)	171 (36)	83 (36)	88 (37)
Medium (4-5)	117 (25)	58 (25)	59 (25)
High (6-9)	181 (39)	91 (39)	90 (38)
Balance time score, 0-3 [1]	1.9 [1.0]	1.8 [1.0]	2.0 [0.9]
Low (0-1)	156 (33)	90 (39)	66 (27)
Medium (2)	146 (31)	65 (28)	81 (34)
High (3)	171 (36)	76 (33)	95 (39)
Waist to hip ratio			
Age 43	0.83 [0.09]	**0.76 [0.06]** *	0.90 [0.05]
Age 53	0.86 [0.08]	**0.79 [0.05]** *	0.92 [0.05]
Age 60-64	0.91 [0.08]	**0.86 [0.06]** *	0.96 [0.06]
Age 69	0.91 [0.08]	**0.86 [0.07]** *	0.96 [0.06]
Waist hip ratio score, 0-8 [1]	4.0 [2.5]	4.0 [2.5]	4.1 [2.5]
Low (0-2)	136 (31)	68 (32)	68 (31)
Medium (3-5)	158 (36)	77 (36)	81 (36)
High (6-8)	144 (33)	70 (32)	74 (33)

* p value ≤ 0.001, † p value ≤ 0.01, ‡ p value ≤ 0.05.

[1] No statistical tests performed as adulthood exposure was modelled in sex-specific tertiles/categories; hence no differences in proportions per category by sex were expected.

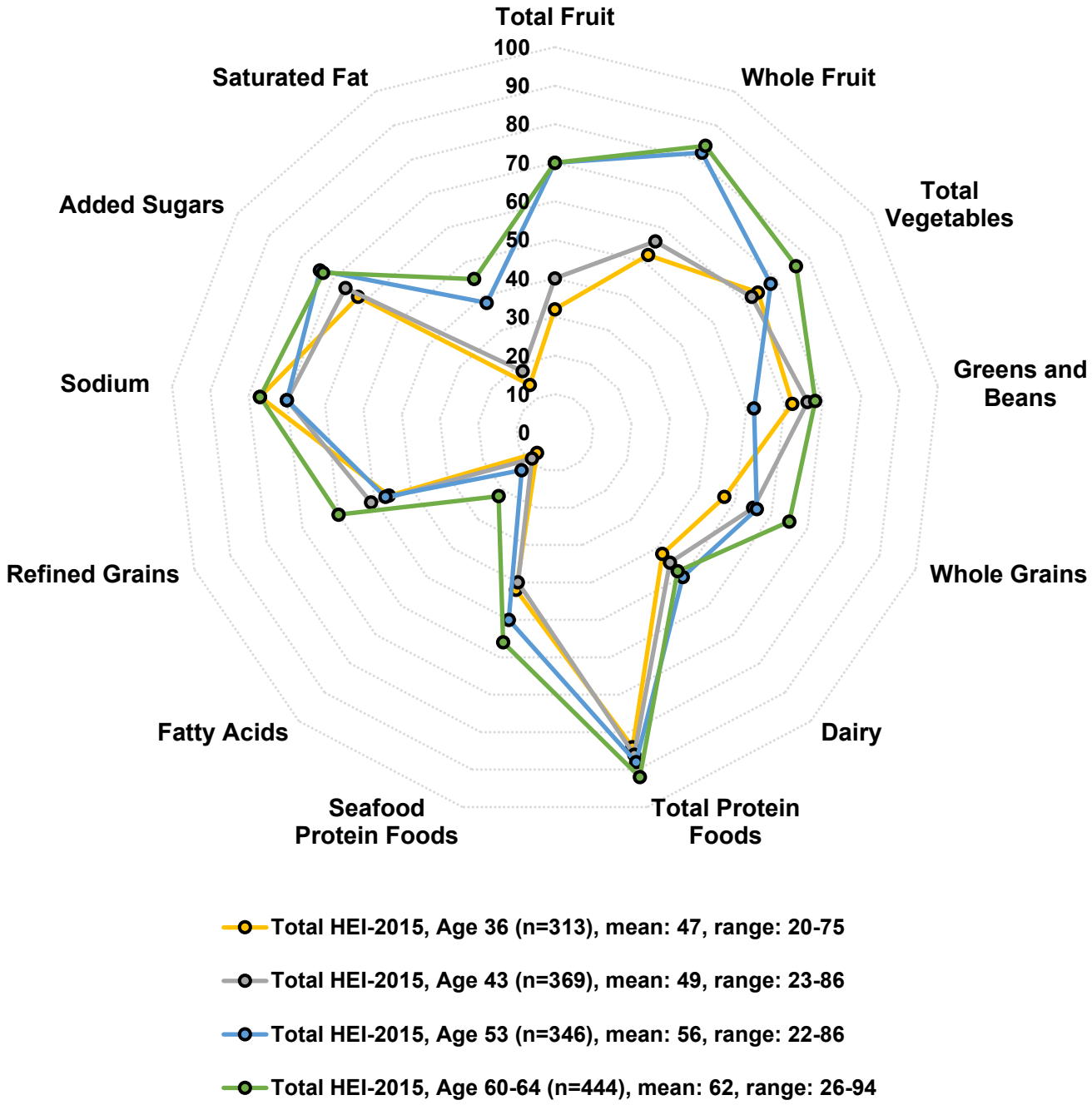

Figure 6.2 Radar plot of HEI-2015 score by age of dietary assessment[21]

[21] The percentage of maximum points received for each component on average is presented, with 0% in the centre and 100% at the outer edge.

Table 6.3 The HEI-2015 total and component scores by age of dietary assessment

Age of assessment, years	**36**		**43**		**53**		**60-64**	
Number of participants	313		369		346		444	
	Mean [sd]							
Age, years	36.3 [0.2]		43.4 [0.2]		53.4 [0.2]		63.3 [1.0]	
HEI-2015, 0-100	47 [11]		49 [12]		56 [13]		62 [13]	
Component scores, range	Mean [sd], n max score [1] (%)							
Adequacy								
Total Fruit, 0-5	1.6 [1.5]	27 (9)	2.0 [1.6]	48 (13)	3.5 [1.6]	155 (45)	**3.6 [1.5]** *	195 (44)
Whole Fruit, 0-5	2.6 [1.8]	81(26)	2.8 [1.8]	118 (32)	4.2 [1.5]	248 (72)	**4.3 [1.4]** *	332 (75)
Total Vegetables, 0-5	3.2 [1.0]	38 (12)	3.2 [1.1]	61 (17)	3.4 [1.2]	98 (28)	**3.8 [1.1]** *	172 (39)
Greens & Beans, 0-5	3.2 [1.6]	107 (34)	3.5 [1.5]	140 (38)	2.7 [1.8]	96 (28)	**3.5 [1.7]** *	191 (43)
Whole Grains, 0-10	4.7 [3.9]	77 (25)	5.5 [3.8]	107 (29)	5.7 [3.8]	107 (31)	**6.5 [3.5]** *	164 (37)
Dairy, 0-10	4.2 [2.0]	7 (2)	4.5 [2.3]	16 (4)	5.1 [2.4]	23 (7)	**4.8 [2.3]** *	23 (5)
Total Protein Foods, 0-5	4.6 [0.7]	238 (76)	4.3 [1.0]	241 (65)	4.4 [0.9]	237 (69)	4.6 [0.8]	335 (76)
Seafood Protein Foods, 0-5	2.9 [1.9]	107 (34)	3.0 [1.9]	138 (37)	3.2 [1.9]	144 (42)	**3.5 [1.9]** *	237 (53)
Fatty Acids, 0-10	0.5 [1.0]	0 (0)	0.9 [1.5]	1 (0.5)	1.3 [1.9]	3 (1)	**2.2 [2.5]** *	9 (2)
Moderation								
Refined Grains, 0-10	4.6 [3.7]	50 (16)	5.1 [3.5]	70 (19)	4.7 [3.6]	60 (17)	**6.0 [3.5]** *	120 (27)
Sodium, 0-10	7.6 [2.2]	114 (36)	7.1 [2.6]	88 (24)	7.1 [2.5]	71 (21)	7.7 [2.4]	162 (37)
Added Sugars, 0-10	6.2 [2.4]	21 (7)	6.6 [2.3]	46 (13)	7.4 [2.2]	68 (20)	**7.3 [2.1]** *	68 (15)
Saturated Fat, 0-10	0.4 [1.2]	1 (0.5)	1.8 [2.5]	6 (2)	3.9 [3.2]	23 (7)	**4.5 [3.1]** *	31 (7)

* p value ≤ 0.05 per repeated measures analysis of variance or non-parametric equivalent (Friedman's test). Significance levels denote a change from age 36 to 64.
[1] Number of participants who met the dietary recommendation for each component and thus the standard for maximum score in each component.

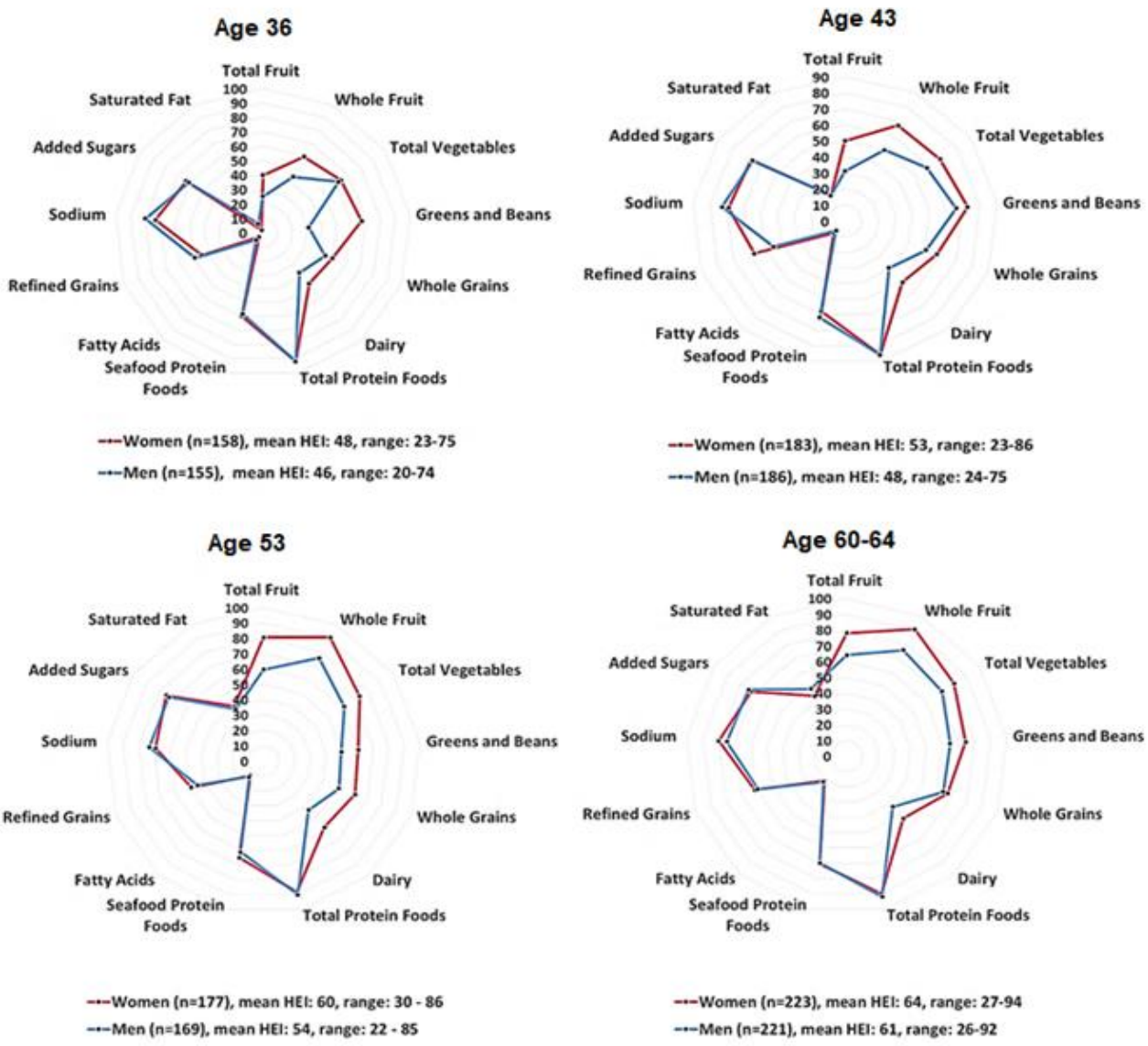

Figure 6.3 Radar plots of HEI-2015 score by sex and by age of dietary assessment[22]

[22] The percentage of maximum points received for each component on average is presented, with 0% in the centre and 100% at the outer edge.

6.4.3 Individual HEI-2015 Trajectories over Adulthood

Selection criteria and analytical procedure for all models tested, are presented in Appendix 11 and Appendix 10. A linear model with fixed and random effects for the initial HEI-2015 levels (intercept) and the linear growth (time) was chosen. There was a significant linear increase in HEI-2015 scores over adulthood (β=0.60, 95% CI=0.54, 0.65) (Table 6.4). The mean estimated HEI-2015 initial status was 41 (95% CI=39, 44). About 63% of within-individual variation was due to linear function of time. There was no indication of differences in the rates of linear increase among participants with high vs low initial HEI-2015 scores (p=0.27). Both sex and occupation were significant predictors of the HEI-2015 score but they were not associated with the linear growth over time (Table 6.4).Those in non-manual occupation had higher mean diet quality than those in manual occupation. Sex interactions were not significant.

Estimated adjusted marginal means of HEI-2015 indicating diet quality with corresponding 95% CIs are presented in Table 6.5 and graphically in Figure 6.4. Women had higher mean diet quality versus men at each time point controlling for baseline occupation. Within sex comparisons also showed consistent improvement of diet quality in men and women over time, independent of occupation at age 36.

Table 6.4 Main effects of linear mixed models of HEI-2015 over adulthood (from age 36 to 64) by sex and occupation at baseline, n=480

Parameter	**Estimates (β)**	**95% CI**
Initial HEI-2015	41	39, 44
Follow-up (years)	0.6	0.54, 0.65
Women vs men	4	3, 6
Non-manual vs manual class	3	1, 6

-2 Log Likelihood: 11,292; BIC: 11,351; AIC: 11,308

Table 6.5 Adjusted estimated marginal means and (95% CI) for HEI-2015 scores by sex and by age of dietary assessment, n=480

Age (years)	**36 (reference)**	**43**	**53**	**60-64**	p-value
Men	44 (43, 45)	**48 (47,49)**	**54 (53, 55)**	**60 (59, 62)**	<0.001‡
Women	48 (47, 50)†	**53 (51, 54)**†	**58 (57, 60)**†	**64 (63, 66)**†	<0.001‡

Adjusted for occupation. † Significant higher HEI-2015 mean scores of women vs men ‡ p-values correspond to the null hypothesis that the means, across all four time-points are equal. Post-hoc analysis was performed with Bonferroni correction to adjust for multiple pairwise comparisons over time within group.

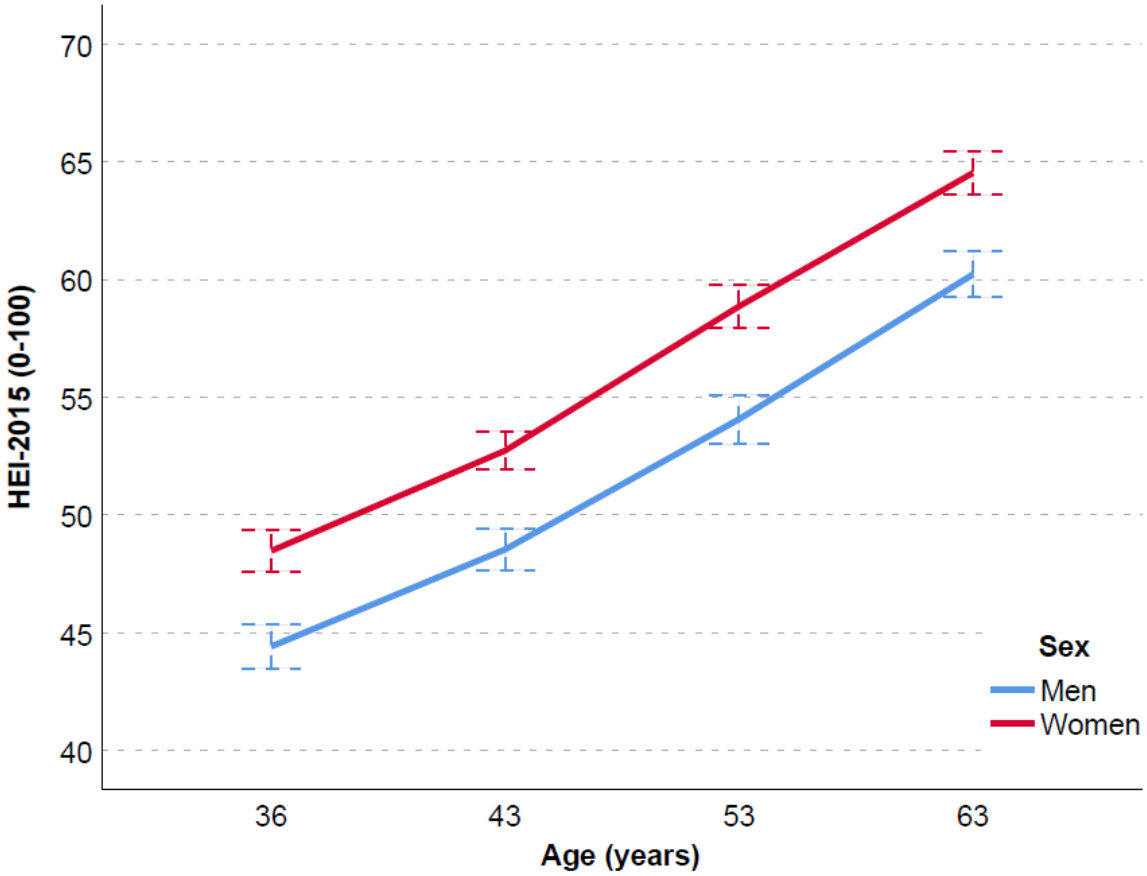

Figure 6.4 Adjusted means of the HEI-2015 scores over adulthood by sex, n=502[23]

[23] The dashed error bars represent 95% CIs of estimated marginal means of HEI scores at each age by sex.

6.4.4 Group-Based HEI-2015 Trajectories over Adulthood

Selection criteria and analytical procedures for all models tested, are presented in and Appendix 12. A three-group model was chosen on the basis of best data fit, parsimony and in agreement with the criteria proposed in Table 6.1. An overview of criteria fulfilment is available in Appendix 13.

Three distinct linear trajectories of overall diet quality over adulthood were observed and may be considered as follows: starting with low diet quality and improving ("Low", 21%), starting with average diet quality and improving ("Medium", 59%) and starting with high diet quality and improving ("High", 20%) (Figure 6.5). An increased likelihood of women of belonging to "High" trajectory of HEI-2015 score (β: 1.97, $p<0.05$) was shown. Table 6.6 shows HEI-2015 total scores per age of dietary assessment for the derived trajectories. HEI-2015 scores increased linearly in all three trajectories over adulthood ($p<0.001$). The "Medium" trajectory had the largest rate of linear growth per year (β: 6.2 points, $p<0.001$) as compared to "High" (β: 5.5 points, $p<0.001$) and "Low" (β: 3.6 points, $p<0.001$), respectively.

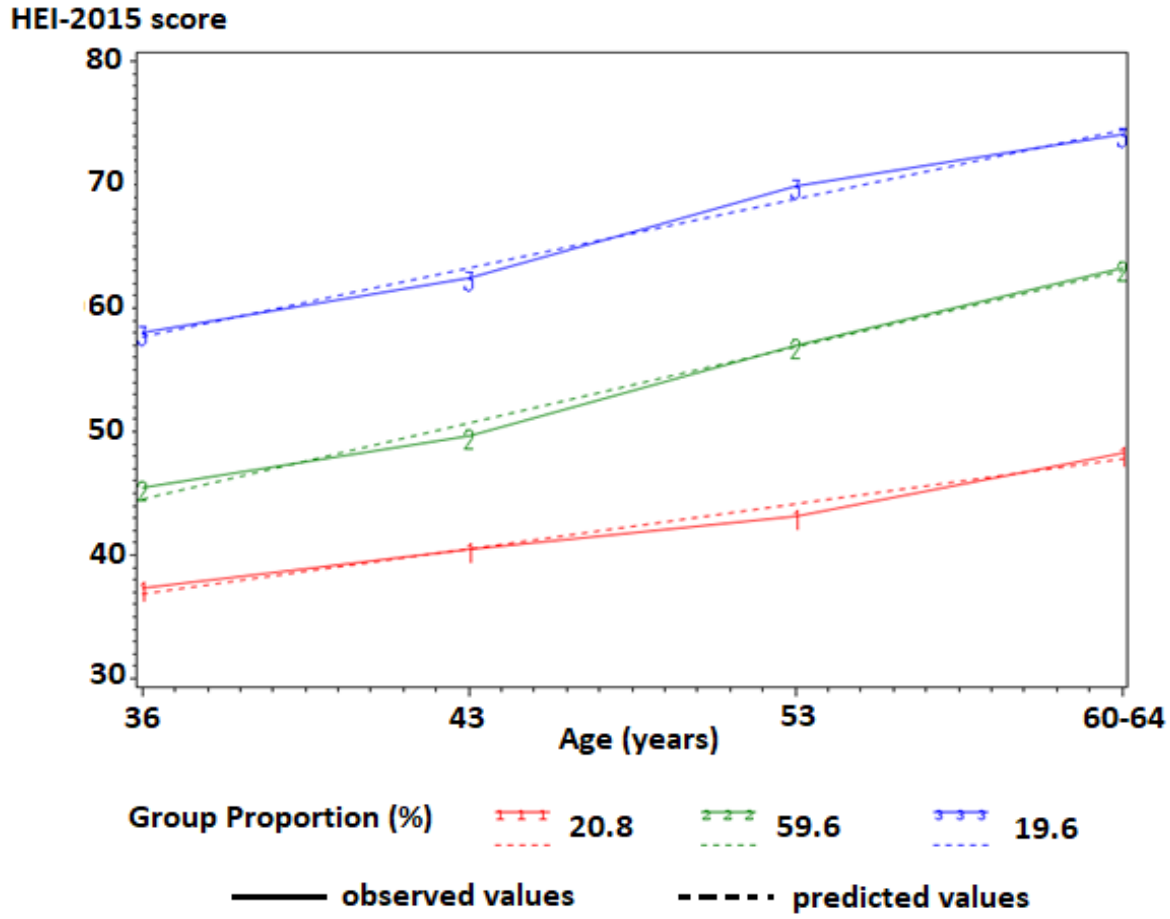

Figure 6.5 HEI-2015 group-based trajectories in Insight 46, n=480[24]

[24] The solid lines represent the average observed values of HEI scores over adulthood and the dashed lines the predicted values by group-based trajectory modelling.

