A life course approach to balance ability

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I, Joanna Marjory Blodgett, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

Balance ability is a crucial component of everyday life, underlying physical movement at all stages in life. Despite this, balance is an overlooked aspect of physical health and ageing, with minimal evidence of how factors throughout life are associated with balance ability. This PhD thesis used a life course approach to investigate how factors across life contribute to standing balance in mid and later life, and to examine associations between balance ability and subsequent falls risk.

Data from the MRC National Survey of Health and Development (NSHD) were used. NSHD is a nationally representative sample of 5362 males and females, born in England, Scotland and Wales in March 1946 and followed up to 24 times across life. One-legged balance time with eyes closed was assessed at ages 53, 60-64 and 69 (n=3111 individuals with a balance time at one or more age). Analytical methods included multilevel models, structural equation models, linear and logistic regressions and receiver-operating characteristic analyses.

In adulthood, disadvantaged socioeconomic position, poor health and adverse health related behaviours were associated with poorer balance ability (Chapter 3). In childhood, disadvantaged socioeconomic position, lower cognitive ability, slower coordination and early or late attainment of motor milestones were associated with poorer balance ability (Chapter 3, 4). Across several domains, higher cognitive ability in midlife was associated with better balance ability (Chapter 5). The association between verbal memory and subsequent balance ability was unidirectional, with some evidence of more complex bidirectional associations with search speed (Chapter 6). Most factors across life demonstrated changing patterns of association with balance with age. Finally, balance ability was associated with subsequent falls, although the one-legged stand did not appear to be a sensitive prognostic indicator of fall risk (Chapter 7).

Better understanding of the socioeconomic, cognitive, behavioural and health pathways across life which relate to subsequent balance ability, identified in this thesis, provides an opportunity to intervene earlier in life to minimise, prevent or delay balance impairment or decline.

IMPACT STATEMENT

This thesis is the first to examine a life course approach to balance ability, providing novel results in every core chapter. The findings have impact within and outside of academia, both by advancing future research and because of direct policy and clinical implications.

First, this thesis has identified multifaceted factors across life that are associated with balance ability. This is crucial in understanding changes in balance ability with age and identifies numerous factors that can be targeted to improve balance ability. The inter-relatedness of cognitive ability and balance ability was specifically highlighted, suggesting that decline in one may help inform decline in the other.

Next, thesis findings can inform at a policy level. Thesis findings of the long-lasting effects of socioeconomic, cognitive and physical developmental circumstances on health highlight the potential long-term impacts of recent cuts to governmental spending on services addressing childhood disadvantages. Taken together with other evidence from a life course approach to healthy ageing, the contribution of early life to physical processes in mid and later life must not be underestimated. Furthermore, findings identified that factors have different patterns and strengths of association with balance at different ages. Each factor examined in this thesis represents either a viable intervention target to improve balance ability or an important factor to identify high risk individuals in need of greater support.

Finally, in addition to potential intervention targets, this thesis can have immediate clinical impact in understanding balance ability and falls risk. Previous falls risk research has nearly entirely focused on those aged ≥65; this thesis found an observational association between balance ability and falls risk at younger ages. Previous research in those aged ≥65 has been prematurely translated to suggest that simple one-legged balance tests can accurately and reliably predict those at risk of falling. This thesis crucially identified a translational gap between explanatory and predictive associations. With an increasing public health focus on reducing falls in older adults, it is important to ensure that reliable and accurate screening recommendations are implemented.

Research findings from this thesis have been disseminated through publications, presentations and public engagement activities. To date, fourteen presentations (six poster, eight oral) at national and international conferences have been delivered. Findings from all thesis chapters have been or will be submitted to peer-reviewed journal articles (one published, one submitted, three in preparation). All papers will be widely advertised to ensure that they have far-reaching impact in research settings. Several public engagement opportunities have already arisen through the PhD process, most notably the inclusion of a balance ability task in two interactive exhibitions (i.e. Tangle and Life Course Golf Course) at the Greenman Festival in Wales. At these two events, in 2017 and 2018 respectively, over 600 and 1500 individuals of all ages were introduced to the concept of life course epidemiology and thesis findings were discussed with them.

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ABBREVIATIONS

ACE-III	Addenbrooke's Cognitive Examination (version III)
AD	Alzheimer's disease
AIC	Akaike Information Criterion
AUC	Area Under the Curve
BBS	Berg Balance Scale
BCS	1970 British Cohort Study
BEST	Balance Evaluation Systems Test
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CCS	Complete Cases Sample
CFI	Comparative Fit Index
CI	Confidence Interval
CoP	Centre of Pressure
CVD	Cardiovascular Disease
DCSM	Dual Change Score Models
GCE	General Certificate of Education
GHQ	General Health Questionnaire
ICD-10	International Classification of Diseases 10th Revision
IQ	Intelligence Quotient
MCI	Moderate Cognitive Impairment
MLM	Multilevel Model
MMSE	Mini-Mental Status Examination
MRC	Medical Research Council
NART	National Adult Reading Test
NCDS	National Childhood Development Study
NFBC	Northern Finland Birth Cohort
NIH	National Institute of Health
NSHD	National Survey of Health and Development
OR	Odds Ratio
PPT	Physical Performance Test
ProFaNE	Prevention of Falls Network Europe
Q1	Quartile One
Q3	Quartile Three
RCT	Randomised Controlled Trials
RMSEA	Root Mean Square Error of Approximation

ROC	Receiver Operating Characteristic
RRR	Relative Risk Ratio
SCI	Subjective Cognitive Impairment
SD	Standard Deviation
SEM	Structural Equation Modelling
SEP	Socioeconomic Position
SPPB	Short Physical Performance Battery
SRMR	Standardised Root Mean Square Residual
TILDA	The Irish Longitudinal Study of Ageing
TLI	Tucker-Lewis Index
TUG	Time Up and Go Test
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

From getting out of bed in the morning to sitting, standing and walking throughout the day, balance ability is a crucial component of everyday life. It underlies nearly all physical movement at every stage in life, from an infant learning to stand to an older adult trying to avoid a fall. Despite this, balance is an under-recognised and frequently overlooked aspect of physical health. Balance decline is concerning as poor balance in older adults is associated with increased risk of falling [1], amongst other outcomes. Falls can have devastating physical and psychological consequences including functional loss, hospitalisation and premature mortality as well as increases in vulnerability and apprehension towards everyday physical movement. Despite evidence of age-associated decline in balance ability [2,3], there has been minimal investigation of how factors across life are associated with balance ability and whether these associations change with age. Where balance has been considered, it is often part of aggregate physical performance measures [4-16]. In clinical and research settings, balance does not become a priority until clinically apparent decline or poor health outcomes arise.