Table 6.6 Matrix of observed and predicted values for mean HEI-2015 group-based trajectories

	HEI-2015 trajectory group		
	Low (21%)	**Medium (60%)**	**High (19%)**
Age 36			
Observed value	37	45	58
Predicted value (95% CI)	37 (34, 40)	45 (43, 46)	58 (55, 61)
Age 43			
Observed value	40	50	62
Predicted value (95% CI)	41 (38, 43)	51 (49, 52)	63 (61, 66)
Age 53			
Observed value	43	57	70
Predicted value (95% CI)	44 (42, 47)	57 (55, 59)	69 (67, 71)
Age 60-64			
Observed value	48	63	74
Predicted value (95% CI)	48 (44, 51)	63 (61, 65)	74 (72, 77)

6.4.5 Associations of HEI-2015 Trajectories and Walking Speed and Cognitive-Motor Interference Cost

Men had faster walking speed than women in all walking tasks ($p<0.001$), but the difference did not hold when normalized for body size differences (Table 6.7). Over a median follow-up period of 27 years, a null overall association between individual and group-based adulthood HEI-2015 trajectories and walking speed or CMI, was observed. However, there was evidence for a modifying effect of sex in the relationship ($p<0.05$). Predicted values of individual HEI-2015 trajectories up to age 64, conditional on all previous ages, were associated with faster walking speed at age 69-71 in women (β: 0.04, 95% CI: 0.01, 0.08), but not men (Table 6.7). The association was attenuated in the multivariable models. There were null overall and sex-specific associations between individual HEI-2015 trajectories and walking speed and CMI cost.

Regarding group-based HEI-2015 trajectories, membership to the “High” HEI-2015 group as compared to “Medium” and “Low”, was associated with faster walking speed in women (β: 0.06, 95% CI: 0.01, 0.11), but this did not remain statistically significant in the multivariable models (Table 6.7). Finally, membership to the “High” trajectory was not a significant predictor of walking speed or CMI cost in any of the models tested. In the sensitivity analysis, application of cut-off points for walking speed values showed similar results with regard to the direction of the association; however statistical significance was not achieved in almost any model (Appendix 16).

Table 6.7 Unstandardized coefficients (β) and 95% confidence intervals [95% CIs] of walking speed at age 69-71 by group-based and individual HEI-2015 trajectories over adulthood (from age 36 to 64) by sex, n=480

		High vs medium/low HEI-2015 trajectory		Individual HEI-2015 trajectory	
		Women	**Men**	**Women**	**Men**
Task 1	n	226	230	213	204
Walking speed, m/s	mean [sd]	1.39 (0.18)	**1.46 (0.20) ***	1.39 (0.18)	**1.46 (0.20) ***
Sex stratified [1]	β [95% CI]	**0.06 [0.01, 0.11]** †	-0.06 [-0.14, 0.03]	**0.04 [0.01, 0.08]** †	-0.01 [-0.04, 0.03]
Multivariable adjusted [2]		0.01 [-0.05, 0.06]	-0.09 [-0.20, 0.01]	0.02 [-0.03, 0.05]	-0.01 [-0.05, 0.03]
Normalized walking speed [3], -		0.47 (0.06)	0.47 (0.06)	0.47 (0.06)	0.47 (0.06)
Sex stratified		**0.02 [0.01, 0.04]** †	-0.02 [-0.05, 0.01]	**0.02 [0.01, 0.03]** †	-0.01 [-0.02, 0.01]
Multivariable adjusted		0.01 [-0.02, 0.02]	0.02 [-0.05, 0.01]	0.01 [-0.01, 0.02]	-0.01 [-0.02, 0.01]
Task 2 [4]	n	224	227	211	205
Walking speed, m/s	mean [sd]	1.20 (0.19)	**1.27 (0.22) ***	1.20 (0.19)	**1.27 (0.22) ***
Sex stratified	β [95% CI]	0.04 [-0.03, 0.01]	-0.07 [-0.17, 0.02]	0.02 [-0.01, 0.03]	0.01 [-0.01, 0.01]
Multivariable adjusted		0.01 [-0.06, 0.07]	-0.09 [-0.20, 0.02]	0.01 [-0.05, 0.05]	-0.01 [-0.02, 0.02]
Normalized walking speed [3], -		0.41 (0.06)	0.41 (0.07)	0.41 (0.06)	0.41 (0.07)
Sex stratified		0.01 [-0.01, 0.03]	-0.03 [-0.06, 0.01]	0.01 [-0.01, 0.02]	-0.01 [-0.01, 0.01]
Multivariable adjusted		0.01 [-0.02, 0.03]	-0.03 [-0.07, 0.01] †	0.01 [-0.01, 0.01]	-0.01 [-0.01, 0.01]
CMI cost, %		-13.7 (9.3)	-13.3 (10.1)	-13.6 (9.1)	-13.4 (10.2)
Sex stratified		-0.9 [-3.8, 1.8]	-1.8 [-6.0, 2.3]	-0.9 [-2.7, 1.0]	-1.8 [-3.6, 0.1]
Multivariable adjusted		-0.4 [-3.7, 3.0]	-2.8 [-7.8, 2.2]	-1.1 [-3.4, 1.2]	-0.8 [-2.9, 1.4]

* p value ≤ 0.001, † p value ≤ 0.01, ‡ p value ≤ 0.05

[1] Sex stratified: Overall model was sex adjusted, sex models were stratified by sex due to significant sex interaction. [2]Additionally adjusted for: higher education attainment (yes), number of comorbidities up to age 64 (reference: zero), adulthood physical activity score (0-10), adulthood smoking habits score (0-10), adulthood grip strength score (0-9), adulthood balance time score (0-3), adulthood waist to hip ratio score (0-8). [3] Not adjusted for waist to hip ratio score because walking speed was already normalized for leg length. [4] Additionally for MMSE score (0-30).

Continued Table 6.7

		High vs medium/low HEI trajectory		Individual HEI-2015 trajectory	
		Women	**Men**	**Women**	**Men**
Task 3	n	221	226	208	204
Walking speed, m/s	mean [sd]	1.17 (0.21)	**1.21 (0.23) ‡**	1.17 (0.21)	**1.21 (0.23) ‡**
Sex stratified [1]	β [95% CI]	0.03 [-0.04, 0.09]	-0.07 [-0.17, 0.02]	0.01 [-0.03, 0.06]	-0.02 [-0.06, 0.02]
Multivariable adjusted [2]		0.01 [-0.07, 0.08]	-0.09 [-0.18, 0.01]	-0.01 [-0.05, 0.05]	-0.02 [-0.07, 0.03]
Normalized walking speed [3], -		0.39 (0.07)	0.39 (0.08)	0.39 (0.07)	0.39 (0.07)
Sex stratified		0.01 [-0.01, 0.03]	-0.03 [-0.06, 0.01]	0.01 [-0.01, 0.02]	-0.01 [-0.02, 0.01]
Multivariable adjusted		0.01 [-0.02, 0.03]	-0.09 [-0.18, 0.01]	0.01 [-0.01, 0.02]	-0.01 [-0.03, 0.01]
CMI cost, %		-15.9 (11.8)	**-17.3 (10.7) ‡**	-15.6 (11.6)	**-17.5 (10.7) ‡**
Sex stratified		-1.6 [-4.9, 1.6]	-2.6 [-7.5, 2.4]	-1.2 [-3.5, 1.0]	-1.7 [-3.7, 0.4]
Multivariable adjusted		-0.1 [-3.9, 3.8]	-3.6 [-9.8, 2.5]	-1.1 [-3.8, 1.6]	-1.3 [-3.8, 1.2]

* p value ≤ 0.001, † p value ≤ 0.01, ‡ p value ≤ 0.05

[1] Sex stratified: Overall model was sex adjusted, sex models were stratified by sex due to significant sex interaction. [2] Additionally adjusted for: higher education attainment (yes), number of comorbidities up to age 64 (reference: zero), adulthood physical activity score (0-10), adulthood smoking habits score (0-10), adulthood grip strength score (0-9), adulthood balance time score (0-3), adulthood waist to hip ratio score (0-8) and for MSSE score (0-30). [3] Not adjusted for waist to hip ratio score because walking speed was already normalized for leg length.

6.5 Discussion

Utilizing longitudinal dietary data from the oldest and longest running post-war British birth cohort, this study showed that women had higher diet quality at each age and over adulthood and steeper rates of diet improvement than men, who also increased diet quality over time. Most notably, the current study showed that, in women, improving overall diet quality as indicated by higher HEI-2015 trajectories over a 27-year adulthood period, was associated with faster walking speed in later life. In addition, the data provided evidence towards a stronger effect on walking speed in women who maintained consistently high diet quality and further improved over adulthood. However, the observed relationships did not hold after adjustment for other factors. Null associations were observed for men or under CMI conditions. It is important that, albeit of low statistical strength, the findings further support the benefit of high diet quality, against age-related physical decline, in particular in women. It is also notable that these findings in women highlight the importance of duration in exposure to high diet quality over adulthood so as to maximize this benefit.

Women who had high probability of membership to the “High” HEI-2015 trajectory over adulthood and higher predicted values of individual HEI-2015 trajectories up to age 64, had faster walking speed at age 71 compared to those in lower trajectories. First, these findings further confirm existing evidence for a protective cumulative effect of healthy diet over adulthood against physical decline [164, 188, 224, 226], which has been discussed in Chapter 2. Second, it may be speculated that cumulative exposure to high diet quality over adulthood as compared to single life stages, might have greater effect in preserving age-related functional status. This is further implied by the fact that although women in the “Medium” trajectory improved their diet over adulthood faster than those in “High”, they still benefited less with regard to walking speed. This finding is only partially in line with a study using data from the same cohort [188], in which despite a cumulative effect of diet on physical performance was also shown, it was found that the strongest associations were for “current” diet in late midlife,

a finding not confirmed in the present study. However, diet quality was defined *a posteriori* and different statistical methods were used to model cumulative dietary exposure.

To date, there is growing evidence for the role of diet protecting against age-related physical [160] and cognitive decline [237]. However, there are only few longitudinal studies on the cumulative effect of healthy dietary exposure as a determinant of aspects of healthy ageing [216, 217, 371, 373], even less on physical capability/performance [186, 188] or cognitive decline [171, 172], and scarce, if any, on walking speed to directly compare with this study. *Robinson et al. (2018)* [188] found that higher cumulative adulthood scores of *a posteriori*, but of similar composition diet as the HEI-2015, were independently associated with objective measures of physical function in late midlife. Data from the Whitehall II Study in the UK, showed strong detrimental effects on walking speed among ~5,700 older people, who were exposed over a 17-year period to unhealthy lifestyle patterns including less of two portions of fruit and vegetables [186]. In line with this, findings from the longitudinal HAPIEE Study in Eastern Europe, including 25,500 middle to older aged men, showed a significant cross-sectional association between the MedDiet and physical function, which might reflect the cumulative dietary habits in earlier life. However no effect was observed on the subsequent trajectories of physical functioning over a 10-year period [226]. Finally, the longitudinal Doetinchem Cohort Study in the Netherlands found no major differences between trajectories of physical functioning with regard to dietary habits (saturated fat, fruit and vegetables, fish consumption) among 4,000 men and women, over 15 years of follow-up [374].

Associations were not significant after adjustment for health and lifestyle factors. The aim of this thesis was to explore the independent effect of diet quality on walking speed; however in everyday life it is challenging to distinguish between single behaviours, as lifestyle habits tend to cluster [309]. A large volume of studies have assessed the combined effect of multiple lifestyle factors, mainly diet, physical activity, smoking habits, alcohol consumption and weight management, on healthy ageing and overall functioning [172, 184-187, 229, 308, 375]. Most evidence

showed a strong cumulative effect with increasing number of clustering factors. For example, disability risk including mobility limitation, increased progressively over a 20-year period among people with increasing number of unhealthy behaviour trajectories from midlife to older age. Behaviours included excessive alcohol consumption, persistent physical inactivity, long-term smoking and poor diet [371]. Similar findings were reproduced in data from the HCS Study, where risk of poor physical function, as indicated by objective measures, dramatically increased with accumulation of unhealthy lifestyle factors such as low diet quality, obesity, physical inactivity, smoking prevalence and excessive alcohol consumption, among older men and women in the UK [184]. This concept is further supported by data in other populations, such as the SWAN Study [187] and the Health ABC [185] in the US.

In the multivariable models, the associations were mainly attenuated when controlling for adulthood exposure to physical activity. This finding is in agreement with a significant amount of published evidence [184-187, 229, 312, 371, 374, 375]. Physical activity has been found to be a strong predictor of physical performance in older people [376], even in comparison to other lifestyle factors [164, 184-186]. For example *Koster et al. (2007)* [185] have shown that low physical activity was the strongest lifestyle predictor of mobility limitation in non-obese adults and the only significant one among obese adults. Furthermore, persistent inactivity or declining physical activity trajectories over a 20-year period starting in midlife, had the strongest and more robust association with subsequent disability including mobility decline, compared to other lifestyle factors, in the Whitehall II Study [371]. Moreover, despite a healthy lifestyle (smoking, diet, and physical activity) score was predictive of faster walking speed and shorter chair rise stand time in the SWAN Study, only regular physical activity in early midlife was independently associated with later life physical performance [187]. Adding to this, physical activity levels and weight status were the only lifestyle factors to predict membership in the limited or declining function trajectories among 4,100 Dutch adults [374]. Research has also suggested a combined effect of diet, in particular protein intake and physical activity, on physical function in epidemiological [375] and intervention studies [229, 377], yet in this study there

was no significant interaction. Nonetheless, the strong effect of physical activity on physical function might indicate reverse causality, with people of worse functional status being also unable to participate in physical activity. Indeed a recent study of 1,200 British older men and women identified walking speed as a significant independent correlate of objectively measured high-impact physical activity [378]. In this study, removing physical activity in the multivariable models modified the estimates away from the null; yet it was kept in the analysis because it is generally considered a strong lifestyle confounder alongside smoking, diet and nutritional status. Finally, there was no interaction between diet and activity levels in this study.

Another important finding was the improvement of overall diet quality over adulthood in both men and women. Trajectory analysis identified three groups which despite starting at different levels of diet quality, all improved over adulthood. These findings further confirm evidence showing a consistent improvement of diet quality among people from earlier to more recent decades [188, 218-220, 248]. Either defined by *a posteriori* methods [188, 219], change in key nutrient intakes [220] or change in food consumption [218], there is a trend towards better diet quality in British [248] and other populations [379], despite some indication of no further improvement in recent years [380]. Changes in dietary intake is a complex phenomenon that is affected by cultural transitions, changes in food habits, food availability and adherence to healthy eating recommendations [381]. In-depth discussions on what influences diet quality in older people and whether observed changes represent “fact or artefact” have already been published [220, 382]. Nevertheless, with participants in this study more likely exposed to the same environmental and cultural changes over adulthood, it can be assumed that observed differences were likely reflective of real changes. Finally, in this study women had higher diet quality at each age and over adulthood, faster rates of improvement than men and were more likely to belong to the healthiest dietary trajectory. This has been replicated by several studies which showed sex differences in diet quality favouring women, possibly because they also tend to be more health conscious than men, with adherence to healthy diet strongly correlating with health consciousness [188, 215, 216, 220].

This study benefited from availability of longitudinal data, which were collected and analysed with consistent methods over adulthood. Methodology of the five-day food diaries, estimation of food and nutrient intakes and calculation of the HEI-2015, were standardized over the 27-year follow-up period. In addition, an objective measure of physical function was used. All these reduced the possibility of measurement error[25]. The use of an overall diet quality index, in agreement with current dietary recommendations [270] was another strength, since it incorporated current evidence in the relationship of diet and health and assessed how close to this evidence was the actual dietary intake of participants in previous decades. Furthermore, the use of longitudinal models (LMM-IGC, GBTM) allowed all available dietary data to be explored, than including only those with complete follow-ups; hence possibility of selection bias was limited.

It is expected that within a healthy ageing population, the rates of mobility decline as indicated by slower walking speed, are likely to be underrepresented with regard to those in the general population. However, internal validity of the findings in this study should not be affected. Despite the thorough design of Insight 46, attrition rates were by definition high as Insight 46 comprises only 9% of the NSHD. Membership of group-based trajectories is not to be interpreted as literal entities or definite groups from which people can step up to another [323]; they rather represent latent strata of individuals following approximately similar developmental growth. However, conditional independence of trajectories can be assumed [324] and is further supported by present findings, which were very similar in both individual and group-based trajectory analyses. There was no baseline measure of walking speed, which limited the possibility to adjust for starting levels or explore speed decline over the follow-up. Yet, only 2% of participants had a value lower than 1.0 m/s, proposed to be a “health indicator” in older people [89] and hence initial levels before follow-up are considered normal for all participants.

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[25] Defined as “*fixed deviation of observed values from the true values of a measure of interest”* [44]. See 7.3 Methodological Considerations

Identification of cumulative exposure to lifestyle confounders was self-reported which may have distorted the observed associations, a consideration to be discussed in the next chapter.

6.6 Conclusion

Using longitudinal data of dietary exposure over a 27-year period in adulthood, this chapter provided further evidence towards a sex-specific protective effect of high diet quality against age-related functional decline, as indicated by walking speed in later life. It also confirmed the general perception that women tend to adhere to healthier lifestyle habits than men, for example having higher diet quality over adulthood. Albeit with limitations, the novel finding in this chapter is the potential importance for women of achieving healthy diet quality, in line with dietary recommendations, as early as possible in adulthood and maintain such quality over the years, so as to maximize the benefit against age-related physical decline. According to the present findings, this may be of less importance for men who tend to be more physically robust than women, despite following a diet of lower quality. Notwithstanding, attenuation of the magnitude of the relationship by other clustering lifestyle factors may indicate the need to investigate cumulative exposure to modifiable behaviours jointly, as a prevention strategy towards healthier age-related well-functioning.

Chapter 7 - General Conclusion

7.1 Summary

This chapter summarizes the main findings from the body of work contained in this thesis and provides further insights by comparisons with recently published evidence. Important methodological considerations for epidemiological studies are also discussed. Finally, future directions for related work and final remarks are provided.

7.2 Summary of Main Findings/Comparison with Literature

The present work in previous chapters provides original evidence for the relationship between diet quality in line with dietary recommendations, across different life stages and later life physical function as indicated by walking speed. It significantly contributes to knowledge with regard to sex differences potentially modifying this relationship, suggesting a beneficial impact predominantly in women. Importantly, it provides novel evidence for the cumulative effect of diet quality over longer periods in adulthood and raises the question regarding the impact of diet quality on age-related overall function, when older people walk under CMI conditions. Findings of this thesis may be of high relevance for older people because walking ability is crucial for living longer and independently with ageing and healthy diet quality the longest possible in adulthood seems to yield benefits on walking performance. These findings may be particularly important for older women who tend to be more vulnerable to physical decline.

More specifically, Chapter 4 assessed the relationship between overall diet quality and its components in late midlife and physical function in later life, as reflected by walking speed. The main finding of this study was that overall high diet quality was independently associated with faster walking speed in women but not men. Of the individual HEI-2015 components, evidence was not consistent or of high magnitude. Adding to the literature summary in Chapter 2, this research question still draws scientific interest, as reflected in the volume of recently

published studies [213, 225, 375, 383-389]. Few studies focus on the protective effect of individual dietary components on physical performance of older adults, such as vitamin D [383] or protein intake [375]; yet research mainly highlights the importance of overall diet quality, indicated by dietary patterns against age-related mobility decline [213, 225, 384-389], in agreement with this thesis. Recently, the prospective British Regional Heart Study of 1,000 older British men found a protective effect of the MedDiet and of a "prudent" diet, similar in composition as the HEI, against subsequent physical frailty [386]. It additionally showed that dietary indices based on WHO dietary guidelines were inversely associated with the likelihood of 15-year incident mobility decline [385]. Regarding walking speed, the cross-sectional CALM Study found that a dietary pattern rich in whole grains, dairy products, fish, legumes, nuts fruits and vegetables, all of which comprise the "adequacy" components of the HEI-2015, was related to faster 400-m walking speed at maximum pace among older Danes [384]. Further evidence for *a priori* diet quality indices such as the HEI-2015, comes from the Seniors-ENRICA cohort, which demonstrated that a dietary pattern of known inflammatory foods and nutrients, was predictive of slow walking speed among 2,000 community-dwelling adults aged over 60 in Spain [388]. Finally, with respect to sex differences in the observed association, in addition to studies discussed in Chapter 4, evidence seems to be inconclusive [213, 225, 386]. *Hagan et al. (2019)* [225], have recently showed 10% lower odds of impaired physical function over a four-year period, among 12,658 men in the Health Professionals Study, who had high aHEI scores, in line with associations shown in women [224]. However, *Jeong et al. (2019)* [213], replicated this result only for women but not men, by showing a protective effect of recommended food scores on physical performance, in line with already discussed studies [195, 204, 227, 390]. Potential explanations have been discussed in Chapter 1 and Chapter 4. Nonetheless, further research is needed regarding the mechanistic pathway of the sex dimorphism (if any) modifying the relationship of diet quality and physical function with ageing. In conclusion, Chapter 4 added to the existing evidence by exploring patterns of diet quality among well-functioning men and women, in relation to objective measures of walking speed, which has been a well-characterized predictor of healthy ageing.

Chapter 5 further investigated the relationship between diet quality in late midlife and objective measures of walking speed under CMI conditions, reflecting overall ability of older adults to utilize limiting resources. Results showed a positive association between HEI-2015 scores and walking speed in women, which was attenuated after consideration of other factors. Moreover, in men an unexpected inverse association between HEI-2015 and walking speed and CMI cost was shown, which was robust after multivariable adjustment. As discussed in Chapter 5, due to methodological limitations in study design, the observed association for men may not reflect a true negative relationship but rather differences in movement strategy between men and women when walking under CMI conditions. This is the first study to investigate the relationship between diet quality and the combined axis of physical and cognitive status via walking speed metrics, which mimic real life conditions such as walking and concurrently performing a cognitive task. In line with literature summary in Chapter 2, recent evidence highlights the importance of adherence to high diet quality to reduce the risk of age-related cognitive decline [389]. Using data from a British older population in the EPIC-Norfolk Study, *Shannon et al. (2019)* [391] found that high adherence to a traditional MedDiet was related to almost two years less cognitive ageing, reflecting all better global cognition, episodic memory and processing speed. In addition, the MIND diet has been shown to be a potential prevention strategy against functional disability, including the ADLs and IADLs, which are tightly linked to everyday tasks [389]. Therefore, considering the limitations in design of the CMI paradigm in Chapter 5, it may be more efficient to investigate the relationship between diet quality and direct measures of cognitive function which are important when walking under CMI conditions. In summary, Chapter 5 provided evidence towards a protective effect of high diet quality on walking speed and a trend towards lower CMI cost in women, which is a novel finding. It also proposed a potential research area to be further explored regarding possible sex differences in the relationship between diet and age-related function when walking under CMI conditions. Finally, it raised the question whether walking speed, which is influenced by multiple body systems and walking conditions, is the optimal outcome of interest when exploring the relationship of diet quality and the combined axis of physical/cognitive function.

Chapter 6 extended the above relationship by exploring the cumulative effect of diet quality trajectories over a 27-year period in adulthood on walking speed and CMI cost in later life. Based on the concept of life course approach that is "*accumulation of environmental influences, causing or modifying the rates of age-related decline*" [305], this chapter found a protective effect of high HEI-2015 trajectories, reflecting high diet quality over adulthood, on walking speed in later life in women but not men. In particular, achieving and maintaining high diet quality for as long as possible over adulthood had a stronger association with walking speed, about two to three fold, compared with findings from Chapter 4 and Chapter 5, which assessed "current" late midlife diet. This finding is in line with the hypothesis that duration and intensity of lifestyle exposure is of major importance in relation to healthy ageing. Findings were similar in women for individual HEI-2015 trajectories indicating current diet in late midlife, conditional on all previous life stages. Attenuation of findings after controlling for lifestyle factors, may pinpoint the importance of assessing clustering lifestyle factors concurrently. Complementary to studies discussed in Chapter 6, recently published evidence further supports this hypothesis, by showing a combined effect of diet and physical activity on cognitive [392] and physical function [375] of older people. For example, a recent RCT of participants aged over 60 found a stronger effect of multicomponent exercise programme plus dietary supplementation on some aspects of cognitive function, compared to exercise only [392]. Overall, Chapter 6 provided novel aspects on the relationship between cumulative exposure of a major modifiable lifestyle factor that is diet quality and age-related overall function. First, it confirmed the hypothesized protective impact of long-term high diet quality on objective age-related functional measures, on both individual and group level and second, it re-proposed sex differences modifying this relationship.

7.3 Methodological Considerations

Apart from the specific strengths and limitations discussed in each chapter, it is crucial to provide further insights regarding methodological considerations of this thesis. In particular,

given the study design, the extensive statistical analysis, the relative low sample size and the borderline significant findings, such implications should always be taken into consideration when interpreting and drawing conclusions from this thesis.

7.3.1 Study Design

This thesis comprised of a prospective longitudinal birth cohort (NSHD) and its prospective two-point sub-cohort (Insight 46), which, accounting for limitations, is the type of observational epidemiological design which provides the best level of evidence [64]. Generally speaking, this design limits the possibility of reversed causality, when the outcome of interest (walking speed decline) would precede the exposure (change in diet quality). This is further highlighted from the longitudinal nature of the study where the exposure (HEI-2015) is a function of multiple assessments at several adulthood ages. In addition, this design reduces the likelihood of recall bias as participants are assessed prospectively and thus they are less likely to mis-recall or mis-report the exposure (HEI-2015), conditional on walking speed status. Moreover, the birth cohort design is further advantaged by the fact that all participants are of the same age and consequently of same historical period and therefore they are very likely to have been exposed to similar environmental and societal conditions. Hence, the likelihood of distortion of the observed associations due to differences in “random” unmeasured factors is largely reduced. For example, it is well-known that all participants in the study lived the first decade under wartime food rationing and limited access to a health care system [393]. All this information is incorporated into exploration of exposure/outcome relationships. Nonetheless, it is important to highlight that all observational studies are indicative of associations rather than causality of outcomes of interest.

However, the thesis comes with a number of limitations deriving from study design. Inclusion criteria of the NSHD only left a small proportion of target population in 1946 not represented (illegitimately born - 4% of births - and not native born - 5% of births-). Furthermore, inclusion

criteria of the Insight 46 were unconditional on any specific outcome (physical or cognitive decline); yet the study comes naturally with “built in selection bias”. This is simply because participation at follow-up is conditional on being alive and having provided life course data, which makes it more likely participants were healthier, more well-functioning and more health conscious (discussed in Chapters 4,5,6). This is further reinforced by the fact that this thesis included only those who were able to perform the gait task in the Insight 46. Related to this, although attrition rates and loss to follow-up were within expected levels (Chapter 3), there was inevitably additional source of selection bias towards non-migration, high education attainment and high socioeconomic status [240]. Therefore, the prevalence estimates of the sample characteristics may be slightly distorted.

Despite the general perception that selection bias itself does not have a strong impact on the observed associations, there are cases in which sampling and study design induce another source of bias, the so-called collider bias due to conditioning. In such cases, selection bias may be considered a form of collider bias, which in turn may distort the observed associations towards or away from any true (or lack of) association [339]. For example, this occurs in cases when a collider factor is controlled by study design (selection bias). Collider bias have been extensively reviewed by *Munafo et al. (2018)* [339], and here a basic example is presented. Consider dietary data at any follow-up (X-exposure), walking speed (Y-outcome) and a selection indicator (Z-indicator of physical activity at previous time points). Given X correlates with data provision of Z, and Y is also correlated with Z in the Insight 46 (people who provided physical activity data were more health conscious or/and healthy and thus more likely to be of better ability to perform gait task), there is high likelihood that the causal association between X and Y is now conditional on Z (all participants share the same Z). This may lead to spurious associations if models are adjusted for Z; yet it can be stated that there was no evidence for such indicators in this thesis, at least to such extent that could have largely biased the estimates, which is further supported by all sensitivity analysis performed.

7.3.2 Sources of Bias

Most findings in this thesis were borderline statistically significant or non-significant or were attenuated in the multivariable models, although direction of the observed associations was consistent, overall and sex-specific throughout the analyses. Hence, it is important to provide potential sources of bias that may have influenced findings.

Random Error

This source of bias refers to the chance deviation of measurements of individuals from the mean population measurement and is present in every observational study [44]. When of high degree, “random error” results in low precision of the coefficient estimation. In this thesis, precision of findings was indicated by 95% CIs, which largely depend on the sample size, in particular the number of observations. When 95% CI did not include 0 ($p<0.05$), the null hypothesis H_0 (X-HEI-2015 has no effect on Y-walking speed) was rejected. Although the statistical analysis approach justified sample size to achieve 80% statistical power (probability of correctly rejecting H_0), the possibility of findings due to type I (to reject H_0 when true) or type II (to not reject H_0 when false) cannot be excluded. For example, with associations for women being marginally statistically non-significant or borderline significant (95% CIs close to 0), it may be the case that type I error can partially explain the observed positive results or that type II error influenced non-significant findings towards the null. Nevertheless, it is very important to consider that 95% CI and p values do not indicate if an association is real or spurious, which can only be concluded based on published evidence and biological plausibility [64]. Importantly, there were multiple days and ages of dietary assessment which lower the magnitude of random (within-person) error and provide better approximation of dietary intakes. In addition when the second phase of Insight 46 is complete, the number of walking speed observations will increase and will thus limit the effect of random error.

Systematic Error

This source of bias refers to fixed deviation of observed values from the true values of a measure of interest [44]. Unlike random error, it is not reduced by increasing sample size and if high degree, it can move the estimates towards, away or across the null [64]. This section will discuss three major types: measurement error of exposure (diet quality), measurement error of outcome (walking speed) and confounding bias (controlling factors in multivariable models)[26].

Bias related to measurement error of exposure occurs at the time of data collection and during modelling of exposure. Diet was assessed by self-reported food diaries, which albeit considered the "gold standard" in self-report dietary assessment [45], they are associated with measurement error *per se* to some extent, due to within person variation and misreporting [44]. Moreover, they represent a "snapshot" in time and do not capture the dynamic nature of change; yet repeated measures of diet partially accounted for this. In addition, food coding was dependent on the coder and clarity of coding instructions. Coding staff changed over the years and most importantly coding defaults were not consistent. For example, at age 53 the default milk choice shifted to semi-skimmed compared to previous years, due to published evidence towards healthy dietary choices [220]. Another example is disaggregation of composite dishes which was available at age 60-64 but not earlier [218]. This made it difficult to have a consistent measure of fruit and vegetable intake across adulthood. Seasonality and food availability issues have already been discussed. However, even "random" events such as growth in the importation by air of products from tropical and subtropical countries after 1982 or health promotion campaigns towards healthier eating such as the "Eatwell Guide" [274] have made it difficult to distinct between real changes in diet quality or artefact changes due

[26] For an overview of all sources of bias, see *Greenwood & Darren (2012)* [394] and *Delgado-Rodriguez & Llorca (2004)* [395].

to food choice. This may have introduced further measurement error as foods described at age 60-64 may not have similar alternatives in earlier food databases and vice versa. Notwithstanding, the fact that participants were of same age and historical period may have partially counteracted this distortion, as discussed earlier. Despite the standardized procedure, calculation of HEI-2015 component scores may have introduced further bias. For example the “added sugars” component was calculated manually at each age by subtracting “natural sugars” from “total sugars”. Similarly, the breakdown of fatty acids into MUFAs, PUFAs and saturated was not available at all ages; therefore at ages 36 and 43 it was generated from raw data. Nonetheless, it can be assumed the above mentioned bias does not depend on walking speed values (“non-differential bias”) considering the prospective design and therefore if and to which direction it may have influenced the estimates cannot be predicted, though the possibility cannot be disregarded. It is important to remember that non-differential systematic bias of exposure generally biases the association towards the null but it has also been reported it may bias estimates away from the null [64].

There may be cases where measurement error of exposure is related to the outcome or broadly speaking to other characteristics relating to outcome (“differential bias”). For example, misreporting is very common among obese vs non-obese people, who tend to under report energy intake and over report intakes of socially desirable foods such as fruit and vegetables and vice versa [396]. Similar to this, mis-reporting has been associated with education attainment, smoking habits, living independently, physical activity levels and even perceptions of “healthy eating” or “healthy body” [397]. Most importantly, well-known sex differences in eating and dieting towards higher degree of health consciousness in women [221] and cultural influences in previous decades, with women more likely to cook in households, may have reinforced further differential bias. Differential measurement error of exposure may shift associations towards or away from the null. For example, if women have under-reported dietary intake compared to men, as suggested by evidence [398], this may have driven their and overall association towards the null. However, this would not explain associations for men,

because if any, limiting measurement error in women would result in a stronger association for them. Furthermore, no misreporting of energy intake was identified in this thesis. Finally, although not a measurement error *per se*, it is likely that people have changed their diet from one assessment to the next or more crucially during follow-up to gait assessment. For example, if those with health or mobility decline have improved their diet, this may have led to biased associations towards the null (reverse causality). This may partially explain the null findings in men. Nevertheless, health and physical function measures at age 60-64 indicated overall healthy adults, the sample was well-functioning compared to those of similar age in other studies and follow-up was relatively long.

With regard to walking speed, there is some source of bias due to measurement error of outcome that needs to be discussed. First, there is "built-in" bias in walking speed values because participants who declared they were unable or unwilling to perform the 10-m walking task were excluded by default. This may be due to objective (due to mobility issues) or subjective (felt uncomfortable) inability, resulting in overall well-functioning sample size. This is indicated by numerous other factors such as walking speed was faster on average compared to other studies, no participants were identified with walking speed <0.8 m/s (frailty criterion) and they were more health conscious (and likely healthy) as they have provided life course data (Table 3.3). It cannot be concluded with certainty whether this bias is non-differential or differential, as for example inability to provide walking speed or providing only for one task may be related to unmeasured personal factors which reflect the exposure (diet quality). For example, according to assessors, gait tasks were performed in an open corridor where there was interference with staff and patients of the clinic and some participants were more motivated to perform the walking test than others and walked at maximum speed. Nonetheless, including only well-functioning people may have biased the observed estimates towards the null and this can partially explain the inconsistent and statistically non-significant associations in men. However, this would not explain the direction of the association in men under CMI conditions. Another source of non-differential measurement error would be the

IMUs metrics which although valid, might have provided overestimation of walking speed values, based on comparisons with age-specific normative values. However, if any, measurement error would be consistent across all walks and in addition sensitivity analysis was conducted. Changes in significance levels of the estimates were more likely due to loss of sample size from applying stricter criteria on walking speed values, rather than bias due to the assessment method. Finally, a major source of measurement error of outcome which has possibly biased the observed estimates is related to the walking tasks under CMI conditions. Performance in the cognitive verbal task was not assessed. Hence the estimated walking speed and most importantly the CMI cost has most likely misclassified participants, based on walking strategy and prioritization of task rather than their ability to utilize limiting resources, which was one of the objectives in the thesis. It cannot be safely stated to which direction estimates were biased but findings of Chapter 5 may be largely explained by this source of bias; however later life cognitive status was considered to mitigate its influence.

The final source of systematic bias, discussed in this thesis, is “confounding bias”. This source of bias occurs when the relationship between the exposure (diet quality) and the outcome (walking speed) is mixed (or “confused”) by another variable (confounder), leading to biased estimates [64]. In order to be considered a confounder, a variable needs to be associated with both the exposure and the outcome and not be in the causal pathway of the relationship (simply not be an effect of the exposure). In all studies, this source of bias was considered by including a wide range of potential confounders, as suggested by prior evidence and biological plausibility, into the multivariable models. Furthermore, there was no strong evidence that factors used was an effect of diet quality (intermediate), perhaps with the exception of weight status. However, because HEI already incorporated energy intake, known to be strong determinant of weight status, this possibility was unlikely. In general, in epidemiological studies, it is rather complicated to test whether a factor is confounder or intermediate in particular when factors are measured at the same time as the exposure [44].

Despite thorough adjustment in all studies, which limited the overall “confusion” in the observed estimates, there is still the possibility of “residual confounding” which refers to bias due to measurement error, mis-modelling or/and unmeasured confounders; yet various important factors of multiple areas were considered including socioeconomic, health, anthropometrics, physical performance and most importantly lifestyle. It could be argued that combining lifestyle factors as a joint clustering behaviour instead of controlling for them would be preferable to model the exposure; however the objective of this thesis was to explore the independent impact of diet quality on later life well-functioning. In addition, according to the International Classification of Functioning, Disability and Health [399] and published evidence [400], the relationship between physical activity and physical function might be more complicated than previously thought, as both affect and get affected by each other. Nevertheless, in this thesis physical activity was considered as a modifiable lifestyle behaviour which clusters with other behaviours and hence it was included as a confounder in all models. When possible, the multivariable models were standardized across the thesis for comparability purposes by using the same/similar confounders and consistent modelling strategies. An exception was inclusion of the MMSE score in Chapter 5 and Chapter 6 to control for cognitive status when walking under CMI conditions. Another exception was the use of continuous scores of cumulative exposure to lifestyle factors in Chapter 6, but this was unavoidable because further categorization would increase the independent predictors and thus endanger statistical power in the models. Although it is difficult to draw certain conclusions regarding whether and to which extent such measurement error might have biased the estimates, it is always important to refer to confounding bias and its potential implications.

7.4 Original Contribution to Knowledge

Exploration of progression patterns of health and disease has revealed that most likely ageing follows the life course hypothesis [305]. This approach supports that differences in ageing trajectories derive from cumulative differential lifetime exposures to damaging physical and

social environments [305]. In particular for physical capability, it has been consistently shown that cumulative exposure to healthy lifestyle factors including diet, physical activity, absence of smoking and normal weight maintenance over the lifespan, may be beneficial against vascular decline [216], bone loss [217] as well muscle mass and strength decline [184, 186, 188]. However, due to complexity of statistical approaches to optimally investigate life course exposures, research to date has failed to consider a continuum of developmental trajectories of diet quality affecting age-related functional decline.

This thesis originally contributes to knowledge by applying a combination of novel statistical techniques to investigate all aspects of growth of a major lifestyle factor – diet quality – over a significant 30-year period in adulthood, at an individual and also at a group level. Adding to existing evidence, this thesis showed that healthier developmental trajectories of diet quality, that is trajectories of participants who started with high diet quality earlier in life and kept improving their diet over adulthood, reflected better physical capability and showed a trend towards better overall function in older life. Another novelty of this thesis is the fact that this pattern was identified for individuals but also for groups, which despite having different starting levels of diet quality, they all improved diet over the years. This finding is of major contribution to knowledge considering that (a) it may reinforce the efficiency and need of continuation of public health and governmental actions (“The 5 A Day”, “Nutrition on the Go”, “Change4Life”, “Healthier You”) and (b) it provides novel insights of existence of distinctive groups of ageing populations regarding dietary intake. Identification of these groups when considering participants in this thesis are overall well-functioning despite ageing, make is plausible to suggest that this thesis uniquely contributes towards the hypothesis that achieving and further improving diet quality over adulthood may yield great benefit on physical function in later life, even among those with lower initial levels who still improve diet quality. This implication carries a strong public health message that “it is never too late to adhere to a healthy diet at any life stage to ensure healthier ageing and quality of life” and that “the earlier in life someone starts

and the longest possible they maintain high diet quality, as one proposed by national dietary guidelines, the greater the benefit will be".

Another original and novel contribution of this thesis was the sex differences that were found to modify the relationship between diet quality and walking speed, indicating physical capability in later life. This finding was persistent and robust when investigating diet quality at late midlife as well as over a 30-year period in adulthood and showed a beneficial effect on walking speed in women but not in men. To date, only few studies have assessed this relationship based on the sex differences hypothesis in ageing and lifestyle behaviours, as thoroughly discussed in page 32. The present thesis adds novel evidence and originally contributes in this area in many ways. First, despite estimates being of low magnitude in relation to walking speed, women who tend to be less physically robust than men, seem to be favored by high diet quality, despite in some cases walking speed values were not lower than those in men after controlling for body size. This may indirectly reflect the positive effect of diet on the musculoskeletal system, which is well established to be influenced by dietary intake [126]. Therefore, this project reinforces the concept of "longevity" which suggests that in order to compensate for lower absolute values of muscle mass and strength and to ensure a smoother decline of functional status, women may be more susceptible to beneficial lifestyle behaviours including diet. Second, this is the first project to extend such sex differences in the relationship of diet and physical capability to a very important indicator of overall functional ability, which is tightly linked to healthy ageing that is walking speed. To date, most research has focused on important functions such as bone and muscle mass and muscle strength; yet despite them being valuable for clinicians and to identify biological ageing, they may be of less practical relevance for the ageing population. On the contrary, walking ability is a very important element of healthy ageing, easy to understand and to communicate to the general public. Hence, this thesis proposes a public health message that "adhering to high diet quality as suggested by dietary guidelines may be beneficial in particular for women to maintain a normal walking speed with ageing, tightly indicating lower risk of disability and comorbidity".

From an overall public health perspective, the novel findings from the current analysis may offer useful information in developing and planning different strategies of lifestyle interventions for men and women, in particular in relation to diet. If current findings are replicated, this may further suggest that public health actions of diet quality towards maintaining physical capability may need to prioritize women versus men and less well-functioning versus well-functioning ageing populations.

7.5 Future Directions

This thesis adds novel evidence regarding diet as a modifiable lifestyle determinant of healthier ageing, notwithstanding the limitations. The quality of data from a well-perceived longitudinal cohort, the meticulous study design and the sophisticated statistical analysis used to capture dietary changes over time, further increase the value of the findings. However, because epidemiological data do not give the final answer but rather raise more questions, further longitudinal studies are needed to confirm or disapprove the present findings.

In the present thesis, a multidimensional index of diet quality over 30 years in adulthood, in line with current dietary recommendations, was found to predict walking speed in later life, even after controlling for a number of other factors. From a public health perspective this may pinpoint the importance of future research to focus on *a priori* dietary patterns in line with dietary guidelines when investigating the effect of diet on age-related functional status, rather than of single nutrients or food items. This approach may carry a more plausible public health message as initiatives of holistic dietary patterns such as the Eatwell Guide can be communicated more effectively and are easier to follow. Diet indices such as the HEI incorporate all fundamental components of a healthy diet, highlight the importance of diet quality independent of quantity and reflect the current trends in diet-health relationship; as such they are highly recommended for future studies of similar research question. In this direction, it will be of great interest to compare the present findings with the upcoming results from the ongoing Baltimore Longitudinal Study of Aging in the US, which is similar to this thesis

regarding study design (longitudinal cohort from 1958), dietary exposure modelling (trajectories of HEI) and outcome of interest (age-related physical function).

Findings in this thesis, despite of magnitude being small, have the potential to inform clinical practice. Considering that even among participants who were overall well-functioning and had fast walking speeds, diet quality was shown to have a significant effect on physical capability, it may be plausible to suggest that future studies focusing on already declined people, may yield stronger benefits of high diet quality. Because of the nature of the dataset in this thesis, exploration of this hypothesis was not possible because there were no participants who had walking speed values of <0.8 m/s, which is suggested to be the cut-off point for physical frailty, disability and sarcopenia [89]. Alternatively, findings in the present thesis may be equally valuable for future studies and clinical practice towards promoting the importance of prevention of age-related functional decline by simple lifestyle modifications, rather than treatment when decline is prevalent. Furthermore, considering functional decline is inevitable to some extent, a potential direction of future research is to re-assess walking speed decline in relation to lifetime diet quality, which will be feasible with upcoming gait data from the second phase of Insight 46. In any case, this thesis sets the platform for future research to further investigate the relationship between diet and functional decline directly as a preventive strategy over the lifespan and indirectly as a treatment intervention in older life.

Another area for future research derives from findings regarding walking under CMI conditions, in particular when considering the limitations mentioned in this thesis. First of all, future studies should aim to design an optimal CMI paradigm that captures overall physical and cognitive capability with ageing. To date, there is no general consensus on such paradigm; yet key research has suggested that a successful CMI paradigm is one to: (a) include a motor and a secondary cognitively demanding task; (b) challenge cognitive aspects that are related to executive functions, processing speed and working memory and (c) assess performance of all tasks, separately and jointly [77]. It would be therefore of great interest to further explore the

impact of diet on measures of overall functioning rather than isolating physical from cognitive functioning. This will likely benefit the ageing population more as most everyday tasks require multi-tasking rather than walking in isolation. In addition, given the complex nature of the walking process which is linked to multiple body systems and functions, future research may target more elements of walking patterns, especially when walking under CMI conditions, rather than simply walking speed. For example, walking speed could be combined with measures of balance, symmetry and variability, as those are well proposed to reflect on the combined motor-cognitive axis. Indeed, IMUs such as the ones used in this thesis, have shown promising findings with regard to walking variability for numerous conditions such as peripheral neuropathy [65], Parkinson's [67] and Huntington's [66] disease, all of which are accompanied by abnormal walking patterns. Therefore, extending exploration of the relationship between diet quality among various age-related cognitive diseases and more parameters of walking, would be an entirely novel and interesting area for future research.