The *overall aim of this PhD project is to use a life course perspective to investigate associations between factors across life and balance ability in mid and later life and to examine how balance ability was associated with subsequent fall risk, using data from the Medical Research Council (MRC) National Survey of Health and Development (NSHD).* This first chapter provides an extensive overview of balance ability as well as predictors and potential consequences of poor balance throughout the life course. First, balance is defined, physiological mechanisms underlying balance ability are explored (section 1.1) and common measurements of balance are outlined (section 1.2). Next, the chapter explores the life course approach to balance and how it changes with age from early child development through to later life (section 1.3). With a focus on balance ability in later life, the second half of the chapter summarises current evidence on factors in early and midlife that play a role in balance ability (section 1.4) and reviews the importance of balance for later life health outcomes (section 1.5). After a brief summary of the literature including the main limitations (section 1.6), the thesis objectives (section 1.7) and structure (section 1.8) are outlined.

1.1 What is balance? Definitions and mechanisms

Balance can be defined as a state of equilibrium where things are of equal weight or force [3,17,18]. In humans, this refers to the ability to maintain control of the body's position in space [19]. An individual's ability to balance in a static situation depends on the position of their centre of gravity (typically located in the pelvis) and the base of support (typically the area between the feet on the surface) [3,20]. *Static balance* refers to the ability to maintain the body's position during standing or sitting, while *dynamic balance* involves maintaining the body's position while the centre of gravity is moving, such as walking or running [3,21]. *Reactive balance* occurs as a response to an external disturbance, such as being bumped into or an unexpected change in the base of support [3]. Finally, *anticipatory balance* refers to the act of making adjustments for an impending "unstabilising" act; this could include a voluntary jump or bracing the body for a change in posture [3].

The ability to balance depends on visual, vestibular and proprioceptive sensory input. The most important pieces of sensory information are perceived by the visual system [22,23], which must keep track of the constantly changing surroundings as well as the movement of the body, head and eyes within the environment itself. Although an individual can maintain balance in a dark environment, balance equilibrium is more easily achieved when there are visual cues available [24]. This explains why balance times are consistently higher on tests with eyes open compared with those with eyes closed [25,26].

The vestibular system provides the majority of information about the head's motion, equilibrium and spatial orientation. Each ear contains three fluid-filled, semi-circular canals and two fluid-filled sacks called the otolith organs. Every time the head rotates or moves up and down, the displacement of fluid inside the canals informs the brain that the head is moving. The otolith organs − the utricle and saccule − are able to detect the position of the head in relation to gravity such as tilting, lying down, or leaning as well as any linear movement [27].

Finally, the brain receives proprioceptive input on how the body's limbs and head are positioned relative to the body's frame. Muscle spindles, mechanoreceptors and Golgi tendon organs send information about the muscle's position, contraction and length to the central nervous system, enabling the individual to sense their position in space [27,28]. Although the visual and vestibular systems provide most of the sensory input needed for balance, Fitzpatrick & McCloskey [29] argue that proprioception is the most sensitive of all three in perceiving changes in centre of gravity while standing and as such, should not be overlooked.

Balance is achieved through the complex interaction and contribution of these three processes (see Figure 1.1). The brainstem sorts the visual, vestibular and proprioceptive sensory information, and organises and integrates this with input from the cerebellum and the cerebrum. The cerebellum is the coordination centre of the brain and regulates posture, movement and balance, while the cerebrum contributes information from past learned experiences. These learned experiences could include walking on a moving bus, avoiding slippery ice in the winters or overall knowledge and awareness of balance hazards. This central nervous system response then allows for postural adjustments to be made in order to maintain balance [30].

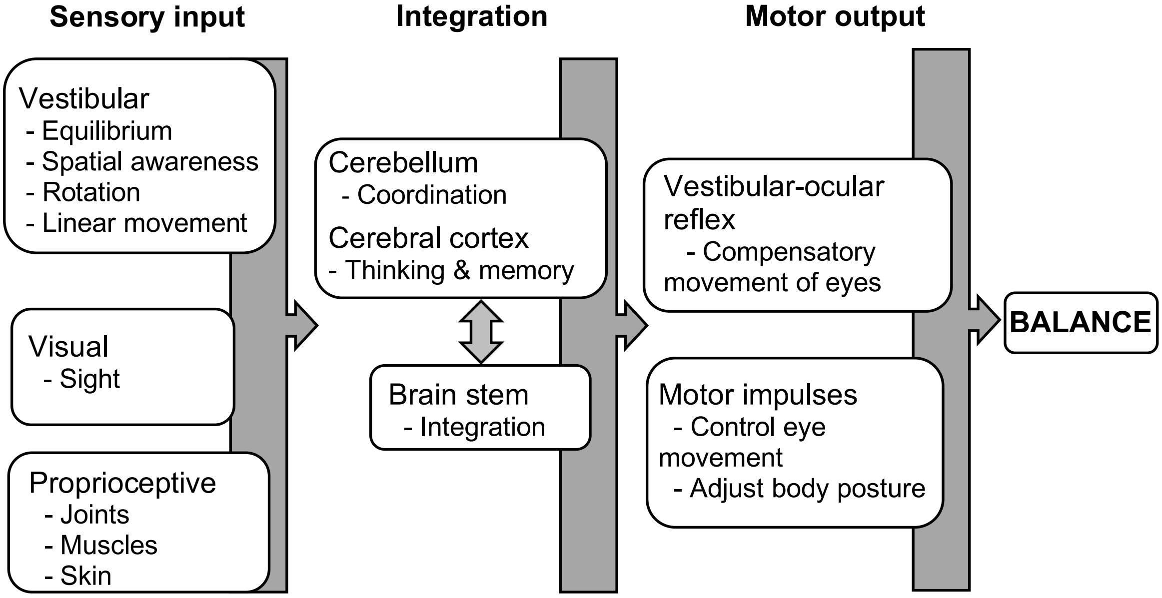


Figure 1.1 Physiological mechanism of balance: sensory input, integration and motor output