With regard to sex differences modifying the association between diet and age-related functional decline, as consistently shown in this thesis, it would be useful for future research to further explore this relationship using additional objective measures of functional decline such as muscle mass and strength, bone density and cognition. In particular given the observational nature of this thesis and the scarce evidence on this research area, whether such sex differences will be evident and robust when objective measures of decline are assessed, this will determine the necessity or not of different lifestyle intervention strategies targeting healthy ageing between men and women. In any case, observational studies reflect only on associations and therefore the biological mechanism and causality of diet exerting its effects differently by sex, can only be proven by clinical trials. However, although there is primitive evidence in this area with clinical trials on MedDiet showing differential effects on inflammatory markers in men versus women [401], there are overall major challenges regarding clinical nutrition research. Quoting Weaver and Miller (2017) [402] there are so many considerations unique to this field including all "baseline nutritional status of participants,

defining appropriate control groups, effective blinding of participants and investigators, the evolving ethics of randomized control trials, and a tension in a priori decisions regarding inclusion of nutritionally vulnerable participants versus representative samples of general populations". Hence, before feasible clinical trials are suggested, there is a great need for establishing plausibility of sex differences from observational studies, as suggested above.

Finally, deriving from findings in this thesis and based on the concept that lifestyle factors tend to cluster [309], exploration of the joint effect of major modifiable factors (diet, physical activity, and smoking) over time, on age-related functioning would be of great interest. Clustering of lifestyle is evident for both unhealthy and healthy factors, with women being more likely to cluster behaviours overall; on the contrary men tend to cluster more often unhealthy factors than women [309]. To date, there are observational studies that investigated simple scores of clustering lifestyle factors in relation to later life functional decline, as discussed in detail in Chapter 2. Findings in this thesis revealed that treating diet quality as continuum developmental trajectories provided novel evidence and demonstrated unique insights of this relationship. Likewise, the same approach with regard to additional lifestyle factors could be adapted in future research, considering the observed clustering of lifestyle behaviours. This was not tested in this thesis but current advances in statistical modelling, such as multi-GBTM, allow for simultaneous modelling of several factors over the lifespan in relation to later life ageing. Potential exploration of this relationship may carry a notable public health message in so it will provide evidence on the overall and individual effect of major lifestyle factors over long periods in adulthood, on later life functioning; thus investigation of this relationship is highly recommended.

7.6 Final Remarks

Based on the findings and their implications discussed in this thesis, using longitudinal data from the oldest and longest running birth cohort worldwide, the British NSHD and its neuroscience sub-study, Insight 46, the following conclusions can be drawn:

- Both men and women improved diet quality during adulthood. Women had higher diet quality at all ages and over time and faster improvement rates than men and were more likely to maintain consistently high diet quality during adulthood (Chapter 4, 5 and 6).
- In women, overall diet quality in late midlife had a positive association with walking speed, indicating better physical function in later life, independent of other factors and there was a null association in men (Chapter 4).
- The association between late midlife diet quality and walking speed and CMI cost, indicating ability to utilize limiting physical and cognitive resources in later life, was positive but not independent of demographic and lifestyle factors in women and was inverse in men; though the latter should be interpreted with caution due to limitations in study design (Chapter 5).
- In women, the magnitude of the positive association was stronger on walking speed but not under CMI conditions, with regard to cumulative exposure to high diet quality over a 27-year period in adulthood compared to late midlife only, but was attenuated when considering other lifestyle factors. There was also a null association for men (Chapter 6).
- The association between diet quality and walking speed and CMI cost was modified between men and women, possibly reflecting sex differences in dietary intake and trajectories of physical and cognitive ageing. This may indicate the need for sex-specific lifestyle intervention strategies towards healthy ageing (Chapter 4, 5 and 6).

This thesis contributes originally and significantly to knowledge because it (a) further confirms that achieving a “healthy diet” in line with current dietary guidelines is important in delaying age-related physical decline in later life, in particular in women, (b) uniquely and novelly highlights the importance of duration and intensity of a healthy diet to yield further benefits to physical function with ageing, (c) provides further evidence and thus reinforces the concept of sex differences likely modifying the relationship between healthy lifestyle behaviours such as diet and well-functioning in later life, (d) confirms proposed trends towards dietary improvement in both men and women from earlier to more recent years and (e) provides novel,

albeit tentative evidence and thus raises the question on the role of overall diet quality on optimal utilization of limiting resources when walking and multitasking in later life. Overall, it carries an important public health message for older people who can yield benefits to their walking ability, a strong predictor of survival and living independently, by following healthy dietary patterns of high quality the longest possible over adulthood.

Appendices

Appendix 1 Public health hazards, aims and methods at each stage of the NSHD study. Modified version of [244]

Assessment Year	Age (years)	Public Health Hazard	Aims	Methods
1946	Birth	Costs of maternity, reason for falling fertility.	To show the cost of and care in pregnancy and child birth.	Health Visitor Midwife Obstetrician
1947-50	1-4	Social class differences in maternal and child mortality and morbidity.	To see whether initial SES differences in weight at birth were reflected in growth, and to show the effectiveness of maternal, and community maternal and child welfare care.	Health Visitor
1951-59	5-15	Increasing the national level of educational attainment. The 'waste of talent' problem, i.e. the apparently low recruitment of high IQ children from poor SES circumstances into higher education.	To study family and environmental effects on growth and educational attainment, and the working of the education system.	Health Visitor School Nurse School Doctor Teacher
1960-76	16-31	Outcomes of education in terms of occupational choice and skills, effects of atmospheric pollution.	To study the occupational and earnings outcomes of education and cognitive development, and pathways to ability and attainment, respiratory disease, and problem behaviour.	Postal Questionnaire Interviewer
1977-present	32-71	Ageing processes, self-care of health, receptivity to health promotion.	To study pathways to physical and cognitive ageing using data collected throughout life, and change in women's health during the menopause transition.	Research Nurse (home visit, clinic visit) Postal Questionnaire

Appendix 2 History of consent and ethical approval of the National Survey of Health and Development (NSHD), Medical Research Council (MRC), NSHD/Insight 46

Throughout the 70-year life of the NSHD study consent for each data collection has been consistent with the highest contemporary standards and best current practice. In scientific studies in the period that pre-dated the MREC/LREC structure, consent was assumed by participation. In this study, the period of assumed consent covers the years from birth to age 35 (from 1946 to 1981). Consent forms have been used since the home visit in 1982 (age 36). At age 43 consent was asked separately for the home nurse interview, the physical measures taken, and for access to hospital records. At age 53, study members gave consent for data to be used ‘ in strictest confidence and only for research purposes’ and consent was obtained separately for the interview, the physical measures, taking a blood sample for cardiovascular and nutritional analyses, taking blood and buccal cell samples for DNA analyses, and accessing hospital records. An ethics advisory committee set up by the previous Director of the study gave guidance on the exact wording of the consent for preparing DNA and undertaking genetic studies, and on the information leaflet sent to participants about the study of genes in NSHD. In the data collection at age 60-64, consent was obtained according to guidelines laid down by COREC. For the first time a postal questionnaire format was used to ask for access to medical records, and for the first time this included access to GP and hospital records. Of those who returned the postal questionnaire 92% were willing to give consent to these records in this way. Ethical permission for the 1982 and 1989 studies was obtained from the local ethical committees that preceded the LRECs and that were run by the teaching hospital to which the NSHD research team were then affiliated (Bristol in 1982 and UCH in 1989). In 1999, MREC approval was obtained for the data collection and its use for research purposes by the team and their collaborators (MREC98/1/121). In 2006, ethical approval for the feasibility study (MREC06/Q1407/26) was obtained from the Central Manchester Research Ethics Committee. Further ethical approval for the extension study (2006-2010) (07/H1008/245) was obtained from the Central Manchester Research Ethics Committee and additional Scottish approval (08/MRE00/12) was granted through the NHS Lothian Research and Development Office. At the 24th follow-up, ethical approval for the postal questionnaire (2014) and home visit (2015-2016) was obtained from the Queen Square Research Ethics Committee (14/LO/1073) and Scotland A Research Ethics Committee (14/SS/1009). Ethical approval for the neuroscience sub-study, Insight 46 (PI Jonathan Schott, DRC, UCL), was obtained from the Queen Square Research Ethics Committee (14/LO/1173).

Appendix 3 Individual components of the HEI-2015 and unit conversion

Component	Unit Conversion [1]	Comment
Adequacy		
Total Fruit	1 cup equals: ~170g fresh fruit ~130g dried fruit ~250g canned/cooked fruit (with water/syrup) ~215g fruit smoothie ~250g fruit juice ~250g juice from concentrate/squash	Includes all consumed fruit (citrus, berries, melons etc.) in any form (fresh, frozen, dried, canned, cooked). Also includes fruit juice, juice from concentrate, juice squashes and fruit smoothies [2]. NSHD database does not distinguish between 100% fruit juice and combinations; hence this component includes squashes and concentrated juices too.
Whole Fruit	1 cup equals: ~170g fresh fruit ~130g dried fruit ~250g canned/cooked fruit (with water/syrup) ~215g fruit smoothie	Includes all intact consumed fruit (citrus, berries, melons etc.) in any form (fresh, frozen, dried, canned, cooked). Also includes fruit smoothies but not any form of juice [2].
Total Vegetables	1 cup equals: ~125g raw vegetables ~200g cooked vegetables ~240g tomato sauce/puree ~225g potatoes and products cooked ~190g pulses/legumes	Includes all consumed vegetables (tomato, tomato sauce, potato and potato products, brassicaceae, other vegetables) in all forms (raw, cooked, boiled) [2]. Yellow, red and dark green vegetables are also included in this component and in the "Greens and Beans" component. NSHD database does not distinguish between raw and cooked vegetables; hence weights were calculated for all.
Greens and Beans	1 cup equals: ~105g raw vegetables ~170g cooked vegetables ~190g pulses/legumes	Includes all consumed yellow, red, dark green and brassicaceae vegetables in all forms (raw, cooked, boiled) [2]. Examples of dark green vegetables include broccoli, rocket and spinach. NSHD database does not distinguish between raw and cooked vegetables; hence weights were calculated for all. Also include legumes, pulses, and nuts.

[1] "What's In The Foods You Eat Search Tool, 2013-2014", Food Surveys Research Group, The United States Department of Agriculture (USDA) [403]. [2] National Diet and Nutrition Survey: UK food consumption and nutrient intakes from the first year of the rolling programme and comparisons with previous surveys [253] [3] USDA database for the added sugars content of selected foods, Release 1 [284]

Continued Appendix 3

Component	Unit Conversion [1]	Comment
Whole Grains	1 oz ~28g of wholemeal bread, oatmeal breakfast cereal, high-fibre breakfast cereal, brown/wheat germ/granary bread	Includes wholegrain products, i.e. foods made from the entire grain kernel (bran, germ and endosperm). Examples include wholemeal bread, oatmeal bread and cereal, high fibre breakfast cereal with no sugar and brown/wheat germ/granary bread [2]. NSHD database does not distinguish between brown and white pasta, rice etc. so none of those were included.
Dairy	1 cup equals ~245g of whole, semi-skimmed, skimmed, plant based, other animal based milk, flavoured milks, cheese including cottage cheese, full and reduced fat yoghurt	Includes milk and dairy products (yoghurts and cheese). Soya drinks are also included [2]. It does not include creams and cream cheese.
Total Protein Foods	1 oz ~28g of eggs, shellfish, whitefish, beef, veal, lamb, other red meat, pork, chicken, other white meat, nuts, seeds, offal, other meat, sausages, burgers, legumes, pulses and baked beans	Includes all protein-rich foods such as meat, fish, eggs, nuts, seeds and soya products (tofu) [2]. As mentioned above, legumes, pulses and baked beans are also included.
Seafood and Plant Proteins	1 oz ~28g of seafood and fish, nuts, seeds, soya products, legumes, pulses and baked beans	Includes seafood and fish, nuts, seeds and soya products (no soya drinks) [2]. Legumes, pulses and baked beans are also included. Introduced because of the presumably health benefits of fish, seafood and vegetarianism, when replacing a portion of meat, as highlighted by the DGAs 2010. With this component, a vegan or vegetarian diet are much more likely to identify if a high score for this component is achieved [266].
Fatty Acids	MUFAs + PUFAS To Saturated	Introduced to highlight the importance of the type of consumed fats than quantity by the DGAs 2010 [266]. It is the sum of mono-unsaturated and poly-unsaturated to saturated fat and emphasizes that saturated fats should be replaced by unsaturated fats.

[1] "What's In The Foods You Eat Search Tool, 2013-2014", Food Surveys Research Group, The United States Department of Agriculture (USDA) [403]. [2] National Diet and Nutrition Survey: UK food consumption and nutrient intakes from the first year of the rolling programme and comparisons with previous surveys [253]
[3] USDA database for the added sugars content of selected foods, Release 1 [284]

Continued Appendix 3

Component	Unit Conversion [1]	Comment
Moderation		
Refined Grains	1 oz ~28g of crisp, white and other bread, low fibre and other cereal, pasta, pizza, rice, processed pies, biscuit snacks, cereal bars, cereal puddings and pastries.	Includes highly refined grain products, products which have been heavily processed, such as such as white flour, bread, rice, pasta and snacks [2]. Refined grains were assigned as a moderation component, due to the worldwide trend of high consumption of savoury snacks and refined products, in particular when away from home [266]. NSHD database does not distinguish between brown and white pasta, rice etc.; hence considered white-refined as this type is consumed more frequently
Sodium	mg or g of sodium intake	As mentioned above, it does not include any table salt or while cooking. It includes only salt naturally present in food.
Added Sugars	Natural Sugars (g) per 100g of product [3]: milk ~5g cream, eggs ~0.7g cheese~2.3g yoghurt full ~5g yoghurt low-Fat ~7g pulses, vegetables ~2-3g nuts/seeds ~4g fresh/puree/canned fruit ~10g dried fruit ~40g fruit juice/concentrate ~12g Added sugars=Total Sugars-Natural Sugars.	Includes all sugars that are not naturally present in food as in fruit and milk and is calculated as total sugars minus naturally present sugars from fruit, milk and vegetables. It was introduced to comply with the DGAs 2015-2020 to limit added sugars intake to less than 10 percent of total daily energy intake and increase fruit, vegetables, and whole grains intakes [270]. Added sugars are converted to kcal in the scoring process (4 kcal per 1 g of added sugars).
Saturated Fat	mg or g of saturated fat	Saturated fat is converted to kcal in the scoring process (9 kcal per 1 g of saturated fat).

[1] "What's In The Foods You Eat Search Tool, 2013-2014", Food Surveys Research Group, The United States Department of Agriculture (USDA) [403]. [2] National Diet and Nutrition Survey: UK food consumption and nutrient intakes from the first year of the rolling programme and comparisons with previous surveys [253]
[3] USDA database for the added sugars content of selected foods, Release 1 [284]

Appendix 4 Standard Operating Procedure of Gait Assessment in Insight 46

3.27 Gait Exam

Purpose

The LPMS-B unit and LPMS control software has been developed by the Movement Science Group at Oxford Brookes University. This will allow us to perform gait analysis and measure a variety of metrics whilst a participant walks unaided (or aided if necessary) and whilst performing a dual cognitive task.

Key Personnel

- The gait exam will be administered by a trained study clinician.

Related Information

- Quick Guide LPMS-B inertial measurement unit – Version 1
- Random Number Generator Spreadsheet

Documents to Print / URLs to Access During Visit

- URL to access XNAT
- Copies of XNAT forms in the event of equipment or internet failure.

Equipment

- Laptop with Bluetooth capability
- LPMS-B inertial measurement unit
- Double sided tape
- Tape measure
- Metre wheel
- Marker tape
- Cone

Exclusion Criteria

- Participants who are unable to walk 20 metres (walking assistance aids can be used)

Procedure

3.27.1 Prior to each visit, the IoN study coordinator will create a random order to performing the conditions using a Random number generator in Excel and upload the sequence to XNAT. The sequence will also be written on the checklist that will be included as part of the package of papers for the clinician on the day of each visit.

3.27.2 On the morning of the visit, ensure that the tape is marked out for the walking trajectory.

3.27.2.1 Preparing the walking trajectory

3.27.2.1.1 Place marker tape at 0m.

3.27.2.1.2 Use metre wheel to mark 10 metres with marker tape.

3.27.2.1.3 Place the cone at 10 metres.

3.27.2.1.4 If the marker tape is left on in position between sessions, always confirm the distances with the metre wheel at the beginning of the session.

3.27.3 As described in the Quick Guide:

3.27.3.1 Start the LPMS Control software.

3.27.3.2 Turn the LPMS_B sensor on by pressing the button on its side – red and green LEDs will flash within the sensor.

3.27.3.3 Match the sensor label under the preferred devices drop-down menu and press the connect button.

3.27.4 Introduction: "How people walk and how that changes as they get older is an important aspect of health and daily function. I would like to assess how you walk over a set distance, and also whilst performing several cognitive tasks. In order to do this I will attach a small device called an accelerometer to your lower back with some sticky tape to record your movements. It will mean I have to lift up the back of your top, if that's alright? Are you happy to proceed?"

3.27.5 Protocol:

3.27.5.1 Upon confirmation that the participant is happy to proceed, affix the LPMS-B to the participant by first affixing double sided tape to the back of the device and then placing on the participant's lower back, using the guidance under "Placing" in the Quick Guide. This should be done in the examination room, not in a common area.

3.27.5.2 Convert the laptop to tablet form so the touchscreen capability is activated.

3.27.5.3 Have the participant complete 1 practice condition, which will involve walking to the cone at 10 metres and immediately turning round and returning to the starting point, so that each trial constitutes a total of 20m (or 2x10m) (see Table 3 on page 172).

3.27.5.4 Instruct the participant to "combine tasks to your best ability" and walk at a self-selected pace. No direction will be given as to prioritisation of gait or task.

3.27.5.4.1 There are 3 experimental conditions (see Table 3 on page 172). Each experimental condition should be performed two times by each participant for a total of 6 tasks.

3.27.5.4.2 The 6 tasks should be completed in the order determined by the Random Number Generator spreadsheet. The conditions are randomly ordered to minimise practice effects.

3.27.5.5 For each experimental condition:

3.27.5.5.1 First create a unique filename in the "1946 Study\Test Data and Video Files\Gait task raw data files" folder on the shared drive using the format: SUBJECT-ID_YYYYMMDD_# (whereby # refers to the task number 1-6)

3.27.5.5.2 Get the participant to stand at the starting point, give the instructions and then start recording. On “3,2,1, Go” let the participant start.

3.27.5.5.3 When the participant has stopped at the end point, leave several seconds with the participant standing before pressing the “Stop record” button.

3.27.5.6 For each experimental condition, a new file should be generated.

3.27.5.7 Although every effort will be made to ensure there are no distractions during completion of the gait analysis task, occasional interruptions will occur. In the instance, the recording for that task should be disregarded, and the task repeated using the alternative letters in the table on page 172.

3.27.5.8 Thank the participant, and warn them before removing the accelerometer. Once the accelerometer is removed take off the double sided tape and discard.

Recording Results

3.27.6 Record in XNAT:

3.27.6.1 If the test was completed.

3.27.6.2 If the participant has an abnormal gait and, if so, the type and severity.

3.27.6.3 If a walking aid was used and, if so, in which hand it was used.

3.27.6.4 Leg length and shoe size (in EU or UK sizing) will have been recorded during the physical exam while the height and weight are measured.

3.27.7 Saving the data files:

3.27.7.1 The data should be visually inspected as it is collected (if Bluetooth signal is lost, the realtime data graphic will stop, in which case, the condition will need to be repeated and that file deleted).

3.27.7.2 The clinician will save the raw data file on the shared study drive in the following location: “1946 Study\Test Data and Video Files\1_Raw Data Files\Gait Task raw data files”.

3.27.7.3 When data has been collected from 50 participants, the IoN study coordinator will send the raw data files to Patrick Esser (pesser@brookes.ac.uk). The raw data files will be accompanied by a spreadsheet that includes the participant IDs, leg length, shoe size, whether a walking aid was used, and in which hand it was held. This Excel spreadsheet will be generated by XNAT.

3.27.7.3.1 Upload the analysed data into XNAT within 48 working hours of receipt from Patrick Esser.

Condition	Cognitive Task	Random Number Generator Task #	Researcher Instructions
0: Wearing equipment as practice	Practice	N/A	"When I say go I would like you to walk to the cone at the other end of the corridor, turn around and return to the start point please. Do you understand? 3,2,1. Go."
1: Undisturbed walking	No cognitive task	1 and 2	"When I say go I would like you to walk to the cone at the other end of the corridor, turn around and return to the start point please. Do you understand? 3,2,1. Go."
2: Walking plus verbal fluency	Single letter cognitive task	3 and 4	"I would like you to walk to the cone and back to the starting point, and at the same time name as many words as you can think of beginning with a letter of the alphabet that I will give you. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will say the letter then the word go. Do you understand? The letter is [S]. 3,2,1. Go. The letter is [B]. 3,2,1. Go." If additional trials are needed, the letters [A] or [D] can be used.
3: Walking plus switching between verbal fluency tasks	Letter switching cognitive task	5 and 6	"I would like you to walk to the cone and back to the starting point, and at the same time name as many words as you can think of alternating between two letters of the alphabet that I will give you. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will say the letters then the word go. Do you understand? The letters are [C] and [T]. 3,2,1. Go. The letters are [P] and [M]. 3,2,1. Go." If additional trials are needed, the letters [R] and [F] or [H] and [L] can be used.

Appendix 5 Identification of additional descriptive characteristics not used in the main analysis of participants over adulthood (from age 36 to 64), n=502

- **Occupational class** up to age 53 was obtained by the National Statistics Classification.

- Prevalence of individual **comorbidities** up to age 53 has been defined in Table 3.5**.**

- Using sex-specific quartiles of **physical performance** for one leg balance test with eyes closed and chair rise stands time at each age, points were allocated to each quartile of the distribution of each participant's ranking; (0=lowest quartile, 1=second quartile, 2=third quartile, 3=highest quartile). Points were summed across all three ages, with 0 reflecting over time low rank in physical performance and 9 the highest rank. High scores for chair rise stands test reflect less time needed to perform 10 stands from sitting position.

- **Body mass index** (from age 36 to 69 – five time points) was categorized according to the WHO criteria as: 0=underweight, 1=normalweight, 2=overweight, 3=obese at each age and a total cumulative score was calculated ranging from 0 (over time lower BMI) to 15 (over time obese).

- Finally, **supplement use** data was available only at age 60-64 via a questionnaire and via food diaries at previous ages; therefore it was not included in current analysis. Besides, five days of food diaries may not capture supplements taken on a less frequent basis and may result in biased estimations of total dietary intake [248].

Appendix 6 Procedure of testing best fit of linear mixed models

- Unconditional model (intercept fixed) as a baseline model.
- Mean unconditional model (intercept fixed and random) to capture mean inter-individual differences in total diet quality.
- Unconditional growth model (intercept fixed and random, time fixed) to assess baseline function of time.
- Unconditional growth model (intercept and time fixed and random) allowing for different slopes between individuals.
- Higher-order quadratic model (intercept and time fixed and random, time*time fixed).
- No prior hypothesis of a specific pattern in the covariance matrix was assumed; therefore the unstructured covariance was used for random effects to allow for different (co)variance at each time point and for each time pairing. Other types of covariance structure were also tested with the first-order autoregressive showing similar overall fit of the data; however, correlations of HEI-2015 over time were not very strong (r: 0.37-0.47).

Appendix 7 Additional descriptive characteristics of participants over adulthood (from age 36 to 64), n=502

	Overall (n=502)	**Women (n=246)**	**Men (n=256)**
	Mean [sd], n (%)		
Occupation, age 53			
Professional/Non-manual	426 (85)	214 (87)	212 (83)
Semi-skilled/Manual/Unskilled	76 (15)	32 (13)	44 (17)
Number of comorbidities, up to age 53	0.8 [0.6]	0.7 [0.6]	0.8 [0.6]
CVD	19 (4)	10 (4)	9 (4)
Diabetes	5 (1)	2 (1)	3 (1)
Hyperlipidaemia	11 (2)	1 (0.4)	10 (4)
Hypertension	320 (65)	139 (57)	181 (73)
Cancer	13 (3)	10 (4)	3 (1)
Chair rise stand time score, 0-9	4.6 [2.6]	4.6 [2.6]	4.6 [2.5]
Low (0-3)	158 (36)	77 (36)	81 (36)
Medium (4-5)	119 (27)	60 (28)	59 (27)
High (6-9)	161 (37)	78 (36)	83 (37)
Balance time score, eyes closed, 0-9	4.6 [2.3]	4.5 [2.4]	4.6 [2.2]
Low (0-3)	154 (34)	83 (37)	71 (30)
Medium (4-5)	134 (30)	53 (24)	81 (35)
High (6-9)	167 (36)	87 (39)	80 (35
Body mass index, kg/m^2			
Age 36	23.7 [3.1]	22.9 [3.2]	24.5 [2.8]
Age 43	25.1 [3.3]	24.6 [3.7]	25.4 [2.8]
Age 53	27.1 [4.2]	26.9 [4.9]	27.1 [3.4]
Age 64	27.7 [4.4]	27.6 [4.9]	27.8 [3.7]
Age 71	27.8 [4.6]	27.6 [5.2]	27.9 [3.9]
Body mass index score, 0-15	8.7 [2.9]	8.3 [3.1]	9.0 [2.8]
Low (0-6)	143 (31)	74 (33)	69 (29)
Medium (7-10)	165 (36)	67 (31)	98 (41)
High (11-15)	153 (33)	79 (36)	74 (30)

Appendix 8 Descriptive characteristics by HEI-2015 group based trajectories over adulthood (from age 36 to 64), n=480

	HEI-2015 trajectories					
	Low (n=87)		Medium (n=308)		High (n=85)	
	Women (n=27)	Men (n=60)	Women (n=149)	Men (n=159)	Women (n=60)	Men (n=25)
	Mean [sd], n by sex by group (%)					
Education up to 26y						
None	6 (23)	14 (24)	19 (13)	22 (14)	12 (21)	0 (0)
Formal	8 (31)	17 (29)	59 (40)	37 (24)	14 (24)	6 (26)
≥ Secondary	12 (46)	28 (47)	69 (47)	94 (61)	32 (55)	17 (74)
Number of comorbidities	1.5 [1.4]	1.4 [0.9]	1.2 [1.0]	1.5 [1.0]	1.0 [0.9]	1.3 [0.9]
CVD	7 (26)	10 (17)	18 (12)	27 (17)	10 (17)	5 (20)
Diabetes	4 (15)	7 (12)	6 (4)	13 (8)	2 (3)	1 (4)
Hyperlipidaemia	5 (19)	22 (37)	34 (23)	53 (33)	5 (8)	8 (32)
Hypertension	16 (59)	44 (75)	97 (65)	124 (78)	36 (60)	18 (72)
Cancer	8 (30)	4 (7)	21 (14)	13 (8)	7 (12)	1 (4)
Physical activity score, 0-10	3.6 [2.6]	4.4 [2.6]	4.7 [2.9]	5.0 [2.8]	6.2 [2.6]	5.7 [3.2]
None/Low exposure (0-3)	13 (48)	23 (38)	54 (36)	44 (28)	9 (15)	8 (32)
Medium exposure (4-6)	6 (22)	19 (32)	38 (26)	45 (28)	19 (32)	5 (20)
High exposure (7-10)	4 (15)	13 (22)	42 (28)	47 (30)	26 (43)	10 (40)
Smoking habits score, 0-10	4.3 [2.9]	4.5 [3.3]	3.6 [3.1]	3.7 [2.8]	3.3 [2.8]	3.6 [2.6]
None/Low exposure (0-4)	6 (22)	17 (28)	54 (36)	50 (31)	23 (40)	8 (33)
Medium exposure (5)	12 (44)	13 (22)	46 (31)	67 (42)	25 (44)	10 (42)
High exposure (6-10)	5 (19)	24 (40)	38 (26)	26 (16)	9 (16)	6 (25)
Max grip strength score, 0-9	3.8 [2.6]	4.1 [2.8]	4.7 [2.6]	4.5 [2.7]	4.5 [2.6]	5.1 [2.4]
Low (0-3)	12 (48)	22 (39)	48 (34)	58 (39)	19 (33)	6 (26)
Medium (4-5)	7 (28)	15 (26)	32 (23)	36 (24)	17 (29)	6 (26)
High (6-9)	6 (24)	20 (35)	60 (43)	55 (37)	22 (38)	11 (48)
Balance time score, eyes open, 0-3	1.8 [1.0]	2.1 [0.9]	1.8 [1.0]	2.0 [0.9]	1.9 [1.0]	2.5 [0.8]
Low (0-1)	8 (36)	16 (28)	57 (40)	45 (29)	23 (39)	3 (13)
Medium (2)	7 (32)	18 (32)	38 (27)	54 (35)	15 (25)	5 (22)
High (3)	7 (32)	23 (40)	47 (33)	54 (35)	21 (36)	15 (65)
Waist hip ratio score, 0-8	3.8 [2.5]	4.1 [2.7]	3.8 [2.6]	3.9 [2.5]	4.8 [2.2]	4.9 [2.4]
Low (0-2)	9 (38)	16 (30)	43 (33)	46 (33)	9 (17)	5 (22)
Medium (3-5)	8 (33)	18 (34)	47 (36)	49 (35)	21 (40)	8 (35)
High (6-8)	7 (29)	19 (36)	40 (31)	44 (32)	22 (42)	10 (43)

Appendix 9 Total HEI-2015 and component scores by age of dietary assessment by sex, n=502

Age (years)	36				43				53				60-64			
	Women (n=158)		**Men (n=155)**		**Women (n=183)**		**Men (n=186)**		**Women (n=177)**		**Men (n=169)**		**Women (n=223)**		**Men (n=221)**	
HEI-2015, 0-100																
Median (range)	48 (23-75)		45 (20-74)		53 (23-86)		47 (24-75)		60 (30-86)		52 (22-85)		65 (27-94)		60 (26-92)	
Mean [sd]	48 [11]		46 [11]		53 [11]		47 [12]		59 [12]		54 [13]		64 [13]		61 [13]	
Component scores,	**Mean [sd], n max score [1] (%)**															
Adequacy																
Total Fruit, 0-5	**2.0***	23	1.2	4	**2.5***	39	1.5	9	**4.0***	106	3.0	49	**3.9***	120	3.2	75
	[1.6]	(3)	[1.1]	(3)	**[1.7]**	(21)	[1.4]	(5)	**[1.4]**	(60)	[1.6]	(29)	**[1.4]**	(54)	[1.6]	(34)
Whole Fruit, 0-5	**3.0***	58	2.2	23	**3.4***	81	2.2	37	**4.5***	148	3.8	100	**4.5***	187	4.0	145
	[1.8]	(15)	[1.7]	(15)	**[1.7]**	(44)	[1.8]	(20)	**[1.1]**	(84)	[1.7]	(59)	**[1.1]**	(84)	[1.6]	(66)
Total Vegetables, 0-5	3.2	24	3.2	14	**3.4***	39	2.9	22	**3.7***	66	3.1	32	**4.0***	104	3.6	68
	[1.0]	(9)	[1.0]	(9)	**[1.1]**	(21)	[1.0]	(12)	**[1.2]**	(37)	[1.2]	(19)	**[1.0]**	(47)	[1.1]	(31)
Greens Beans, 0-5	3.4	60	3.1	47	**3.6***	81	3.3	59	**3.0***	64	2.5	32	**3.7***	109	3.2	82
	[1.6]	(30)	[1.6]	(30)	**[1.5]**	(44	[1.5]	(32)	**[1.8]**	(36)	[1.7]	(19)	**[1.5]***	(49)	[1.7]	(37)
Whole Grains, 0-10	4.9	41	4.5	36	5.8	55	5.1	52	**6.2***	62	5.1	45	6.7	88	6.4	76
	[4.0]	(23)	[3.9]	(23)	[3.7]	(30)	[3.9]	(28)	**[3.6]**	(35)	[3.9]	(27)	[3.4]	(39)	[3.6]	(34)
Dairy, 0-10	**4.7***	5	3.7	2	**5.1***	14	3.8	2	**5.8***	19	4.3	4	**5.3***	18	4.3	5
	[2.1]	(1)	[1.8]	(1)	**[2.5]**	(8)	[1.9]	(1)	**[2.5]**	(11)	[2.0]	(2)	**[2.5]**	(8)	[2.1]	(2)
Total Protein, 0-5	4.6	125	4.6	113	4.4	126	4.3	115	4.4	117	4.5	120	4.5	164	4.6	171
	[0.7]	(72)	[0.8]	(73)	[1.1]	(69)	[1.0]	(62)	[1.0]	(66)	[0.8]	(71)	[0.9]	(74)	[0.8]	(77)
Seafood Protein, 0-5	3.0	58	2.9	49	2.9	68	3.1	70	3.3	79	3.1	65	3.5	121	3.5	116
	[1.9]	(31)	[1.8]	(32)	[3.4]	(37)	[1.8]	(38)	[1.9]	(45)	[1.9]	(38)	[1.8]	(54)	[1.9]	(52)
Fatty Acids, 0-10	0.4	0	**0.7***	0	**1.1***	1	0.8	0	1.3	2	1.4	1	2.1	7	2.2	2
	[0.7]	(0)	**[1.1]**	(0)	**[1.6]**	(1)	[1.3]	(0)	[2.0]	(1)	[1.9]	(1)	[2.7]	(3)	[2.3]	(1)
Moderation																
Refined Grains, 0-10	4.4	23	4.9	23	5.7	40	4.5	30	4.8	31	4.5	29	6.1	66	5.8	54
	[3.6]	(15)	[3.8]	(15)	[3.5]	(22)	[3.5]	(16)	[3.7]	(18)	[3.6]	(17)	[3.4]	(30)	[3.5]	(24)
Sodium, 0-10	7.3	45	**7.9***	69	6.9	44	7.3	44	6.9	34	7.3	37	8.0	93	7.5	69
	[2.2]	(44)	**[2.2]**	(45)	[2.7]	(24)	[2.4]	(24)	[2.7]	(19)	[2.3]	(22)	[2.4]	(42)	[2.4]	(31)
Added Sugars, 0-10	6.3	14	6.0	7	6.7	25	6.5	21	7.5	31	7.3	37	7.2	35	7.3	33
	[2.3]	(4)	[2.4]	(5)	[2.3]	(14)	[2.2]	(11)	[2.0]	(18)	[2.3]	(22)	[2.0]	(16)	[2.1]	(15)
Saturated Fat, 0-10	0.2	0	**0.7***	1	1.8	3	1.8	3	3.9	14	3.8	9	4.3	17	4.7	14
	[0.8]	(1)	**[1.4]**	(1)	[2.6]	(2)	[2.4]	(2)	[3.3]	(8)	[3.1]	(5)	[3.1]	(8)	[3.0]	(6)

* p value ≤ 0.05 per analysis of variance or equivalent non-parametric test (Kruskal–Wallis). Significance levels denote difference between women and men.

[1] Number of participants who met the dietary recommendation for each component and thus the standard for maximum score in each component.

Appendix 10 Analytical procedure for selection of best model fit in linear mixed models

- Model 2 showed that around 22% of total variation in diet quality (HEI-2015) was due to between-individual differences. The average stability of HEI-2015 was 0.22, marginally confirming exploration of individual growth curves (suggested cut-off point is 0.25).
- Model 3 had the same BIC as model 4, AIC and -2 Log metrics further declined in model 4.
- Because growth rates may vary between individuals, model 4 (intercept and time fixed and random effects) was tested.
- Model 4 showed best model fit and therefore was chosen for the main analysis.
- Unexplained variability around the mean HEI-2015 and the mean slope of the linear growth was 14.4 points (95% CI: 12.2, 17.2, Wald Z test=5.8, $p<0.001$) and 0.5 points (95% CI: 0.4, 0.5, Wald Z test=2.8, $p<0.001$) respectively; hence exploration of GBTM was supported.

Appendix 11 Selection of best model fit in linear mixed models of HEI-2015 over adulthood (from age 36 to 64)

Model	**-2 Log**	**AIC**	**BIC**	**ΔBIC**
1	11878	11882	11892	n/a
2	11803	11809	11825	67
3	11341	11349	11370	455
4	11327	11339	11370	0
5	11327	11341	11378	+8

-2 Log: likelihood ratio test, AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, ΔBIC: difference between model with k and k-1 parameters. The smaller the number the better fit.

Appendix 12 Analytical procedure for selection of best model fit in group-based trajectory modelling

- Zero-order, linear and quadratic shaped 2-group models were tested.
- Extra groups were added (3 and 4) until the best fitting model was chosen.
- The -1 1- model had the best fit and BIC compared to all 2-group models. Despite comparable model fit, the -1 1- model was preferred to those of quadratic terms as ΔBIC<<10 and due to being more parsimonious.
- The -1 1 1- model had the highest (least negative) BIC compared to all 3-group models. Compared to the most parsimonious -1 1- model, the -1 1 1- model had higher BICn=-5692.3 (BICN=-5697.4) and ΔBICn=17.1 (ΔBICN=15.4).
- Adding quadratic terms did not improve model fit for 3-group higher order models (ΔBIC<<10).
- Adding extra groups (4-group model) classified 0% of participants in the last group and BIC was lower.
- 3-group model with three linear trajectories (1 1 1) showed best model fit alongside parsimony and was chosen for the main analysis.
- Adjusting for sex improved model fit (ΔBIC=6) (“strong” evidence).
- Diagnostics of the sex adjusted models were in high agreement with the unadjusted models.

Appendix 13 Additional criteria fulfilled for group based trajectory modelling selection

- The three-group linear model had adequate proportions and sample size in each group: “Low” 21%, “Medium” 59%, and “High” 20% (Figure 6.5).
- Comparison of observed vs predicted values showed good model fit with reasonably narrow confidence intervals for each group (Table 6.6).
- The average posterior probability value was >0.8 for each group; well above the recommended minimum value of 0.7 (Appendix 14).
- The odds of correct classification based on the posterior probabilities of group membership were >5 for the low and high group and 3 for the middle group, indicating the model had good assignment accuracy for “Low” and “High” HEI reporters (Appendix 14).
- There was adequate agreement between each group’s estimated probability and the proportion of participants assigned to each group according to the maximum posterior probability assignment rule (Appendix 15).

Appendix 14 Average posterior probability value and odds of correct classification for HEI-2015 group-based trajectories

	Group-based trajectory		
	Low	**Medium**	**High**
Average posterior probability value	0.81	0.80	0.80
Odds of correct classification	16.2	2.7	16.4

Appendix 15 HEI-2015 group-based trajectory modelling estimated probability and the proportion of participants classified to each group according to the maximum posterior probability assignment rule

Group	**Estimated group probability**	**Proportion by posterior probability**
Low	20.8	17.3
Medium	59.6	65.7
High	19.6	16.9

Appendix 16 Sensitivity analysis based on maximum age-specific walking speed values from normative tables by sex, n=480

		High vs medium/low HEI-2015 trajectory		Individual HEI-2015, 10-point increment	
		Women	**Men**	**Women**	**Men**
Task 1	n	176	185	164	166
Walking speed, m/s	β [95% CI]	0.03 [-0.02, 0.08]	0.01 [-0.07, 0.07]	0.03 [-0.01, 0.06]	-0.01 [-0.04, 0.02]
Normalized walking speed, -		0.02 [-0.01, 0.04]	-0.01 [-0.04, 0.02]	0.02 [0.01, 0.03]	-0.01 [-0.02, 0.01]
Task 2	n	215	218	202	197
Walking speed, m/s	β [95% CI]	0.04 [-0.02, 0.09]	-0.07 [-0.16, 0.01]	0.04 [-0.01, 0.08]	-0.03 [-0.07, 0.01]
Normalized walking speed, -		0.01 [-0.02, 0.03]	-0.02 [-0.05, 0.02]	**0.01 [0.01, 0.03]** ‡	-0.01 [-0.03, 0.01]
CMI cost, %		-0.5 [-1.7. 0.6]	-0.7 [-2.3, 0.7]	-0.5 [-0.8, 0.7]	-0.5 [-0.9, 0.1]
Task 3	n	216	218	204	
Walking speed, m/s	β [95% CI]	0.01 [-0.05, 0.07]	**-0.01 [-0.20, -0.006]** *	0.02 [-0.03, 0.05]	-0.03 [-0.07, 0.01]
Normalized walking speed, -		0.06 [-0.02, 0.03]	**-0.03 [-0.06, -0.001]** *	0.01 [-0.01, 0.02]	-0.01 [-0.03, 0.01]
CMI cost, %		-2.5 [-6.4, 1.3]	-3.9 [-8.9, 0.9]	-0.5 [-3.1, 2.1]	-2.1 [-4.4, 0.1]

‡ $p<0.05$, * p-value (0.04-0.045) was close to alpha level: 0.05 and the upper 95% CI limit was marginally zero. Therefore these findings are prone to statistical error due to multiple tests with reduced power and therefore likely to be spurious and will not be discussed further

References

1. World Health Organization. World report on ageing and health. 2015 [cited 2018 9 November]; Available from: Available: http://www.who.int/ageing/events/world-report-2015-launch/en/.

2. United Nations, Department of Economic and Social Affairs, and Population Division. World Population Prospects: The 2017 Revision, Key Findings and Advance Tables. Working Paper No. ESA/P/WP/248. . 2017; Available from: https://esa.un.org/unpd/wpp/Publications/Files/WPP2017_KeyFindings.pdf.

3. Sanders, S., National life tables, UK: 2015 to 2017. 2018, Office for National Statistics.

4. GBD Mortality and Causes of Death and Collaborators, Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet, 2015. 385(9963): p. 117-71.

5. Kuh, D., et al., A life-course approach to healthy ageing: maintaining physical capability. Proc Nutr Soc, 2014. 73(2): p. 237-48.

6. World Health Organization, International classification of functioning, disability and health: ICF. 2001: Geneva: World Health Organization.

7. Cohen, J.A., J. Verghese, and J.L. Zwerling, Cognition and gait in older people. Maturitas, 2016. 93: p. 73-77.

8. Cooper, R., et al., Objectively measured physical capability levels and mortality: systematic review and meta-analysis. BMJ, 2010. 341: p. c4467.

9. Manini, T.M., Mobility decline in old age: a time to intervene. Exerc Sport Sci Rev, 2013. 41(1): p. 2.

10. Brach, J.S. and J.M. VanSwearingen, Physical impairment and disability: relationship to performance of activities of daily living in community-dwelling older men. Phys Ther, 2002. 82(8): p. 752-61.

11. McLeod, M., et al., Live strong and prosper: the importance of skeletal muscle strength for healthy ageing. Biogerontology, 2016. 17(3): p. 497-510.

12. Panel on Prevention of Falls in Older Persons, American Geriatrics Society, and British Geriatrics Society, Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc, 2011. 59(1): p. 148-57.

13. Harada, C.N., M.C. Natelson Love, and K.L. Triebel, Normal cognitive aging. Clin Geriatr Med, 2013. 29(4): p. 737-52.

14. Salthouse, T., Consequences of age-related cognitive declines. Annu Rev Psychol, 2012. 63: p. 201-26.

15. Burton, C.L., et al., Cognitive functioning and everyday problem solving in older adults. Clin Neuropsychol, 2006. 20(3): p. 432-52.

16. Phillips, W.J., D.W. Hine, and E.B. Thorsteinsson, Implicit cognition and depression: a meta-analysis. Clin Psychol Rev, 2010. 30(6): p. 691-709.

17. Vance, D., et al., Comorbidities and cognitive functioning: implications for nursing research and practice. J Neurosci Nurs, 2011. 43(4): p. 215-24.

18. Hayat, S.A., et al., Understanding the relationship between cognition and death: a within cohort examination of cognitive measures and mortality. Eur J Epidemiol, 2018. 33(11): p. 1049-1062.

19. Hanlon, P., et al., Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health, 2018. 3(7): p. e323-e332.

20. Barnett, K., et al., Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet, 2012. 380(9836): p. 37-43.

21. Kingston, A., et al., Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. Age and Ageing, 2018. 47(3): p. 374-380.

22. Tieland, M., I. Trouwborst, and B.C. Clark, Skeletal muscle performance and ageing. J Cachexia Sarcopenia Muscle, 2018. 9(1): p. 3-19.