Disruptions to any of these sensory systems can cause impaired balance. Temporary disturbances occur frequently in the form of motion sickness or as a result of repetitive spinning. Persistent dysfunction to any of the balance-related sensory input or output areas can result in more serious balance problems; examples of vestibular-related balance disorders include vertigo, Ménière's disease, vestibular neuritis, and perilymph fistula. While some individuals in the general population may be affected by these acute or chronic conditions, this PhD thesis focuses on the balance ability of the general population (e.g. representative birth cohort; as described in detail in section 2.1) rather than on specific clinical cohorts of patients affected by specific disorders.

1.2 Measurement of balance ability

Numerous tools to measure balance have been developed for use in both clinical and research settings. Finding the optimal equilibrium between a systematic, complex balance assessment and a simple, easy to administer test can be difficult. Furthermore, it can be challenging to isolate balance from other physical components due to the body's reliance on multiple physiological systems within the central and peripheral nervous systems. Some measures exclusively examine certain components of balance − such as static, dynamic or reactionary − while others include balance as an element of a broader physical performance battery. Certain balance tools obtain objectively measured balance assessments with a stopwatch or using recent technological advancements, whereas others are dependent on more subjective measures including self-reported questionnaires or visual assessment of balance capability and postural control. The number of balance measurements continues to grow and diversify [3]. Below, an overview of the most common balance measures used in both research and clinical practice is provided.

1.2.1 Functional balance tests

The *one-legged stand test* − also known as the unipedal stance test or the flamingo stand − assesses the maximum time that an individual can stand on one foot. The upper time limit differs widely among published protocol, ranging from 5 [31,32] to 60 seconds [33] to failure [27]. This test of static balance is commonly used in epidemiological studies due to its low cost, feasibility and replicability [34,35].

In the *Romberg test*, an assessor compares postural control of a two-legged feet-together stance with eyes open and eyes closed [36,37]. Qualitative observation of abnormal sway or loss of balance suggests a neurological-related proprioceptive deficit [36,38]. While the test is extremely simple to administer, it is often criticized due to its "crude test of proprioception" [39], lack of specificity [40] and sensitivity [41] and subjective nature. Several modified Romberg tests that alter the stance (feet together, tandem, semi-tandem) or surface (firm and compliant support) are commonly used in both research and clinical environments [42]. One example of a modified test is the *Clinical Test of Sensory Interaction and Balance* [43]. The subject is asked to maintain balance under three different visual situations (eyes open, eyes closed, conflict dome on head) and on two different surfaces (hard surface, foam surface) [44]. A conflict dome is a static dome placed over the individual's head that aims to produce inaccurate visual input by restricting peripheral vision at the top, bottom and sides [44].

The *functional reach test* assesses dynamic balance by measuring the maximum distance that an individual can reach forward without losing their balance [45]. Individuals stand in a fixed position, holding their arms parallel with the floor. Low functional reach score has been associated with increased falls risk [46-49] and mobility difficulties [50], however evidence suggests no difference in functional reach between individuals with and without known balance impairments [51], indicating that the specificity of the test may be low.

1.2.2 Ordinal scale measures of balance

The *Berg Balance Scale (BBS*) is a performance-oriented measure of balance typically used in older individuals, often in clinical practice [52]. It consists of 14 items including simple mobility tasks (variations of transfers and standing positions) as well as more difficult tasks (360° turns, picking up objects, etc.). Each task is scored on a scale of 0 to 4 where the 0 represents an inability to do the task and 4 represents no issues in completing the task [52,53]; scores are summed for a maximum of 56 points. The Berg Balance Scale is frequently used as a measure of balance in both clinical and research settings and is commonly used to validate other functional balance measures [54,55]. The subjective assessment of the evaluator is a limitation, as well as its inability to detect variability in younger and healthier samples [3].

Tinetti's balance test − also called the Tinetti Mobility Test or Performance Oriented Mobility Assessment − evaluates an individual's mobility and stability using 9 balance tasks and 7 gait tasks. Items are scored from 0 to 1 or 0 to 2, where 0 represents an inability to perform the task correctly and 1 or 2 represent successful task completion. Individual scores are then summed to create an overall balance assessment (max: 16 points) as well as a gait assessment (max: 12 points) and a total score (max: 28 points). Balance tasks include sitting, standing, transferring from sitting to standing, and turning [56,57]. Similar to the Berg Balance Score, this test is limited by its ceiling effect in younger and healthier samples and its subjective assessment.

1.2.3 Technological measurements of balance

The *National Institutes of Health (NIH) Toolbox* is a comprehensive set of neuro-behavioural measures that assess cognitive, sensory, motor and emotional function in individuals aged 3-85 [58]. This suite of measures was introduced to try to create uniform measures enabling results to be compared across studies. Balance is one of five physical domains assessed in the NIH Toolbox Motor Battery. The NIH Toolbox Standing Balance test incorporates aspects of modified Romberg tests. The test evaluates balance under 6 conditions (eyes open and eyes closed for the following three stances: feet together on hard surface, feet together on foam, tandem stance). The participant wears an accelerometer attached at waist level in order to measure postural sway for each condition [58]. This is a promising tool due to its integration of timed standing balance under multiple conditions with an objective assessment of postural sway.

Technological quantitative measurements of balance have become more common with advancements in computers and technology [17,59,60]. Computerised *force plates* commonly assess four main components of balance: 1) postural sway, 2) symmetry, 3) dynamic stability and 4) motor response to disturbance in platform surface [61]. However, cost is a major limitation, as force plates range in price from $6000 for a basic model to $60 000 for more complex models with dual balance measurement and training functions [3]. The use of mobile devices (e.g. phones, tablets, etc.) to assess balance ability is an encouraging cost-effective approach [62], however a recent systematic review on the topic suggested that the quality of studies examining these devices is currently low [63]. Further research must identify adequate sensitivity of these tools, or await further technological advancements, before they can be implemented as an alternative to high cost force plates.

1.2.4 Other considerations on balance measurements

Other balance measures not listed above include the Postural Stress Test, Brunei Balance Assessment, Four Step Square Test, Dynamic Gait Index, Balance Evaluation Systems Test, sternal shove or nudge test, Fullerton Advanced

Balance Scale and Activities-Specific Balance Confidence Scale. There are also a number of physical mobility instruments that include a component of balance including the Physical Performance Test (PPT), the Short Physical Performance Battery (SPPB) and the Timed Up and Go [12,64,65]. While these tests contain a balance component, they do not distinctly assess balance ability. Often mobility is a driving factor of performance and one must exercise caution when using these tests to infer conclusions about balance ability. Aggregate instruments such as the SPPB and the PPT both include a specific test of balance similar to the modified Romberg test; individuals must maintain progressive position of feet together, semi-tandem and full-tandem stands for ten seconds each [14,65]. Despite this, there has been little attempt to distinguish the balance component when trying to better understand associations of physical performance with either risk factor or health outcomes. Composite measures are useful for summarising the overall physical capability of an individual, however it is difficult to ascertain the role of each individual component. Balachandran and Signorile [66] have suggested that all studies reporting associations with composite physical performance batteries should also report associations with the individual components of the aggregate measure. This would enable better understanding of distinct domains of physical capability when trying to understand the aetiology of physical capability.

While the main strength of standing balance tests is their ability to separate balance from other measures of physical capability, everyday environmental factors that impact balance are omitted. Many of these tests focus on quantifying balance impairments within a laboratory setting, which may be unrealistic compared with the physical environment in which everyday balance is used. The skills required to maintain static, dynamic, reactionary and anticipatory balance differ from the skills required to maintain a standing position in a controlled environment. This must be considered when generalising findings from a balance test to the general, everyday environment.

Many of these balance tests have been developed and validated in adults in later life, due to the increase in balance impairments with age. This limits the ability of some tests to capture meaningful variation in balance in younger populations, who are generally healthier and more likely to be able to successfully complete the test. Conversely, balance tests designed to examine balance in young, fit individuals or athletes [67] have floor effects, as the tasks tend to be too physically demanding for many older individuals to successfully attempt. For example, the star excursion balance test incorporates the one-legged stand with a maximum extension and reach of the other leg, while the modified Bass test is a series of jumps and one-legged landings [68-70]. These tests may not be feasible in older adults due to high injury risk and a hypothesised floor effect. This is further explored in the next section which discusses how balance ability changes with age.

1.3 Considering a life course approach to balance ability

1.3.1 Introducing a life course approach

Life course epidemiology was defined by Kuh and colleagues [71] as "...the study of long-term biological, behavioural, and psychosocial processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life, or across generations." This approach initially focused on specific clinical disease endpoints but has evolved to consider longitudinal trajectories of function throughout life and subsequently, a life course approach to ageing [72]. Where previous ageing research has focused on adult risk factors, a life course approach aims to identify various factors across life and consider how these factors may interact with one another to contribute to any given health risk (e.g. chronic diseases, physical capability, markers of healthy ageing) [71,73,74].

Several pathways across various health domains have been proposed including socioeconomic, cognitive, physical and biological pathways [75]. These pathways can include sensitive or critical periods in early life; this is explored further in section 4.1 (Chapter 4) in the context of cognitive and physical development in childhood. Pathways can also show indication of risk accumulation, where there is an additive effect of exposure to a factor at multiple life stages (e.g. poor socioeconomic position in both childhood and adulthood)

Previous research has considered how life course epidemiology can contribute to understanding of different components of healthy ageing including the maintenance of physical capability [74]. Meaningful variation in physical performance (e.g. balance ability, grip strength, walking) is present across adulthood [74], which is important for two main reasons. First, it also allows factors across life that are associated with this meaningful variation in physical capability to be investigated. Second, it allows associations between this variation and future adverse health outcomes to be identified [76,77]. This approach has not been applied to balance, which is what this thesis aims to do (as outlined in sections 1.7 and 1.8).

In the following subsections, balance ability across the life course will be described; this includes balance development in childhood (section 1.3.2) as well as evidence of variation in balance ability throughout adulthood (section 1.3.3). Section 1.4 will introduce factors across life that may contribute to balance ability, while section 1.5 considers the important health outcomes that are known to be associated with balance ability.

1.3.2 Balance ability in childhood

Humans are not born with the inherent ability to balance. Individuals develop this ability early in life, generally experience few problems in the middle years before experiencing a decline in balance ability in old age. Postural instability is highest in young children and older adults, with balance performance following an inverse U-shaped trajectory across the life course [78,79]. Development of balance ability in early life can be identified by several milestones including sitting, standing and walking. The development of these fundamental motor skills in early childhood is hypothesised to be crucial for future motor capability throughout life [80,81]; balance, in particular, is thought to be a fundamental foundation required for any future physical activity [82,83].

Before learning to stand and walk on their own, infants develop postural control as they learn to orientate their head and body in space [84]. A minimal level of postural control is necessary for an infant to successfully exhibit reaching, sitting and locomotor behaviours [85-87]. Infants do not reach these major postural milestones at the same time, with variability in rates of development [82,88]; infants start sitting at an average age of about 6 months of age [82,89], crawl at 8 months, and can independently stand and walk by an average age of 12 months [82,89]. Variability in the age of attainment of these milestones is common, although exceptionally late development can serve as a clinical flag. For example, it has been recommended that referrals are sought if a child is unable to sit by 12 months, stand by 18 months or walk by 24 months [90,91].