23. Roberts, S., et al., Ageing in the musculoskeletal system. Acta Orthop, 2016. 87(sup363): p. 15-25.

24. Bishop, N.A., T. Lu, and B.A. Yankner, Neural mechanisms of ageing and cognitive decline. Nature, 2010. 464(7288): p. 529-35.

25. Bettio, L.E.B., L. Rajendran, and J. Gil-Mohapel, The effects of aging in the hippocampus and cognitive decline. Neurosci Biobehav Rev, 2017. 79: p. 66-86.

26. Finkel, D., O. Sternang, and A. Wahlin, Genetic and Environmental Influences on Longitudinal Trajectories of Functional Biological Age: Comparisons Across Gender. Behav Genet, 2017. 47(4): p. 375-382.

27. Nakamura, E. and K. Miyao, Sex differences in human biological aging. J Gerontol A Biol Sci Med Sci, 2008. 63(9): p. 936-44.

28. Studenski, S., et al., Gait speed and survival in older adults. JAMA, 2011. 305(1): p. 50-8.

29. Kim, K.M., et al., Longitudinal Changes in Muscle Mass and Strength, and Bone Mass in Older Adults: Gender-Specific Associations Between Muscle and Bone Losses. J Gerontol A Biol Sci Med Sci, 2018. 73(8): p. 1062-1069.

30. Anderson, L.J., H. Liu, and J.M. Garcia, Sex Differences in Muscle Wasting. Adv Exp Med Biol, 2017. 1043: p. 153-197.

31. Buchman, A.S., et al., Gender differences in upper extremity motor performance of older persons. Geriatr Gerontol Int, 2005. 5(1): p. 59-65.

32. Hughes, V.A., et al., Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. J Gerontol A Biol Sci Med Sci, 2001. 56(5): p. B209-17.

33. McCarrey, A.C., et al., Sex differences in cognitive trajectories in clinically normal older adults. Psychol Aging, 2016. 31(2): p. 166-75.

34. Luders, E., et al., Why sex matters: brain size independent differences in gray matter distributions between men and women. J Neurosci, 2009. 29(45): p. 14265-70.

35. Gur, R.C., et al., Sex Differences in Brain Gray and White Matter in Healthy Young Adults: Correlations with Cognitive Performance. The Journal of Neuroscience, 1999. 19(10): p. 4065-4072.

36. Sowell, E.R., et al., Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb Cortex, 2007. 17(7): p. 1550-60.

37. Cowell, P.E., et al., Sex differences in aging of the human frontal and temporal lobes. J Neurosci, 1994. 14(8): p. 4748-55.

38. Moffat, S.D., E. Hampson, and M. Hatzipantelis, Navigation in a “Virtual” Maze: Sex Differences and Correlation With Psychometric Measures of Spatial Ability in Humans. Evolution and Human Behavior, 1998. 19(2): p. 73-87.

39. Bixo, M., et al., Estradiol and testosterone in specific regions of the human female brain in different endocrine states. J Steroid Biochem Mol Biol, 1995. 55(3-4): p. 297-303.

40. Holtzer, R., et al., Stress and gender effects on prefrontal cortex oxygenation levels assessed during single and dual-task walking conditions. Eur J Neurosci, 2017. 45(5): p. 660-670.

41. Dao, M.C., et al., Dietary assessment toolkits: an overview. Public Health Nutr, 2019. 22(3): p. 404-418.

42. Thompson, F.E., et al., The National Cancer Institute's Dietary Assessment Primer: A Resource for Diet Research. J Acad Nutr Diet, 2015. 115(12): p. 1986-95.

43. Shim, J.S., K. Oh, and H.C. Kim, Dietary assessment methods in epidemiologic studies. Epidemiol Health, 2014. 36: p. e2014009.

44. Willett, W., Nutritional epidemiology. Vol. 40. 2012: Oxford University Press.

45. Ortega, R.M., C. Perez-Rodrigo, and A.M. Lopez-Sobaler, Dietary assessment methods: dietary records. Nutr Hosp, 2015. 31 Suppl 3: p. 38-45.

46. Whittle, M.W., Gait analysis: an introduction. 2014: Butterworth-Heinemann.

47. Esser, P., et al., IMU: inertial sensing of vertical CoM movement. J Biomech, 2009. 42(10): p. 1578-81.

48. Wong, W.Y., M.S. Wong, and K.H. Lo, Clinical applications of sensors for human posture and movement analysis: a review. Prosthet Orthot Int, 2007. 31(1): p. 62-75.

49. Chambers, H.G. and D.H. Sutherland, A practical guide to gait analysis. J Am Acad Orthop Surg, 2002. 10(3): p. 222-31.

50. Baker, R., et al., Gait analysis: clinical facts. Eur J Phys Rehabil Med, 2016. 52(4): p. 560-74.

51. Kuo, A.D. and J.M. Donelan, Dynamic principles of gait and their clinical implications. Phys Ther, 2010. 90(2): p. 157-74.

52. Greenwood, D.T., Principles of dynamics. 1988: Prentice-Hall Englewood Cliffs, NJ.

53. Buczek, F.L., et al., Performance of an inverted pendulum model directly applied to normal human gait. Clin Biomech (Bristol, Avon), 2006. 21(3): p. 288-96.

54. Neumann, D.A., Kinesiology of the musculoskeletal system-e-book: foundations for rehabilitation. 2013: Elsevier Health Sciences.

55. Omer, A., et al., Study of Bipedal Robot Walking Motion in Low Gravity: Investigation and Analysis. International Journal of Advanced Robotic Systems, 2014. 11(9): p. 139.

56. Caldas, R., et al., A systematic review of gait analysis methods based on inertial sensors and adaptive algorithms. Gait Posture, 2017. 57: p. 204-210.

57. Levine, D., J. Richards, and M.W. Whittle, Whittle's gait analysis. 2012: Elsevier Health Sciences.

58. Wallmann, H.W., Introduction to observational gait analysis. Home health care management & practice, 2009. 22(1): p. 66-68.

59. Toro, B., C. Nester, and P. Farren, A review of observational gait assessment in clinical practice. Physiotherapy theory and practice, 2003. 19(3): p. 137-149.

60. Baker, R., Gait analysis methods in rehabilitation. J Neuroeng Rehabil, 2006. 3: p. 4.

61. Petraglia, F., et al., Inertial sensors versus standard systems in gait analysis: a systematic review and meta-analysis. Eur J Phys Rehabil Med, 2019. 55(2): p. 265-280.

62. Muro-de-la-Herran, A., B. Garcia-Zapirain, and A. Mendez-Zorrilla, Gait analysis methods: an overview of wearable and non-wearable systems, highlighting clinical applications. Sensors (Basel), 2014. 14(2): p. 3362-94.

63. Steins, D., et al., A smart device inertial-sensing method for gait analysis. J Biomech, 2014. 47(15): p. 3780-5.

64. Rothman, K.J., S. Greenland, and T.L. Lash, Modern epidemiology. Vol. 3. 2008: Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia.

65. Esser, P., et al., Single Sensor Gait Analysis to Detect Diabetic Peripheral Neuropathy: A Proof of Principle Study. Diabetes Metab J, 2018. 42(1): p. 82-86.

66. Collett, J., et al., Insights into gait disorders: walking variability using phase plot analysis, Huntington's disease. Gait Posture, 2014. 40(4): p. 694-700.

67. Esser, P., et al., Insights into gait disorders: walking variability using phase plot analysis, Parkinson's disease. Gait Posture, 2013. 38(4): p. 648-52.

68. Esser, P., et al., Assessment of spatio-temporal gait parameters using inertial measurement units in neurological populations. Gait Posture, 2011. 34(4): p. 558-60.

69. Punt, M., et al., Clinimetric properties of a novel feedback device for assessing gait parameters in stroke survivors. J Neuroeng Rehabil, 2014. 11: p. 30.

70. Craig, J.J., et al., Instrumented balance and walking assessments in persons with multiple sclerosis show strong test-retest reliability. J Neuroeng Rehabil, 2017. 14(1): p. 43.

71. Tao, W., et al., Gait Analysis Using Wearable Sensors. Sensors, 2012. 12(2): p. 2255.

72. Woollacott, M. and A. Shumway-Cook, Attention and the control of posture and gait: a review of an emerging area of research. Gait Posture, 2002. 16(1): p. 1-14.

73. Patel, P., M. Lamar, and T. Bhatt, Effect of type of cognitive task and walking speed on cognitive-motor interference during dual-task walking. Neuroscience, 2014. 260: p. 140-8.

74. Bayot, M., et al., The interaction between cognition and motor control: A theoretical framework for dual-task interference effects on posture, gait initiation, gait and turning. Neurophysiol Clin, 2018. 48(6): p. 361-375.

75. Beurskens, R. and O. Bock, Age-related deficits of dual-task walking: a review. Neural Plast, 2012. 2012: p. 131608.

76. Yogev-Seligmann, G., J.M. Hausdorff, and N. Giladi, The role of executive function and attention in gait. Mov Disord, 2008. 23(3): p. 329-42; quiz 472.

77. Al-Yahya, E., et al., Cognitive motor interference while walking: a systematic review and meta-analysis. Neurosci Biobehav Rev, 2011. 35(3): p. 715-28.

78. Abernethy, B., Dual-task methodology and motor skills research: some applications and methodological constraints. Journal of human movement studies, 1988. 14(3): p. 101-132.

79. Leone, C., et al., Cognitive-motor dual-task interference: A systematic review of neural correlates. Neurosci Biobehav Rev, 2017. 75: p. 348-360.

80. Hamacher, D., et al., Brain activity during walking: A systematic review. Neurosci Biobehav Rev, 2015. 57: p. 310-27.

81. Beurskens, R. and O. Bock, Does the walking task matter? Influence of different walking conditions on dual-task performances in young and older persons. Hum Mov Sci, 2013. 32(6): p. 1456-66.

82. Plummer, P., et al., Cognitive-motor interference during functional mobility after stroke: state of the science and implications for future research. Arch Phys Med Rehabil, 2013. 94(12): p. 2565-2574 e6.

83. Pashler, H., Dual-task interference in simple tasks: data and theory. Psychol Bull, 1994. 116(2): p. 220-44.

84. Verghese, J., et al., Epidemiology of gait disorders in community-residing older adults. J Am Geriatr Soc, 2006. 54(2): p. 255-61.

85. Bruce-Keller, A.J., et al., Assessment of cognition, physical performance, and gait in the context of mild cognitive impairment and dementia. J Am Geriatr Soc, 2012. 60(1): p. 176-7.

86. Beauchet, O., et al., Poor Gait Performance and Prediction of Dementia: Results From a Meta-Analysis. J Am Med Dir Assoc, 2016. 17(6): p. 482-90.

87. Rota, V., et al., Walk ratio (step length/cadence) as a summary index of neuromotor control of gait: application to multiple sclerosis. Int J Rehabil Res, 2011. 34(3): p. 265-9.

88. Schwenk, M., et al., Frailty and technology: a systematic review of gait analysis in those with frailty. Gerontology, 2014. 60(1): p. 79-89.

89. Middleton, A., S.L. Fritz, and M. Lusardi, Walking speed: the functional vital sign. J Aging Phys Act, 2015. 23(2): p. 314-22.

90. Salbach, N.M., et al., Reference values for standardized tests of walking speed and distance: a systematic review. Gait Posture, 2015. 41(2): p. 341-60.

91. Bohannon, R.W. and A. Williams Andrews, Normal walking speed: a descriptive meta-analysis. Physiotherapy, 2011. 97(3): p. 182-9.

92. Tibaek, S., et al., Reference values of maximum walking speed among independent community-dwelling Danish adults aged 60 to 79 years: a cross-sectional study. Physiotherapy, 2015. 101(2): p. 135-40.

93. Liu, B., et al., Usual walking speed and all-cause mortality risk in older people: A systematic review and meta-analysis. Gait Posture, 2016. 44: p. 172-7.

94. Auvinet, B., et al., Reference data for normal subjects obtained with an accelerometric device. Gait Posture, 2002. 16(2): p. 124-34.

95. Bohannon, R.W., Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. Age Ageing, 1997. 26(1): p. 15-9.

96. Bohannon, R.W., A.W. Andrews, and M.W. Thomas, Walking speed: reference values and correlates for older adults. J Orthop Sports Phys Ther, 1996. 24(2): p. 86-90.

97. Pamoukdjian, F., et al., Measurement of gait speed in older adults to identify complications associated with frailty: A systematic review. J Geriatr Oncol, 2015. 6(6): p. 484-96.

98. Abellan van Kan, G., et al., Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging, 2009. 13(10): p. 881-9.

99. Montero-Odasso, M., et al., Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. J Gerontol A Biol Sci Med Sci, 2005. 60(10): p. 1304-9.

100. Cesari, M., et al., Prognostic value of usual gait speed in well-functioning older people--results from the Health, Aging and Body Composition Study. J Am Geriatr Soc, 2005. 53(10): p. 1675-80.

101. Fonseca Alves, D.J., et al., Walking Speed, Risk Factors, and Cardiovascular Events in Older Adults-Systematic Review. J Strength Cond Res, 2017. 31(11): p. 3235-3244.

102. Hardy, S.E., et al., Improvement in usual gait speed predicts better survival in older adults. J Am Geriatr Soc, 2007. 55(11): p. 1727-34.

103. Arjunan, A., N.M. Peel, and R.E. Hubbard, Gait Speed and Frailty Status in Relation to Adverse Outcomes in Geriatric Rehabilitation. Arch Phys Med Rehabil, 2019. 100(5): p. 859-864.

104. Abellan van Kan, G., et al., The assessment of frailty in older adults. Clin Geriatr Med, 2010. 26(2): p. 275-86.

105. Lee, L., et al., Screening for frailty in primary care: Accuracy of gait speed and hand-grip strength. Can Fam Physician, 2017. 63(1): p. e51-e57.

106. Rodriguez-Manas, L., et al., Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci, 2013. 68(1): p. 62-7.

107. Hayashida, I., et al., Correlation between muscle strength and muscle mass, and their association with walking speed, in community-dwelling elderly Japanese individuals. PLoS One, 2014. 9(11): p. e111810.

108. Song, S. and H. Geyer, Predictive neuromechanical simulations indicate why walking performance declines with ageing. J Physiol, 2018. 596(7): p. 1199-1210.

109. Auyeung, T.W., et al., Age-associated decline of muscle mass, grip strength and gait speed: a 4-year longitudinal study of 3018 community-dwelling older Chinese. Geriatr Gerontol Int, 2014. 14 Suppl 1: p. 76-84.

110. Ostir, G.V., et al., Gait Speed and Dismobility in Older Adults. Arch Phys Med Rehabil, 2015. 96(9): p. 1641-5.

111. Kwon, J., et al., Association between change in bone mineral density and decline in usual walking speed in elderly community-dwelling Japanese women during 2 years of follow-up. J Am Geriatr Soc, 2007. 55(2): p. 240-4.

112. Atkinson, H.H., et al., Predictors of combined cognitive and physical decline. J Am Geriatr Soc, 2005. 53(7): p. 1197-202.

113. Castell, M.V., et al., Frailty prevalence and slow walking speed in persons age 65 and older: implications for primary care. BMC Fam Pract, 2013. 14: p. 86.

114. Jung, H.W., et al., Usual gait speed is associated with frailty status, institutionalization, and mortality in community-dwelling rural older adults: a longitudinal analysis of the Aging Study of Pyeongchang Rural Area. Clin Interv Aging, 2018. 13: p. 1079-1089.

115. Peel, N.M., et al., The Association Between Gait Speed and Cognitive Status in Community-Dwelling Older People: A Systematic Review and Meta-analysis. J Gerontol A Biol Sci Med Sci, 2019. 74(6): p. 943-948.

116. Demnitz, N., et al., Cognition and mobility show a global association in middle- and late-adulthood: Analyses from the Canadian Longitudinal Study on Aging. Gait Posture, 2018. 64: p. 238-243.

117. Demnitz, N., et al., A systematic review and meta-analysis of cross-sectional studies examining the relationship between mobility and cognition in healthy older adults. Gait Posture, 2016. 50: p. 164-174.

118. Mielke, M.M., et al., Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the Mayo Clinic Study of Aging. J Gerontol A Biol Sci Med Sci, 2013. 68(8): p. 929-37.

119. Bohannon, R.W. and S.S. Glenney, Minimal clinically important difference for change in comfortable gait speed of adults with pathology: a systematic review. J Eval Clin Pract, 2014. 20(4): p. 295-300.

120. Yogev-Seligmann, G., J.M. Hausdorff, and N. Giladi, Do we always prioritize balance when walking? Towards an integrated model of task prioritization. Mov Disord, 2012. 27(6): p. 765-70.

121. Lee, K., Effects of single and dual tasks during walking on spatiotemporal gait parameters of community-dwelling older. J Phys Ther Sci, 2017. 29(10): p. 1874-1877.

122. Smith, E., T. Cusack, and C. Blake, The effect of a dual task on gait speed in community dwelling older adults: A systematic review and meta-analysis. Gait Posture, 2016. 44: p. 250-8.

123. Ruffieux, J., et al., Changes in Standing and Walking Performance Under Dual-Task Conditions Across the Lifespan. Sports Med, 2015. 45(12): p. 1739-58.

124. Hollman, J.H., J.W. Youdas, and D.J. Lanzino, Gender differences in dual task gait performance in older adults. Am J Mens Health, 2011. 5(1): p. 11-7.

125. Milaneschi, Y., T. Tanaka, and L. Ferrucci, Nutritional determinants of mobility. Curr Opin Clin Nutr Metab Care, 2010. 13(6): p. 625-9.

126. Cruz-Jentoft, A.J., et al., Nutrition, frailty, and sarcopenia. Aging Clin Exp Res, 2017. 29(1): p. 43-48.

127. Shlisky, J., et al., Nutritional Considerations for Healthy Aging and Reduction in Age-Related Chronic Disease. Adv Nutr, 2017. 8(1): p. 17-26.

128. World Health Organization, Diet, nutrition and the prevention of chronic diseases, in World Health Organ Tech Rep Ser. 2003: Geneva (Switzerland). p. i-viii, 1-149, backcover.

129. World Health Organization. Preventing chronic diseases: a vital investment. 2005 [cited 2018 09 November]; Available from: http://www.who.int/chp/chronic_disease_report/en/.

130. Martinez-Gonzalez, M.A. and N. Martin-Calvo, Mediterranean diet and life expectancy; beyond olive oil, fruits, and vegetables. Curr Opin Clin Nutr Metab Care, 2016. 19(6): p. 401-407.

131. Trichopoulou, A., et al., Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med, 2003. 348(26): p. 2599-608.

132. Govindaraju, T., et al., Dietary Patterns and Quality of Life in Older Adults: A Systematic Review. Nutrients, 2018. 10(8): p. 971.

133. Schwingshackl, L., B. Bogensberger, and G. Hoffmann, Diet Quality as Assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension Score, and Health Outcomes: An Updated Systematic Review and Meta-Analysis of Cohort Studies. J Acad Nutr Diet, 2018. 118(1): p. 74-100 e11.

134. Sofi, F., et al., Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr, 2014. 17(12): p. 2769-82.

135. Wang, Y., et al., Adherence to the Mediterranean Diet and the Risk of Frailty in Old People: A Systematic Review and Meta-Analysis. J Nutr Health Aging, 2018. 22(5): p. 613-618.

136. Kojima, G., et al., Adherence to Mediterranean Diet Reduces Incident Frailty Risk: Systematic Review and Meta-Analysis. J Am Geriatr Soc, 2018. 66(4): p. 783-788.

137. Coelho-Junior, H.J., et al., Relative Protein Intake and Physical Function in Older Adults: A Systematic Review and Meta-Analysis of Observational Studies. Nutrients, 2018. 10(9).

138. Paddon-Jones, D. and B.B. Rasmussen, Dietary protein recommendations and the prevention of sarcopenia. Curr Opin Clin Nutr Metab Care, 2009. 12(1): p. 86-90.

139. Halfon, M., O. Phan, and D. Teta, Vitamin D: a review on its effects on muscle strength, the risk of fall, and frailty. Biomed Res Int, 2015. 2015: p. 953241.

140. Stocks, J. and A. Valdes, A meta-analysis of the effect of dietary omega-3 fatty acid supplementation on walking speed and inflammatory markers in older healthy adults. Journal of Frailty & Aging, 2018. 7(1): p. 148.

141. Welch, A.A., et al., Dietary fat and fatty acid profile are associated with indices of skeletal muscle mass in women aged 18-79 years. J Nutr, 2014. 144(3): p. 327-34.

142. Welch, A.A., et al., Cross-Sectional Associations Between Dietary Antioxidant Vitamins C, E and Carotenoid Intakes and Sarcopenic Indices in Women Aged 18-79 Years. Calcif Tissue Int, 2019.

143. Bartali, B., et al., Intake of antioxidants and subsequent decline in physical function in a racially/ethnically diverse population. J Nutr Health Aging, 2015. 19(5): p. 542-7.

144. Scott, D., et al., Associations between dietary nutrient intake and muscle mass and strength in community-dwelling older adults: the Tasmanian Older Adult Cohort Study. J Am Geriatr Soc, 2010. 58(11): p. 2129-34.

145. Lauretani, F., et al., Low plasma carotenoids and skeletal muscle strength decline over 6 years. J Gerontol A Biol Sci Med Sci, 2008. 63(4): p. 376-83.

146. Cesari, M., et al., Antioxidants and physical performance in elderly persons: the Invecchiare in Chianti (InCHIANTI) study. Am J Clin Nutr, 2004. 79(2): p. 289-94.

147. Lozano-Montoya, I., et al., Nonpharmacological interventions to treat physical frailty and sarcopenia in older patients: a systematic overview - the SENATOR Project ONTOP Series. Clin Interv Aging, 2017. 12: p. 721-740.

148. Welch, A.A., Nutritional influences on age-related skeletal muscle loss. Proc Nutr Soc, 2014. 73(1): p. 16-33.

149. Tieland, M., et al., Low vitamin D status is associated with reduced muscle mass and impaired physical performance in frail elderly people. Eur J Clin Nutr, 2013. 67(10): p. 1050-5.

150. Wicherts, I.S., et al., Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab, 2007. 92(6): p. 2058-65.

151. Houston, D.K., et al., Association between vitamin D status and physical performance: the InCHIANTI study. J Gerontol A Biol Sci Med Sci, 2007. 62(4): p. 440-6.

152. Bischoff-Ferrari, H.A., et al., Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. Am J Clin Nutr, 2004. 80(3): p. 752-8.

153. Sharkey, J.R., et al., Summary measure of dietary musculoskeletal nutrient (calcium, vitamin D, magnesium, and phosphorus) intakes is associated with lower-extremity physical performance in homebound elderly men and women. Am J Clin Nutr, 2003. 77(4): p. 847-56.

154. Bischoff-Ferrari, H.A., et al., Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ, 2009. 339: p. b3692.

155. Mulla, U.Z., et al., Adult macronutrient intake and physical capability in the MRC National Survey of Health and Development. Age Ageing, 2013. 42(1): p. 81-7.

156. Munro, C.A., Patterns of protein consumption throughout adulthood and physical capability in later life. 2014.

157. Bartali, B., et al., Serum micronutrient concentrations and decline in physical function among older persons. JAMA, 2008. 299(3): p. 308-15.

158. Hayhoe, R.P.G., et al., Cross-sectional associations of dietary and circulating magnesium with skeletal muscle mass in the EPIC-Norfolk cohort. Clin Nutr, 2019. 38(1): p. 317-323.

159. Welch, A.A., J. Skinner, and M. Hickson, Dietary Magnesium May Be Protective for Aging of Bone and Skeletal Muscle in Middle and Younger Older Age Men and Women: Cross-Sectional Findings from the UK Biobank Cohort. Nutrients, 2017. 9(11).

160. Granic, A., A.A. Sayer, and S.M. Robinson, Dietary Patterns, Skeletal Muscle Health, and Sarcopenia in Older Adults. Nutrients, 2019. 11(4).

161. Robinson, S.M., et al., Does nutrition play a role in the prevention and management of sarcopenia? Clin Nutr, 2018. 37(4): p. 1121-1132.

162. Isanejad, M., et al., Association of the Baltic Sea and Mediterranean diets with indices of sarcopenia in elderly women, OSPTRE-FPS study. Eur J Nutr, 2018. 57(4): p. 1435-1448.

163. Samieri, C., et al., The association between dietary patterns at midlife and health in aging: an observational study. Ann Intern Med, 2013. 159(9): p. 584-91.

164. Kelaiditi, E., et al., Measurements of skeletal muscle mass and power are positively related to a Mediterranean dietary pattern in women. Osteoporos Int, 2016. 27(11): p. 3251-3260.

165. Lorenzo-Lopez, L., et al., Nutritional determinants of frailty in older adults: A systematic review. BMC Geriatr, 2017. 17(1): p. 108.

166. Nowson, C.A., et al., The Impact of Dietary Factors on Indices of Chronic Disease in Older People: A Systematic Review. J Nutr Health Aging, 2018. 22(2): p. 282-296.

167. Shikany, J.M., et al., Macronutrients, diet quality, and frailty in older men. J Gerontol A Biol Sci Med Sci, 2014. 69(6): p. 695-701.

168. Kojima, G., et al., Fruit and Vegetable Consumption and Frailty: A Systematic Review. J Nutr Health Aging, 2018. 22(8): p. 1010-1017.

169. Phillips, C., Lifestyle Modulators of Neuroplasticity: How Physical Activity, Mental Engagement, and Diet Promote Cognitive Health during Aging. Neural Plast, 2017. 2017: p. 3589271.

170. Cooper, C., et al., Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. Am J Psychiatry, 2015. 172(4): p. 323-34.

171. Sabia, S., et al., Health behaviors from early to late midlife as predictors of cognitive function: The Whitehall II study. Am J Epidemiol, 2009. 170(4): p. 428-37.

172. Cadar, D., et al., The role of lifestyle behaviors on 20-year cognitive decline. J Aging Res, 2012. 2012: p. 304014.

173. Abbatecola, A.M., M. Russo, and M. Barbieri, Dietary patterns and cognition in older persons. Curr Opin Clin Nutr Metab Care, 2018. 21(1): p. 10-13.

174. McKhann, G.M., et al., The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement, 2011. 7(3): p. 263-9.

175. Solfrizzi, V., et al., Nutritional Intervention as a Preventive Approach for Cognitive-Related Outcomes in Cognitively Healthy Older Adults: A Systematic Review. J Alzheimers Dis, 2018. 64(s1): p. S229-S254.

176. Loughrey, D.G., et al., The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis. Adv Nutr, 2017. 8(4): p. 571-586.

177. Petersson, S.D. and E. Philippou, Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review of the Evidence. Adv Nutr, 2016. 7(5): p. 889-904.

178. Wu, L. and D. Sun, Adherence to Mediterranean diet and risk of developing cognitive disorders: An updated systematic review and meta-analysis of prospective cohort studies. Sci Rep, 2017. 7: p. 41317.

179. Solfrizzi, V., et al., Relationships of Dietary Patterns, Foods, and Micro- and Macronutrients with Alzheimer's Disease and Late-Life Cognitive Disorders: A Systematic Review. J Alzheimers Dis, 2017. 59(3): p. 815-849.

180. Martinez-Lapiscina, E.H., et al., Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry, 2013. 84(12): p. 1318-25.

181. Smyth, A., et al., Healthy eating and reduced risk of cognitive decline: A cohort from 40 countries. Neurology, 2015. 84(22): p. 2258-65.

182. Shakersain, B., et al., The Nordic Prudent Diet Reduces Risk of Cognitive Decline in the Swedish Older Adults: A Population-Based Cohort Study. Nutrients, 2018. 10(2).

183. Moffitt, T.E., et al., The Longitudinal Study of Aging in Human Young Adults: Knowledge Gaps and Research Agenda. J Gerontol A Biol Sci Med Sci, 2017. 72(2): p. 210-215.

184. Robinson, S.M., et al., Clustering of lifestyle risk factors and poor physical function in older adults: the Hertfordshire cohort study. J Am Geriatr Soc, 2013. 61(10): p. 1684-91.

185. Koster, A., et al., Lifestyle factors and incident mobility limitation in obese and non-obese older adults. Obesity (Silver Spring), 2007. 15(12): p. 3122-32.

186. Sabia, S., et al., Cumulative associations between midlife health behaviors and physical functioning in early old age: a 17-year prospective cohort study. J Am Geriatr Soc, 2014. 62(10): p. 1860-8.

187. Sternfeld, B., et al., The Effect of a Healthy Lifestyle on Future Physical Functioning in Midlife Women. Med Sci Sports Exerc, 2017. 49(2): p. 274-282.

188. Robinson, S.M., et al., Adult Lifetime Diet Quality and Physical Performance in Older Age: Findings From a British Birth Cohort. J Gerontol A Biol Sci Med Sci, 2018. 73(11): p. 1532-1537.

189. Robinson, S.M., et al., Diet and its relationship with grip strength in community-dwelling older men and women: the Hertfordshire cohort study. J Am Geriatr Soc, 2008. 56(1): p. 84-90.

190. Waters, D.L., et al., Sexually dimorphic patterns of nutritional intake and eating behaviors in community-dwelling older adults with normal and slow gait speed. J Nutr Health Aging, 2014. 18(3): p. 228-33.

191. Ten Haaf, D.S.M., et al., Effects of protein supplementation on lean body mass, muscle strength, and physical performance in nonfrail community-dwelling older adults: a systematic review and meta-analysis. Am J Clin Nutr, 2018. 108(5): p. 1043-1059.

192. Zhu, L.Y., et al., Effects of exercise and nutrition supplementation in community-dwelling older Chinese people with sarcopenia: a randomized controlled trial. Age Ageing, 2019. 48(2): p. 220-228.

193. Fougere, B., et al., Omega-3 fatty acid levels in red blood cell membranes and physical decline over 3 years: longitudinal data from the MAPT study. Geroscience, 2017. 39(4): p. 429-437.

194. Annweiler, C., et al., Vitamin D and walking speed in older adults: Systematic review and meta-analysis. Maturitas, 2017. 106: p. 8-25.

195. Martin, H., et al., Does diet influence physical performance in community-dwelling older people? Findings from the Hertfordshire Cohort Study. Age Ageing, 2011. 40(2): p. 181-6.

196. Milaneschi, Y., et al., Mediterranean diet and mobility decline in older persons. Exp Gerontol, 2011. 46(4): p. 303-8.

197. Alipanah, N., et al., Low serum carotenoids are associated with a decline in walking speed in older women. J Nutr Health Aging, 2009. 13(3): p. 170-5.

198. Lauretani, F., et al., Carotenoids as protection against disability in older persons. Rejuvenation Res, 2008. 11(3): p. 557-63.

199. Semba, R.D., et al., Oxidative stress and severe walking disability among older women. Am J Med, 2007. 120(12): p. 1084-9.

200. Hu, F.B., Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol, 2002. 13(1): p. 3-9.

201. Hengeveld, L.M., et al., Prospective Associations of Diet Quality With Incident Frailty in Older Adults: The Health, Aging, and Body Composition Study. J Am Geriatr Soc, 2019. 67(9): p. 1835-1842.

202. Struijk, E.A., et al., Mediterranean Dietary Patterns and Impaired Physical Function in Older Adults. J Gerontol A Biol Sci Med Sci, 2018. 73(3): p. 333-339.

203. Bibiloni, M.D.M., et al., Western and Mediterranean Dietary Patterns and Physical Activity and Fitness among Spanish Older Adults. Nutrients, 2017. 9(7).

204. Perala, M.M., et al., A healthy Nordic diet and physical performance in old age: findings from the longitudinal Helsinki Birth Cohort Study. Br J Nutr, 2016. 115(5): p. 878-86.

205. Leon-Munoz, L.M., et al., Major dietary patterns and risk of frailty in older adults: a prospective cohort study. BMC Med, 2015. 13: p. 11.

206. Leon-Munoz, L.M., et al., Mediterranean diet and risk of frailty in community-dwelling older adults. J Am Med Dir Assoc, 2014. 15(12): p. 899-903.

207. Zbeida, M., et al., Mediterranean diet and functional indicators among older adults in non-Mediterranean and Mediterranean countries. J Nutr Health Aging, 2014. 18(4): p. 411-8.

208. Bollwein, J., et al., Dietary quality is related to frailty in community-dwelling older adults. J Gerontol A Biol Sci Med Sci, 2013. 68(4): p. 483-9.

209. Shahar, D.R., et al., Adherence to mediterranean diet and decline in walking speed over 8 years in community-dwelling older adults. J Am Geriatr Soc, 2012. 60(10): p. 1881-8.

210. Xu, B., et al., Higher Healthy Eating Index-2005 scores are associated with better physical performance. J Gerontol A Biol Sci Med Sci, 2012. 67(1): p. 93-9.

211. Talegawkar, S.A., et al., A higher adherence to a Mediterranean-style diet is inversely associated with the development of frailty in community-dwelling elderly men and women. J Nutr, 2012. 142(12): p. 2161-6.

212. Tomata, Y., et al., Dietary patterns and incident functional disability in elderly Japanese: the Ohsaki Cohort 2006 study. J Gerontol A Biol Sci Med Sci, 2014. 69(7): p. 843-51.

213. Jeong, G.W., et al., Associations of recommended food score and physical performance in Korean elderly. BMC Public Health, 2019. 19(1): p. 128.

214. Wheaton, F.V. and E.M. Crimmins, Female disability disadvantage: a global perspective on sex differences in physical function and disability. Ageing Soc, 2016. 36(6): p. 1136-1156.

215. Panizza, C.E., et al., Testing the Predictive Validity of the Healthy Eating Index-2015 in the Multiethnic Cohort: Is the Score Associated with a Reduced Risk of All-Cause and Cause-Specific Mortality? Nutrients, 2018. 10(4).

216. Maddock, J., et al., Adherence to a Dietary Approaches to Stop Hypertension (DASH)-type diet over the life course and associated vascular function: a study based on the MRC 1946 British birth cohort. Br J Nutr, 2018. 119(5): p. 581-589.

217. Ward, K.A., et al., Life Course Dietary Patterns and Bone Health in Later Life in a British Birth Cohort Study. J Bone Miner Res, 2016. 31(6): p. 1167-76.

218. Pot, G.K., et al., Trends in food consumption over 30 years: evidence from a British birth cohort. Eur J Clin Nutr, 2015. 69(7): p. 817-23.

219. Mishra, G.D., et al., Longitudinal changes in dietary patterns during adult life. Br J Nutr, 2006. 96(4): p. 735-44.

220. Prynne, C.J., et al., Changes in intake of key nutrients over 17 years during adult life of a British birth cohort. Br J Nutr, 2005. 94(3): p. 368-76.

221. Kiefer, I., T. Rathmanner, and M. Kunze, Eating and dieting differences in men and women. Journal of Men's Health and Gender, 2005. 2(2): p. 194-201.

222. Leblanc, V., et al., Gender differences in the long-term effects of a nutritional intervention program promoting the Mediterranean diet: changes in dietary intakes, eating behaviors, anthropometric and metabolic variables. Nutr J, 2014. 13: p. 107.

223. Wu, F., et al., Associations of dietary patterns with bone mass, muscle strength and balance in a cohort of Australian middle-aged women. Br J Nutr, 2017. 118(8): p. 598-606.

224. Hagan, K.A., et al., Greater Adherence to the Alternative Healthy Eating Index Is Associated with Lower Incidence of Physical Function Impairment in the Nurses' Health Study. J Nutr, 2016. 146(7): p. 1341-7.

225. Hagan, K.A. and F. Grodstein, The Alternative Healthy Eating Index and Physical Function Impairment in Men. J Nutr Health Aging, 2019. 23(5): p. 459-465.

226. Stefler, D., et al., Mediterranean diet and physical functioning trajectories in Eastern Europe: Findings from the HAPIEE study. PLoS One, 2018. 13(7): p. e0200460.

227. Perala, M.M., et al., The healthy Nordic diet predicts muscle strength 10 years later in old women, but not old men. Age Ageing, 2017. 46(4): p. 588-594.

228. Xu, F., et al., Relationship between Diet Quality, Physical Activity and Health-Related Quality of Life in Older Adults: Findings from 2007-2014 National Health and Nutrition Examination Survey. J Nutr Health Aging, 2018. 22(9): p. 1072-1079.

229. Kwon, J., et al., Effects of a combined physical training and nutrition intervention on physical performance and health-related quality of life in prefrail older women living in the community: a randomized controlled trial. J Am Med Dir Assoc, 2015. 16(3): p. 263 e1-8.

230. Craig, J.V., et al., Relationship between the Mediterranean dietary pattern and musculoskeletal health in children, adolescents, and adults: systematic review and evidence map. Nutr Rev, 2017. 75(10): p. 830-857.

231. Welch, A.A., et al., Dietary Magnesium Is Positively Associated With Skeletal Muscle Power and Indices of Muscle Mass and May Attenuate the Association Between Circulating C-Reactive Protein and Muscle Mass in Women. J Bone Miner Res, 2016. 31(2): p. 317-25.

232. Granic, A., et al., Effect of Dietary Patterns on Muscle Strength and Physical Performance in the Very Old: Findings from the Newcastle 85+ Study. PLoS One, 2016. 11(3): p. e0149699.

233. McClure, R. and A. Villani, Mediterranean Diet attenuates risk of frailty and sarcopenia: New insights and future directions. JCSM Clinical Reports, 2017. 2(2).

234. Semba, R.D., F. Lauretani, and L. Ferrucci, Carotenoids as protection against sarcopenia in older adults. Arch Biochem Biophys, 2007. 458(2): p. 141-5.

235. Semba, R.D., et al., Carotenoid and vitamin E status are associated with indicators of sarcopenia among older women living in the community. Aging Clin Exp Res, 2003. 15(6): p. 482-7.

236. Vidoni, M.L., et al., Vitamin B12 and Homocysteine Associations with Gait Speed in Older Adults: The Baltimore Longitudinal Study of Aging. J Nutr Health Aging, 2017. 21(10): p. 1321-1328.

237. Chen, X., et al., Dietary Patterns and Cognitive Health in Older Adults: A Systematic Review. J Alzheimers Dis, 2019. 67(2): p. 583-619.

238. Wadsworth, M.E., Follow-up of the first national birth cohort: findings from the Medical Research Council National Survey of Health and Development. Paediatr Perinat Epidemiol, 1987. 1(1): p. 95-117.

239. Douglas, J.W.B. and J. Blomfield, Children under Five. The Results of a National Survey made by a Joint Committee of the Institute of Child Health (University of London), the Society of Medical Officers of Health and the Population Investigation Committee. 1958.

240. Wadsworth, M.E., et al., Loss and representativeness in a 43 year follow up of a national birth cohort. J Epidemiol Community Health, 1992. 46(3): p. 300-4.

241. Wadsworth, M., et al., Cohort Profile: The 1946 National Birth Cohort (MRC National Survey of Health and Development). Int J Epidemiol, 2006. 35(1): p. 49-54.

242. Kuh, D., et al., Cohort profile: updating the cohort profile for the MRC National Survey of Health and Development: a new clinic-based data collection for ageing research. Int J Epidemiol, 2011. 40(1): p. e1-9.

243. Kuh, D., et al., The MRC National Survey of Health and Development reaches age 70: maintaining participation at older ages in a birth cohort study. Eur J Epidemiol, 2016. 31(11): p. 1135-1147.

244. Wadsworth, M.E., et al., The life course prospective design: an example of benefits and problems associated with study longevity. Soc Sci Med, 2003. 57(11): p. 2193-205.

245. Lane, C.A., et al., Study protocol: Insight 46 - a neuroscience sub-study of the MRC National Survey of Health and Development. BMC Neurol, 2017. 17(1): p. 75.

246. James, S.N., et al., Using a birth cohort to study brain health and preclinical dementia: recruitment and participation rates in Insight 46. BMC Res Notes, 2018. 11(1): p. 885.

247. Stafford, M., et al., Using a birth cohort to study ageing: representativeness and response rates in the National Survey of Health and Development. Eur J Ageing, 2013. 10(2): p. 145-157.

248. Prynne, C.J., W. Nip, and A. Lennox, MRC National Survey of Health and Development (MRC NSHD). Dietary Data Report 2006-11. 2011, MRC National Survey of Health and Development (MRC NSHD): Cambridge.

249. Price, G.M., et al., Measurement of diet in a large national survey: comparison of computerized and manual coding of records in household measures. Journal of Human Nutrition and Dietetics, 1995. 8(6): p. 417-428.

250. Braddon, F.E., et al., Social and regional differences in food and alcohol consumption and their measurement in a national birth cohort. J Epidemiol Community Health, 1988. 42(4): p. 341-9.

251. McCance, R.A., Food Standards Agency. McCance and Widdowson's The Composition of Foods. Seventh Summary Edition. 2015, Cambridge: The Royal Society of Chemistry.

252. Mills, A., Food Standards Agency: Food Portion Sizes. TSO: London, 2002.

253. Whitton, C., et al., National Diet and Nutrition Survey: UK food consumption and nutrient intakes from the first year of the rolling programme and comparisons with previous surveys. Br J Nutr, 2011. 106(12): p. 1899-914.

254. Stephen, A., et al., National Diet and Nutrition Survey Rolling Programme.Comparison Study: A comparison of results by dietary assessment method: repeat 24-hour recall and four-day estimated diet diary. Report prepared for the Food Standards Agency. 2008.

255. Bingham, S.A., et al., Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. Int J Epidemiol, 1997. 26 Suppl 1: p. S137-51.

256. Bingham, S.A., et al., Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. Br J Nutr, 1994. 72(4): p. 619-43.

257. Bingham, S.A., et al., Validation of weighed records and other methods of dietary assessment using the 24 h urine nitrogen technique and other biological markers. Br J Nutr, 1995. 73(4): p. 531-50.

258. Day, N., et al., Epidemiological assessment of diet: a comparison of a 7-day diary with a food frequency questionnaire using urinary markers of nitrogen, potassium and sodium. Int J Epidemiol, 2001. 30(2): p. 309-17.

259. McKeown, N.M., et al., Use of biological markers to validate self-reported dietary intake in a random sample of the European Prospective Investigation into Cancer United Kingdom Norfolk cohort. Am J Clin Nutr, 2001. 74(2): p. 188-96.

260. Prentice, R.L., et al., Evaluation and comparison of food records, recalls, and frequencies for energy and protein assessment by using recovery biomarkers. Am J Epidemiol, 2011. 174(5): p. 591-603.

261. Pollard, J., et al., Comparison of plasma biomarkers with dietary assessment methods for fruit and vegetable intake. Eur J Clin Nutr, 2003. 57(8): p. 988-98.

262. Tucker, K.L., Dietary patterns, approaches, and multicultural perspective. Appl Physiol Nutr Metab, 2010. 35(2): p. 211-8.

263. Bowman, S.A., M.L.S.A. Gerrior, and P.P. Basiotis, The healthy eating index, 1994-96. Family Economics and Nutrition Review, 1998. 11(3): p. 2.

264. Krebs-Smith, S.M., et al., Update of the Healthy Eating Index: HEI-2015. J Acad Nutr Diet, 2018. 118(9): p. 1591-1602.

265. Guenther, P.M., J. Reedy, and S.M. Krebs-Smith, Development of the Healthy Eating Index-2005. J Am Diet Assoc, 2008. 108(11): p. 1896-901.

266. Guenther, P.M., et al., Update of the Healthy Eating Index: HEI-2010. J Acad Nutr Diet, 2013. 113(4): p. 569-80.

267. Varraso, R., et al., Alternate Healthy Eating Index 2010 and risk of chronic obstructive pulmonary disease among US women and men: prospective study. BMJ, 2015. 350: p. h286.

268. Fallaize, R., et al., Association between Diet-Quality Scores, Adiposity, Total Cholesterol and Markers of Nutritional Status in European Adults: Findings from the Food4Me Study. Nutrients, 2018. 10(1).

269. Guenther, P., et al., Diet quality of Americans in 2001-02 and 2007-08 as measured by the Healthy Eating Index-2010. Nutr Insight, 2013. 51: p. 18.

270. US Department of Health and Human Services and US Department of Agriculture. 2015 - 2020 Dietary Guidelines for Americans. 2015 [cited 2019 20th May]; Edition 8th [Available from: Available: https://health.gov/dietaryguidelines/2015/guidelines.

271. Guenther, P.M., et al., The Healthy Eating Index-2010 is a valid and reliable measure of diet quality according to the 2010 Dietary Guidelines for Americans. J Nutr, 2014. 144(3): p. 399-407.

272. Erickson, J. and J. Slavin, Total, added, and free sugars: are restrictive guidelines science-based or achievable? Nutrients, 2015. 7(4): p. 2866-78.

273. Scientific Advisory Committee on Nutrition, Dietary Reference Values for Energy. 2011: The Stationery Office, London.

274. Public Health England, The Eatwell Guide. How does it differ to the eatwell plate and why? 2016.

275. Ruanpeng, D., et al., Sugar and artificially sweetened beverages linked to obesity: a systematic review and meta-analysis. QJM, 2017. 110(8): p. 513-520.