Adolph and colleagues suggest that each motor developmental milestone is a gradual progression in balance control that requires different parameters [86,92-94]. They argue that sitting, crawling and walking require different muscle groups, different vantage points and different somatosensory input. Infants continually, albeit subconsciously, alter their balance and, as a result, learn the maximum threshold of postural sway needed to successfully execute each of these skills [86,92-94]. This is consistent with evidence from the World Health Organisation (WHO) that has shown that at least 90% of children achieved milestones in a common sequence: sitting, standing with help, walking with help, standing unassisted, and walking unassisted [89].

Research investigating posture in infants has demonstrated the early importance of the neural processes required to maintain balance. Infants fall less, walk further and exhibit less postural sway when the task requires higher concentration [95-97]. For example, infants fell half as much when walking with an object [97], and exhibited less postural sway while holding a toy in a goal-directed task [95,96]. It appears that with increasing complexity and subsequent concentration, infants are able to adopt adaptive postural patterns and exhibit more complex postural sway than originally thought [96].

As a child continues to physically develop, the ability to balance improves substantially. Several studies have sought to characterise normal developmental balance curves in children [98-100]. For example, cross-sectional data showed that performance on the one-legged stand test of nearly 500 Swiss children improved from age 5 to 18 [99]. There was a large degree of inter-individual variation at all ages, reiterating that variation in balance ability between individuals of the same age is normal. [99]. Other studies have emphasised a non-linear pattern in the development of postural control [84,101-103]; these studies identified specific ages at which postural response changed substantially. The first turning point commonly arose at age 8 [84,101-103], while the second turning point occurred at age 13, at which point balance ability was considered to be nearly equivalent to adult-like performance [84,104-106]. Girls developed postural control and general balance ability at an earlier age than boys, consistently outperforming boys of the same age on balance tests [104,105,107-109]. These developmental sex differences are consistent with slower physical growth and neuromuscular development in males [110]. Sex differences in balance ability are explored further in section 1.4.1.

1.3.3 Balance ability in adulthood

Research on balance ability in early to mid-adulthood is limited. This may be because balance impairments in earlier adulthood are rare and nearly always due to a specific clinical balance disorder. Balance research within this age groups tends to focus on two groups at opposite ends of the balance spectrum: those with clinically diagnosed disorders and high-performance athletes. Understanding why balance is higher in physically elite subsamples can inform balance-related interventions in the normal population. For example, gymnasts [111,112], football players [113,114] and swimmers [113] tend to have better balance ability than other athletes. Understanding what movements and training regimens help consolidate balance could lead to targeted interventions in other populations. Furthermore, athletes who include balance exercises in their training regime have a lower likelihood of ankle injury compared with those who do not [115-118]. This is consistent with studies showing that interventions that reduce ankle weakness and instability in older adults could contribute to decreased risk of falls [119,120].

Aside from elite athletes and those with diagnosed disorders, it has been proposed that meaningful variability in balance capability does not begin to emerge until later life. However, limited data examining the variability in balance ability throughout adulthood has demonstrated a slight decline from age 18 to 50, before a starker decline from age 50 through to age 100 [25,121]. Data from a small cross-sectional study (n=775) has suggested that physical trajectories differ depending on domain (balance, mobility, strength and endurance); balance and chair stand performance declined as early as 50 years of age while decreases in gait speed and aerobic endurance were not seen until 60 years of age [121]. Other studies reported similar age-related trends [53,122-124], although further research must examine longitudinal trajectories in a larger sample. Despite evidence of variation throughout adulthood, research on balance ability has nearly primarily focused on those aged ≥65 [125].

The relationship between increasing age and a higher prevalence of balance impairment has been consistently demonstrated across different countries, in community-dwelling and institutionalised samples, in men and women, and in individuals with specific clinical diagnoses (e.g. chronic stroke, Parkinson's disease, etc.) [26,126-133]. In addition to age, there are many different factors across the life course that contribute to heterogeneity in balance ability. The next section summarises factors throughout life that may help explain individual variation in balance ability and its age-associated changes.

1.4 Factors that may contribute to balance in later life

Despite limited data on trajectories of balance ability across the life course, there is substantial variability amongst the general population in their peak balance ability, maintenance over time, time of onset of decline and rate of decline [25,121]. It is not well understood why some individuals exhibit early decline in balance and others maintain their balance ability in later life. Here, evidence on various factors across life and their associations with subsequent balance ability are summarised; these include sociodemographic, behavioural, developmental and cognitive factors, as well as psychological and physical health.

1.4.1 Sociodemographic factors: sex and socioeconomic position

1.4.1.1 Sex and anthropometric differences

Different motor development patterns between boys and girls are well-recognised [134-136], as discussed above (see section 1.3.2). While girls consistently perform better on balance tests than boys [104,105,107-109], this pattern seems to reverse from adolescence onwards [137-140]. The majority of studies report that women have poorer balance performance as well as higher rates of falls in adulthood [137-140]. The supporting argument for better balance in men points to higher age-related physical capability in men [141-146], including strength [141,147], mobility [141,148], lower frailty [142,146], and lower disability [143,145].

Height, weight or body mass index (BMI) may explain some sex differences in balance ability. For example, one study [149] showed that sex differences in functional reach score were no longer found when scores were normalised to body height. Another study reported that height and weight were major determinants of balance performance in women, but were not associated with balance in men [150]. Beyond sexual dimorphism in height and weight, differences in body composition, strength or cognitive processing could also contribute to sex differences. Studies that have controlled for body composition, height, and strength report no sex differences in balance ability after these adjustments [126,128,149,151]. Similarly, one study found poorer balance in women only if visual and proprioceptive input were compromised [137]. This suggests differences in underlying mechanisms used to maintain postural balance such as motor (muscle strength and reaction speed) or cognitive (delays in sensing stimuli, in processing stimuli, in sending neural motor signals or in coordination of motor recruitment) factors [150,152-154]. Further investigation is necessary to understand how balance differs between men and women.