276. Narain, A., C.S. Kwok, and M.A. Mamas, Soft drinks and sweetened beverages and the risk of cardiovascular disease and mortality: a systematic review and meta-analysis. Int J Clin Pract, 2016. 70(10): p. 791-805.

277. Kirkpatrick, S.I., et al., Applications of the Healthy Eating Index for Surveillance, Epidemiology, and Intervention Research: Considerations and Caveats. J Acad Nutr Diet, 2018. 118(9): p. 1603-1621.

278. Reedy, J., et al., Evaluation of the Healthy Eating Index-2015. J Acad Nutr Diet, 2018. 118(9): p. 1622-1633.

279. Onvani, S., et al., Adherence to the Healthy Eating Index and Alternative Healthy Eating Index dietary patterns and mortality from all causes, cardiovascular disease and cancer: a meta-analysis of observational studies. J Hum Nutr Diet, 2017. 30(2): p. 216-226.

280. Bowman, S., et al., Food Patterns Equivalents Database 2011–12: Methodology and User Guide. Worldwide Web Site: Food Surveys Research Group, 2014.

281. Moshfegh, A., Food and Nutrient Database for Dietary Studies (FNDDS).

282. Bowman, S.A., J.E. Friday, and A.J. Moshfegh, MyPyramid equivalents database, 2.0 for USDA survey foods, 2003-2004: Documentation and user guide. US Department of Agriculture, 2008.

283. David, H., L. Linda, and P. Pamela. USDA National Nutrient Database for Standard Reference, Release 24 [Internet]. Beltsville: Nutrient Data Laboratory, USDA National Nutrient Database for Standard Reference. 2016 20 March 2018].

284. Pehrsson, P., et al. USDA database for the added sugars content of selected foods. Home Page 2005 [cited 2017 1 March].

285. Azais-Braesco, V., et al., A review of total & added sugar intakes and dietary sources in Europe. Nutr J, 2017. 16(1): p. 6.

286. Verlinden, V.J., et al., Cognition and gait show a distinct pattern of association in the general population. Alzheimers Dement, 2014. 10(3): p. 328-35.

287. Esser, P., et al., Validity and inter-rater reliability of inertial gait measurements in Parkinson's disease: a pilot study. J Neurosci Methods, 2012. 205(1): p. 177-81.

288. Kao, P.C., M.A. Pierro, and K. Booras, Effects of motor fatigue on walking stability and variability during concurrent cognitive challenges. PLoS One, 2018. 13(7): p. e0201433.

289. Zijlstra, W., Assessment of spatio-temporal parameters during unconstrained walking. Eur J Appl Physiol, 2004. 92(1-2): p. 39-44.

290. Peel, N.M., S.S. Kuys, and K. Klein, Gait speed as a measure in geriatric assessment in clinical settings: a systematic review. J Gerontol A Biol Sci Med Sci, 2013. 68(1): p. 39-46.

291. Kempen, J.C., et al., Community walking can be assessed using a 10-metre timed walk test. Mult Scler, 2011. 17(8): p. 980-90.

292. Peters, D.M., S.L. Fritz, and D.E. Krotish, Assessing the reliability and validity of a shorter walk test compared with the 10-Meter Walk Test for measurements of gait speed in healthy, older adults. J Geriatr Phys Ther, 2013. 36(1): p. 24-30.

293. Leerar, P.J. and E.W. Miller, Concurrent Validity of Distance-Walks and Timed-Walks in the Well-Elderly. Journal of Geriatric Physical Therapy, 2002. 25(2): p. 3-6.

294. Kim, H.J., et al., The reliability and validity of gait speed with different walking pace and distances against general health, physical function, and chronic disease in aged adults. J Exerc Nutrition Biochem, 2016. 20(3): p. 46-50.

295. Graham, J.E., et al., Assessing walking speed in clinical research: a systematic review. J Eval Clin Pract, 2008. 14(4): p. 552-62.

296. Macfarlane, P.A. and M.A. Looney, Walkway length determination for steady state walking in young and older adults. Res Q Exerc Sport, 2008. 79(2): p. 261-7.

297. Strand, B.H., et al., Lifelong socioeconomic position and physical performance in midlife: results from the British 1946 birth cohort. Eur J Epidemiol, 2011. 26(6): p. 475-83.

298. Lyu, J., CUMULATIVE SOCIOECONOMIC STATUS AND COGNITION TRAJECTORIES IN LATER LIFE: DIFFERENCES BY GENDER AND RACE. The Gerontologist, 2015. 55(Suppl_2): p. 115-116.

299. Russo, A., et al., Lifetime occupation and physical function: a prospective cohort study on persons aged 80 years and older living in a community. Occup Environ Med, 2006. 63(7): p. 438-42.

300. Seblova, D., R. Berggren, and M. Lövdén, Education and age-related decline in cognitive performance: Systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev, 2020. 58: p. 101005.

301. Wood, N., et al., Marriage and physical capability at mid to later life in England and the USA. PLOS ONE, 2019. 14(1): p. e0209388.

302. Håkansson, K., et al., Association between mid-life marital status and cognitive function in later life: population based cohort study. Bmj, 2009. 339: p. b2462.

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

304. Stenholm, S., et al., Comorbidity and Functional Trajectories From Midlife to Old Age: The Health and Retirement Study. The Journals of Gerontology: Series A, 2014. 70(3): p. 332-338.

305. Kuh, D. and N. New Dynamics of Ageing Preparatory, A life course approach to healthy aging, frailty, and capability. J Gerontol A Biol Sci Med Sci, 2007. 62(7): p. 717-21.

306. Atkinson, H.H., et al., Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci, 2007. 62(8): p. 844-50.

307. Strand, B.H., et al., Smoking history and physical performance in midlife: results from the British 1946 birth cohort. J Gerontol A Biol Sci Med Sci, 2011. 66(1): p. 142-9.

308. Mori, K., et al., Relationship of dietary intake and lifestyle factors to health-related quality of life in the community-dwelling elderly. J Nutr Sci Vitaminol (Tokyo), 2010. 56(6): p. 364-71.

309. Poortinga, W., The prevalence and clustering of four major lifestyle risk factors in an English adult population. Prev Med, 2007. 44(2): p. 124-8.

310. Olivera-Pueyo, J. and C. Pelegrín-Valero, Dietary supplements for cognitive impairment. Actas Esp Psiquiatr, 2017. 45(Supplement): p. 37-47.

311. Denison, H.J., et al., Patterns of dietary supplement use among older men and women in the UK: findings from the Hertfordshire Cohort Study. J Nutr Health Aging, 2012. 16(4): p. 307-11.

312. Hardy, R., et al., Body mass index, muscle strength and physical performance in older adults from eight cohort studies: the HALCyon programme. PLoS One, 2013. 8(2): p. e56483.

313. Dodds, R.M., et al., Can measures of physical performance in mid-life improve the clinical prediction of disability in early old age? Findings from a British birth cohort study. Exp Gerontol, 2018. 110: p. 118-124.

314. Hardy, R., et al., Is chair rise performance a useful measure of leg power? Aging Clin Exp Res, 2010. 22(5-6): p. 412-8.

315. Cooper, R., et al., Physical capability in mid-life and survival over 13 years of follow-up: British birth cohort study. BMJ, 2014. 348: p. g2219.

316. Cooper, R., et al., Objective measures of physical capability and subsequent health: a systematic review. Age and Ageing, 2010. 40(1): p. 14-23.

317. Hof, A., Scaling gait data to body size. Gait & Posture - GAIT POSTURE, 1996. 4: p. 222-223.

318. Kelly, V.E., A.A. Janke, and A. Shumway-Cook, Effects of instructed focus and task difficulty on concurrent walking and cognitive task performance in healthy young adults. Exp Brain Res, 2010. 207(1-2): p. 65-73.

319. Simon, S.D., Statistical Evidence in Medical Trials: What Do the Data Really Tell Us? Proceedings (Baylor University. Medical Center), 2006. 19(4): p. 419-419.

320. Singer, J.D. and J.B. Willett, Applied longitudinal data analysis: Modeling change and event occurrence. 2003: Oxford university press.

321. Stamm, K.E., L.L. Harlow, and T.A. Walls, An Introduction to Latent Variable Growth Curve Modeling: Concepts, Issues, and Applications (2nd ed.). Structural Equation Modeling: A Multidisciplinary Journal, 2007. 14(4): p. 701-706.

322. Frankfurt, S., et al., Using Group-Based Trajectory and Growth Mixture Modeling to Identify Classes of Change Trajectories. The Counseling Psychologist, 2016. 44(5): p. 622-660.

323. Nagin, D.S., Analyzing developmental trajectories: A semiparametric, group-based approach. Psychological Methods, 1999. 4(2): p. 139-157.

324. Nagin, D.S., Group-based trajectory modeling: an overview, in Handbook of quantitative criminology. 2010, Springer. p. 53-67.

325. Green, S.B., How Many Subjects Does It Take To Do A Regression Analysis. Multivariate Behav Res, 1991. 26(3): p. 499-510.

326. Tu, Y.K., et al., A critical evaluation of statistical approaches to examining the role of growth trajectories in the developmental origins of health and disease. Int J Epidemiol, 2013. 42(5): p. 1327-39.

327. Cohen, J., et al., Applied multiple regression/correlation analysis for the behavioral sciences, 3rd ed. Applied multiple regression/correlation analysis for the behavioral sciences, 3rd ed. 2003, Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers. xxviii, 703-xxviii, 703.

328. Draper, N.R. and H. Smith, Applied regression analysis. Vol. 326. 1998: John Wiley & Sons.

329. Phillips, S.K., et al., Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. Clin Sci (Lond), 1993. 84(1): p. 95-8.

330. Cooper, R., G. Muniz-Terrera, and D. Kuh, Associations of behavioural risk factors and health status with changes in physical capability over 10 years of follow-up: the MRC National Survey of Health and Development. BMJ Open, 2016. 6(4): p. e009962.

331. Perala, M.M., et al., The Healthy Nordic Diet and Mediterranean Diet and Incidence of Disability 10 Years Later in Home-Dwelling Old Adults. J Am Med Dir Assoc, 2019. 20(5): p. 511-516 e1.

332. Xu, B., et al., The association between Healthy Eating Index-2005 scores and disability among older Americans. Age Ageing, 2012. 41(3): p. 365-71.

333. Houston, D.K., et al., Dairy, fruit, and vegetable intakes and functional limitations and disability in a biracial cohort: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr, 2005. 81(2): p. 515-22.

334. Soysal, P., et al., Oxidative stress and frailty: A systematic review and synthesis of the best evidence. Maturitas, 2017. 99: p. 66-72.

335. Bjorklund, G. and S. Chirumbolo, Role of oxidative stress and antioxidants in daily nutrition and human health. Nutrition, 2017. 33: p. 311-321.

336. Shardell, M., et al., Association of low vitamin D levels with the frailty syndrome in men and women. J Gerontol A Biol Sci Med Sci, 2009. 64(1): p. 69-75.

337. Coyle, J.T. and P. Puttfarcken, Oxidative stress, glutamate, and neurodegenerative disorders. Science, 1993. 262(5134): p. 689-95.

338. Willcox, J.K., S.L. Ash, and G.L. Catignani, Antioxidants and prevention of chronic disease. Crit Rev Food Sci Nutr, 2004. 44(4): p. 275-95.

339. Munafo, M.R., et al., Collider scope: when selection bias can substantially influence observed associations. Int J Epidemiol, 2018. 47(1): p. 226-235.

340. Bates, B., et al., National Diet and Nutrition Survey: Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009-2011/2012): A survey carried out on behalf of Public Health England and the Food Standards Agency. 2014: Public Health England.

341. Anastasiou, C.A., et al., Mediterranean diet and cognitive health: Initial results from the Hellenic Longitudinal Investigation of Ageing and Diet. PLoS One, 2017. 12(8): p. e0182048.

342. Wade, A.T., et al., A Mediterranean diet supplemented with dairy foods improves mood and processing speed in an Australian sample: results from the MedDairy randomized controlled trial. Nutr Neurosci, 2018: p. 1-13.

343. Gu, Y., et al., Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology, 2015. 85(20): p. 1744-51.

344. Luciano, M., et al., Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. Neurology, 2017. 88(5): p. 449-455.

345. Lau, H., et al., Relationships between dietary nutrients intake and lipid levels with functional MRI dorsolateral prefrontal cortex activation. Clin Interv Aging, 2019. 14: p. 43-51.

346. Jackson, P.A., et al., Promoting brain health through exercise and diet in older adults: a physiological perspective. J Physiol, 2016. 594(16): p. 4485-98.

347. Aspell, N., B. Lawlor, and M. O'Sullivan, Is there a role for vitamin D in supporting cognitive function as we age? Proc Nutr Soc, 2018. 77(2): p. 124-134.

348. van Schoor, N.M., et al., Cross-sectional and longitudinal associations between serum 25-hydroxyvitamin D and cognitive functioning. Int Psychogeriatr, 2016. 28(5): p. 759-68.

349. Staubo, S.C., et al., Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness. Alzheimers Dement, 2017. 13(2): p. 168-177.

350. Castonguay, N., et al., Executive functions in men and postmenopausal women. J Clin Exp Neuropsychol, 2015. 37(2): p. 193-208.

351. Taylor, S.E., et al., Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight. Psychol Rev, 2000. 107(3): p. 411-29.

352. Croll, P.H., et al., Better diet quality relates to larger brain tissue volumes: The Rotterdam Study. Neurology, 2018. 90(24): p. e2166-e2173.

353. Yogev-Seligmann, G., et al., How does explicit prioritization alter walking during dual-task performance? Effects of age and sex on gait speed and variability. Phys Ther, 2010. 90(2): p. 177-86.

354. Stoet, G., Sex differences in the Simon task help to interpret sex differences in selective attention. Psychol Res, 2017. 81(3): p. 571-581.

355. Weiss, E.M., et al., Sex differences in cognitive functions. Personality and individual differences, 2003. 35(4): p. 863-875.

356. Hirsch, P., I. Koch, and J. Karbach, Putting a stereotype to the test: The case of gender differences in multitasking costs in task-switching and dual-task situations. PLoS One, 2019. 14(8): p. e0220150.

357. Wellmon, R., Does the attentional demands of walking differ for older men and women living independently in the community? J Geriatr Phys Ther, 2012. 35(2): p. 55-61.

358. Beilharz, J.E., J. Maniam, and M.J. Morris, Diet-Induced Cognitive Deficits: The Role of Fat and Sugar, Potential Mechanisms and Nutritional Interventions. Nutrients, 2015. 7(8): p. 6719-38.

359. Dumas, J.A., et al., Dietary saturated fat and monounsaturated fat have reversible effects on brain function and the secretion of pro-inflammatory cytokines in young women. Metabolism, 2016. 65(10): p. 1582-8.

360. Frison, E., et al., Plasma fatty acid biomarkers are associated with gait speed in community-dwelling older adults: The Three-City-Bordeaux study. Clin Nutr, 2017. 36(2): p. 416-422.

361. Weiser, M.J., C.M. Butt, and M.H. Mohajeri, Docosahexaenoic Acid and Cognition throughout the Lifespan. Nutrients, 2016. 8(2): p. 99.

362. Morris, M.C., et al., MIND diet slows cognitive decline with aging. Alzheimers Dement, 2015. 11(9): p. 1015-22.

363. Morris, M.C. and C.C. Tangney, Dietary fat composition and dementia risk. Neurobiol Aging, 2014. 35 Suppl 2: p. S59-64.

364. Barnard, N.D., A.E. Bunner, and U. Agarwal, Saturated and trans fats and dementia: a systematic review. Neurobiol Aging, 2014. 35 Suppl 2: p. S65-73.

365. McIsaac, T.L., E.M. Lamberg, and L.M. Muratori, Building a framework for a dual task taxonomy. Biomed Res Int, 2015. 2015: p. 591475.

366. Roivainen, E., Gender differences in processing speed: A review of recent research. Learning and Individual Differences, 2011. 21(2): p. 145-149.

367. Mantyla, T., Gender differences in multitasking reflect spatial ability. Psychol Sci, 2013. 24(4): p. 514-20.

368. Hollman, J.H., E.M. McDade, and R.C. Petersen, Normative spatiotemporal gait parameters in older adults. Gait Posture, 2011. 34(1): p. 111-8.

369. Moeller, S.M., et al., Dietary patterns: challenges and opportunities in dietary patterns research an Experimental Biology workshop, April 1, 2006. J Am Diet Assoc, 2007. 107(7): p. 1233-9.

370. Mertens, E., et al., Stability of physical activity, fitness components and diet quality indices. Eur J Clin Nutr, 2017. 71(4): p. 519-524.

371. Artaud, F., et al., Trajectories of Unhealthy Behaviors in Midlife and Risk of Disability at Older Ages in the Whitehall II Cohort Study. J Gerontol A Biol Sci Med Sci, 2016. 71(11): p. 1500-1506.

372. Thorstensson, A. and H. Roberthson, Adaptations to changing speed in human locomotion: speed of transition between walking and running. Acta Physiologica Scandinavica, 1987. 131(2): p. 211-214.

373. Batis, C., et al., Dietary pattern trajectories during 15 years of follow-up and HbA1c, insulin resistance and diabetes prevalence among Chinese adults. J Epidemiol Community Health, 2014. 68(8): p. 773-9.

374. Rooth, V., et al., Common trajectories of physical functioning in the Doetinchem Cohort Study. Age and Ageing, 2016. 45(3): p. 382-388.

375. Sjoblom, S., et al., Interaction of recommended levels of physical activity and protein intake is associated with greater physical function, and lower fat mass in older women: Kuopio OSTPRE- Fracture Prevention Study. Br J Nutr, 2020: p. 1-36.

376. Cooper, R., G.D. Mishra, and D. Kuh, Physical activity across adulthood and physical performance in midlife: findings from a British birth cohort. Am J Prev Med, 2011. 41(4): p. 376-84.

377. van Dongen, E.J.I., et al., Effectiveness of a Diet and Resistance Exercise Intervention on Muscle Health in Older Adults: ProMuscle in Practice. J Am Med Dir Assoc, 2020.

378. Elhakeem, A., et al., Correlates of high-impact physical activity measured objectively in older British adults. J Public Health (Oxf), 2018. 40(4): p. 727-737.

379. Rehm, C.D., et al., Dietary Intake Among US Adults, 1999-2012. JAMA, 2016. 315(23): p. 2542-2553.

380. Gose, M., et al., Trends in food consumption and nutrient intake in Germany between 2006 and 2012: results of the German National Nutrition Monitoring (NEMONIT). Br J Nutr, 2016. 115(8): p. 1498-507.

381. Foster, R. and J. Lunn, 40th Anniversary Briefing Paper: Food availability and our changing diet. Nutrition Bulletin, 2007. 32(3): p. 187-249.

382. Bloom, I., et al., What influences diet quality in older people? A qualitative study among community-dwelling older adults from the Hertfordshire Cohort Study, UK. Public health nutrition, 2017. 20(15): p. 2685-2693.

383. Vaes, A.M.M., et al., The association between 25-hydroxyvitamin D concentration, physical performance and frailty status in older adults. Eur J Nutr, 2019. 58(3): p. 1173-1181.

384. Schacht, S.R., et al., Development of a Mobility Diet Score (MDS) and Associations With Bone Mineral Density and Muscle Function in Older Adults. Front Nutr, 2019. 6: p. 114.

385. Parsons, T.J., et al., Healthier diet quality and dietary patterns are associated with lower risk of mobility limitation in older men. Eur J Nutr, 2019. 58(6): p. 2335-2343.

386. Parsons, T.J., et al., Physical frailty in older men: prospective associations with diet quality and patterns. Age Ageing, 2019. 48(3): p. 355-360.

387. McClure, R. and A. Villani, Greater adherence to a Mediterranean Diet is associated with better gait speed in older adults with type 2 diabetes mellitus. Clinical Nutrition ESPEN, 2019. 32: p. 33-39.

388. Laclaustra, M., et al., The inflammatory potential of diet is related to incident frailty and slow walking in older adults. Clin Nutr, 2019.

389. Agarwal, P., et al., Dietary Patterns and Self-reported Incident Disability in Elderly. J Gerontol A Biol Sci Med Sci, 2018.

390. Mishra, S., et al., Association between dietary protein intake and grip strength among adults aged 51 years and over: What We Eat in America, National Health and Nutrition Examination Survey 2011-2014. PLoS One, 2018. 13(1): p. e0191368.

391. Shannon, O.M., et al., Mediterranean diet adherence and cognitive function in older UK adults: the European Prospective Investigation into Cancer and Nutrition-Norfolk (EPIC-Norfolk) Study. Am J Clin Nutr, 2019. 110(4): p. 938-948.

392. Imaoka, M., et al., Effect of Multicomponent Exercise and Nutrition Support on the Cognitive Function of Older Adults: A Randomized Controlled Trial. Clin Interv Aging, 2019. 14: p. 2145-2153.

393. Wadsworth, A., Birth Cohort Studies, in Encyclopedia of Biostatistics. 2005.

394. Greenwood, D.C., Measurement errors in epidemiology, in Modern Methods for Epidemiology. 2012, Springer. p. 33-55.

395. Delgado-Rodríguez, M. and J. Llorca, Bias. Journal of Epidemiology and Community Health, 2004. 58(8): p. 635-641.

396. Mattisson, I., et al., Misreporting of energy: prevalence, characteristics of misreporters and influence on observed risk estimates in the Malmö Diet and Cancer cohort. British Journal of Nutrition, 2005. 94(5): p. 832-842.

397. Rasmussen, L.B., et al., Characteristics of misreporters of dietary intake and physical activity. Public Health Nutrition, 2007. 10(3): p. 230-237.

398. Cook, A., J. Pryer, and P. Shetty, The problem of accuracy in dietary surveys. Analysis of the over 65 UK National Diet and Nutrition Survey. Journal of Epidemiology and Community Health, 2000. 54(8): p. 611-616.

399. Stucki, G., et al., Application of the International Classification of Functioning, Disability and Health (ICF) in clinical practice. Disability and Rehabilitation, 2002. 24(5): p. 281-282.

400. Matta, J., et al., Interrelated factors favoring physical performance and activity in older adults from the NuAge cohort study. Exp Gerontol, 2014. 55: p. 37-43.

401. Bedard, A., et al., Sex differences in the impact of the Mediterranean diet on systemic inflammation. Nutr J, 2015. 14: p. 46.

402. Weaver, C.M. and J.W. Miller, Challenges in conducting clinical nutrition research. Nutr Rev, 2017. 75(7): p. 491-499.

403. US Department of Agriculture. Food and nutrient database for dietary studies. 2011 [cited 2018 1 March].