1.4.1.2 Socio-economic position

Studies that have examined childhood socioeconomic position (SEP) in relation to standing balance in later life have demonstrated consistently strong associations between higher SEP and higher balance ability [155-158]. A meta-analysis based on 11 studies of standing balance in adulthood reported that those with the lowest childhood SEP were 1.26 (95% Confidence Interval (CI): 1.02-1.55) times more likely to be unable to balance for 5 seconds or more (eyes open) compared with those with the highest childhood SEP [159]. Childhood SEP likely influences balance ability through a series of indirect pathways including cognitive and motor development, health behaviours, education and cognitive ability, which are explored further below. This is supported by the attenuated association in models adjusted for adulthood SEP, whereby higher SEP in adulthood remained associated with better standing balance [160,161]. Adult SEP may influence balance through a similar mechanism to childhood SEP, with current physical and cognitive health playing a direct role. Associations between socioeconomic factors and balance, as well as any differences in patterns of association between men and women, are explored in the first analytical chapter (Chapter 3).

1.4.2 Early development

There is growing evidence that positive motor development in infancy and childhood is associated with various benefits in adolescence or adulthood [156,162-170], however only one study has investigated how early motor development is associated with balance in midlife. This study suggested that those who attained milestones at an average age had better balance ability at age 53 compared to early or late developers [169]. With such little evidence, further research is warranted to examine how variability in motor development in childhood may be associated with balance in later life. Higher cognitive ability in childhood has also demonstrated associations with better balance in mid or later life [171,172]. Section 4.1 (Chapter 4) provides an in-depth review of the literature on these early life factors and later life balance.

1.4.3 Behavioural risk factors

1.4.3.1 Physical activity and exercise

The majority of research examining associations between health behaviours and balance has focused on physical activity. Numerous randomised controlled trials (RCTs) have reported a positive effect of exercise interventions in older adults on performance-based balance [173-179]. Examples of interventions include structured inclusive exercise programmes [173,180], aerobic walking programmes [175] and aquatic training [176]. Balance-specific training may be necessary to improve balance, as isolated strength-based interventions have limited efficacy in improvement in balance [181-184]. A meta-analysis of stepping interventions established strong balance improvements and reduced falls risk in adults over the age of 60. The reduction in falls was thought to be mediated by improvements in balance, balance recovery and gait but, interestingly, not strength [185]. Most of these exercise interventions are physically strenuous, so they may not be appropriate for older populations experiencing declines in physical capability and increased risk of falls. RCTs have shown that low-impact interventions such as Tai Chi – a Chinese martial art consisting of slow sequential movements executed in a slow and flowing manner [186,187] – has a substantial impact on balance, postural control and spinal flexibility [186-191].

The above RCTs demonstrate the usefulness of various physical interventions to improve balance ability, thus reducing falls risk and other adverse health outcomes. However, these RCTs tend to target healthy and intrinsically motivated individuals, without any illness or disease. Observational studies allow long-term associations between physical activity and later life physical capability to be examined. There is considerable evidence supporting physical activity as a modifiable lifestyle factor for higher physical capability levels in mid and later life [192-199]. Specific research examining the influence of physical activity on subsequent balance performance is limited, with only a few studies reporting the positive effect of adulthood physical activity on subsequent balance in mid and late life [197-199].

1.4.3.2 Other health behaviours

Other health behaviours such as smoking [200], alcohol use [201] and poor diet [202] are associated with poor health outcomes, although the evidence is less extensive for these behaviours in relation to balance. Limited evidence has shown that smoking has both acute and long-term associations with balance. A small laboratory-based study demonstrated that individuals have increased postural sway immediately after smoking a cigarette [203], while longitudinal studies have shown that past smoking habits are strongly associated with lower balance ability [161,204]. The acute effect (within minutes or hours) of alcohol consumption on balance is well established [205-207], however there is no known evidence on the long-term effects of alcohol consumption on balance. Finally, there is some evidence that higher quality diet in childhood (high milk and protein consumption and low fat intake) [208] and adulthood (high consumption of fruit, vegetable and whole grain bread) [209] or reduced consumption of white bread, chips, sugar and full-fat dairy products [193] are associated with better balance ability. Many of these associations may be confounded by SEP, where those with lower SEP are more likely to participate in poor health behaviours and more likely to have poor balance [155,157-159,169]; this is further investigated in Chapter 3.

1.4.4 Cognition

As reported in section 1.1, cognitive processing of sensory and motor input is an important component of the balancing process [210]. This is a complex process made less clear by a lack of evidence on the direction, temporality and magnitude of the association between balance ability and cognition [211]. This section provides an overview of how cognition may impact balance ability; section 1.5.3 examines the reverse relationship in more detail. Chapters 5 and 6 will then provide a more comprehensive review to identify gaps and limitations of the literature, before investigating specific aims related to cognition and balance.

Briefly, cognitive ability in both childhood and adulthood has been associated with better balance performance in midlife, with evidence that distinct cognitive domains (i.e. memory, fluency, processing speed, executive function) all have specific associations with balance ability [169,171,212]. Individuals with steeper progression of dementia also experienced steeper declines in mobility and balance [213]. Several studies have found that neuropathological markers of cognitive impairment may predict impaired balance in older adults [214,215]. For example, moderate and severe age-related white matter change is associated with deterioration in balance over time [215], while another study demonstrated that grey matter density predicted balance instability and falls risk with a magnitude comparable to age alone [214].

Computer-based cognitive training interventions, similar to the physical interventions described above in section 1.4.3.1, improved multiple components of balance including decreased body sway [216], improved centre of gravity alignment [216], and improved speed on the time up and go (TUG) test [217]. Interactive dual training, which targets both cognitive and physical processes, has also shown efficacy in improving balance [185,218]. This evidence points to the preservation of cognitive function as an important aspect needed to maintain balance control throughout the life course. Many studies have examined associations between cognition and overall physical capability [4-7] as measured by an aggregate physical performance battery. By combining balance in an overall physical capability battery [8-11], it is not possible to draw conclusions about the association between cognition and balance as an individual component (as discussed in section 1.2.4). There are many longitudinal studies with available data on multiple measures of balance ability and cognition over time, however there is very little published on their associations. Section 5.1.3 provides a comprehensive review of these studies and hypothesises why evidence on the topic is scarce in comparison to the availability of the data.

1.4.5 Physical and psychological health

1.4.5.1 Physical health

As with many domains of physical capability, individuals in poor health commonly exhibit lower balance ability. Problems of old age rarely occur in isolation [219], thus the co-occurrence of poor balance ability alongside other morbidities is expected. Poor balance is common in individuals with various comorbidities including knee osteoarthritis [220], history of fractures [221], frailty [222], diabetes [223,224] and muscle weakness [13]. Several health conditions may contribute directly to balance performance. For example, vision deterioration would reduce visual sensory information required in balance, while physical morbidities such as osteoarthritis, previous fractures or sarcopenia impact the musculoskeletal function required to maintain a balance position [220,221,225]. Due to physical limitations and comorbidities at older ages, these associations may become larger with increasing age. The contribution of various physical health indicators to balance is explored further in Chapter 3. Balance ability, along with grip strength, walking speed and chair rises, are frequently used as markers of physical capability. While these physical performance tests are strongly correlated, they are physically distinct constructs and should be considered as such. It is unclear if deterioration in one area acts as a catalyst for deterioration in other areas or if decline occurs concurrently.

1.4.5.2 Psychological health

Most research on factors associated with balance has focused on the role of environmental and physical factors, while investigation into psychological factors, such as fear of falling, depression and well-being [226-229], is less common. Limited evidence suggests that depression and balance performance are associated with one another; this relationship may be mediated by cognitive decline [230] or psychomotor retardation [231]. Those with depression report decreased attention, processing speed and motivation [232-234] and as such, may be less able to successfully integrate the input necessary to maintain balance. Balance impairment may also precede the development of depressive symptoms as a result of activity restriction, social isolation or fear of falling [229,235,236].

The association of fear of falling and of depressive symptoms with falls may be mediated by balance ability [237]. Individuals who fear falling often unintentionally adjust their body position and gait [232]. As a result, fearful individuals may walk slower and take a wider stance with shorter strides [238,239], involuntarily stiffen or over adjust their posture [240,241] and avoid any non-essential physical activity [242]. These maladaptive movements and self-imposed activity restrictions can reduce stability [242], cause muscle weakness [226] and ironically, increase balance impairment and risk of falling [226,232]. Kvelde [243] suggested that the association between depression and falls risk is mediated through a strength pathway and an executive function pathway, with both of these mediating falls risk via balance.

1.5 Factors that balance may contribute to in later life

As explored in section 1.4, associations between factors across life and balance ability can be complex. For example, associations between aspects of physical, psychological or cognitive health and balance ability may be bidirectional. Maintaining balance ability in mid and late life may facilitate preservation of cognitive and physical health in ageing and decrease risk of various adverse health outcomes such as falls [52,244-246], poor recovery from illness [132] and premature mortality [247]. There is growing awareness of the importance of balance ability in the ageing process, as shown by recent physical activity guidelines that recommend specific balance activities for older adults [248-250]. In this section, the importance of maintaining balance ability in older age is summarised and associations of poor balance with outcomes such as mortality, falls, and cognition are discussed.

1.5.1 Mortality

A systematic review by Cooper et al. [77] reported that poorer balance – as well as other physical capability measures – was associated with higher rates of all-cause mortality in older community dwelling populations. Further studies confirmed that impaired balance was associated with pre-mature mortality in midlife [247,251], independent of demographic characteristics, lifestyle factors, body size, health status and socioeconomic factors [251].

1.5.2 Falls

Falls are a leading cause of injury, functional impairment, and death in older adults [252]. Nearly 50% of individuals over the age of 65 report falling in the previous 12 months [1,253-256]. These falls account for up to half of all hospitalisations in older adults [257,258]. Full recovery from falls after hospitalisation is difficult [259,260] and prognostic outcomes of falls are not well understood. A proactive approach to identifying risk factors for falls has focused on balance impairment. Numerous studies, across heterogeneous samples, have demonstrated that poor balance ability is associated with falls in older adults [46,48,52,56,244-246,255,261-272], although there have also been null findings [47,131,273,274]. A major limitation of the evidence on balance and falls has been the lack of discrimination between regression-based associations and prognostic accuracy of the balance test. The presence of an association, using standardised analyses such as regressions, does not infer that the test can be used as an accurate and reliable screening tool to identify high-risk individuals. The evidence on this topic is complex and an extensive literature review along with a summary of limitations of current research is explored in section 7.1.4 and 7.1.5 (Chapter 7).

There is evidence to suggest that balance training interventions can significantly decrease the risk of falling [275-280]. A systematic review investigated which characteristics of exercise programmes were associated with larger reductions in falls, concluding that greatest effects occurred in programmes that focused on balance [278,281]. As physical activity interventions are increasingly used to target overall health in older adults [282], policy makers must consider the inclusion of a balance component in training programmes to reduce falls risk.

Sex differences in balance ability were discussed in section 1.4.1. Women consistently have higher rates of falls [137,257] when compared with men and as such, the mechanism through which balance impacts falls risk could be mediated by sex differences. Some of these potential mediators in the causal pathway are likely to be due to intrinsic differences in physical strength [147,283], mobility [79,284] and overall health status [285], as women often have lower mean strength and mobility as well as higher prevalence of morbidities than men [141-143,145-148]. Pereira et al. [286] demonstrated that sex differences in falls risk disappear when comorbidities, lean and fat body mass, and balance ability were similar. This is consistent with studies that found no sex differences in balance when controlling for specific body composition differences [126,128,151].

1.5.3 Cognition

In section 1.4.4, evidence of the association between cognition and subsequent balance was summarised. While the majority of research has assessed this association in a cognition to balance direction, there is also some evidence of an association in the reverse direction. For example, balance impairment may be an indicator of future cognitive decline. While most of the evidence that showed that poor balance is more common in patients with Alzheimer’s disease (AD) was cross-sectional [287-289], evidence from longitudinal studies has also suggested that poorer balance ability at baseline is associated with higher risk of dementia over 2 to 12 years of follow-up [290-292]. A study of individuals aged ≥90, who were dementia-free at baseline, showed that one-legged balance was more strongly associated with dementia onset than comparable associations of walking speed and grip strength [291]. There was no association between chair stands and dementia [291,292]. Although this sample is affected by survivor bias (e.g. survivors of an earlier retirement cohort study [293]), these findings lend support to the importance of motor and sensory coordination in cognitive ageing processes. It suggests that balance-based physical performance measures may be better indicators of cognitive decline than strength-based physical performance measures. Whether balance ability can provide an earlier marker of underlying cognitive processes requires further investigation.

One study proposed that balance is more than an indicator of underlying cognitive decline and instead found that a balance training intervention improved cognition [294]. In a healthy sample of individuals aged 19-65 (n=40), the authors reported that twelve-week, twice-weekly balance training program significantly improved memory and spatial cognition, although had no effect on executive function. The authors speculated that balance training induces changes in the hippocampus and parietal cortex. This could have important implications for targeting cognition throughout adulthood, which would be particularly important when age-related cognitive decline emerges.

There is also some evidence that neuropathological markers of cognitive decline may mediate the association between balance and subsequent cognitive decline. Impaired balance is associated with both clinically evident cognitive decline as well as early pathological changes in the brain [33]. Studies have identified significant correlations between poor balance and brain lesions including brain stem lesions, white matter lesions and periventricular lesions [295,296]. These lesions, particularly white matter lesions, are frequently observed as neuropathological indicators of Alzheimer's disease [297]. Given the complex association between cognition and balance outlined here and in sections 1.4.4, Chapter 6 will further explore the evidence that has assessed directionality of the association.

1.6 Summary of literature review

This chapter defined balance and its underlying physiological mechanisms, and explored characteristics of changes in balance with age. Balance ability is lowest during development in childhood and age-associated decline in later life and highest during adolescence and early adulthood, demonstrating an inverse U-shaped distribution. Predictors and outcomes associated with balance ability have been summarised; current evidence suggests that early development, health behaviours, physical and psychological health, and cognition play a role in subsequent balance performance. The relationship between some domains is often complex and bidirectional. Low balance ability is also associated with increased risk of premature mortality, falls and lower cognitive ability.

The follow-up length of many of the studies described in this chapter is short, with negligible evidence examining the possible influence of these factors across the life course on balance. Furthermore, no study has examined how these associations may differ at different ages in adulthood. There is substantial evidence of RCTs examining both the impact of health behaviours on balance and the benefits of structured balance training programmes. However, there has been limited observational work identifying life course characteristics associated with better balance outcomes or investigating the role of balance performance in the ageing process. Despite evidence of differences in developmental pathways of physical capability domains such as balance, strength and mobility, many studies have only examined an overall performance measure and have not considered balance trajectories and rates of decline separately. This is especially true when investigating the multifaceted relationship between balance and cognition. There remain large gaps, not just in the balance literature, but also in the translation of research on balance and falls into clinically-relevant screening tools, guidelines and interventions. Thus, there is a distinct opportunity to explore this using a life course perspective (as described in section 1.3.1) to help inform possible interventions and prevent poor health outcomes such as falls.

1.7 Aims and objectives

The aim of this PhD project is to use a life course perspective to examine the associations of factors across life with standing balance in mid and later life, using data from the MRC National Survey of Health and Development (NSHD).

The specific objectives of this PhD thesis are:

i) To investigate associations between traditional risk factors across life with balance ability and to consider how these associations change with age and sex (Chapter 3)

ii) To investigate associations between neurodevelopmental factors in childhood and balance ability in mid and later life (Chapter 4);

iii) To investigate how different domains of cognition are associated with balance ability in mid and later life (Chapter 5);

iv) To investigate bidirectional associations of cognition and balance in mid and later life (Chapter 6);

v) To investigate explanatory and predictive associations between balance ability and falls in mid and later life (Chapter 7).

It is hypothesized that positive factors across life – including positive childhood development, high SEP in childhood and adulthood, high educational attainment, participation in healthy behaviours and positive health status – will be associated with better balance ability at several ages in mid and later life (Chapters 3, 4). Due to the complex association between balance and cognition, it is expected that there will be different patterns of association for different cognitive domains (Chapter 5) and that there will be a bidirectional association between the two constructs (Chapter 6). Finally, it is expected that there will be strong associations between balance ability and falls risk (Chapter 7); this has positive ramifications for improving population health.

1.8 Structure of the thesis

Chapter 1 examined a theoretical framework of a life course approach to balance by providing definitions and mechanisms of balance, how it changes with age and what factors it is associated with. The conceptual framework for the thesis is presented in Figure 1.2 and outlines the focus of each chapter. Individual conceptual frameworks for each chapter will be provided throughout the thesis. Chapter 2 will describe the MRC National Survey of Health and Development cohort, the measurement of balance ability and key variables as well as discuss analytical strategies that will be used throughout the thesis. Chapters 3 through 7 address each of the five objectives stated above. All chapters will follow a similar structure that includes: a literature review that summarises current evidence and identifies gaps and limitations, a methods section that addresses any analytical considerations specific to that chapter, a traditional results section and finally, a discussion section.

Chapter 3 and Chapter 4 examine associations of traditional risk factors and early life neurodevelopment factors, respectively, with balance ability. Chapters 5 and 6 include a detailed investigation of the complex relationship between balance ability and cognition; Chapter 5 considers how different domains of cognition are associated with balance ability, while Chapter 6 assesses the existence of a bidirectional associations between cognition and balance ability. Chapter 7 compares and contrasts explanatory and predictive associations between balance ability and falls. Finally, Chapter 8 ties together individual findings from each chapter and considers the public health implications and methodological strengths and limitations of this work before finally suggesting areas for future research.

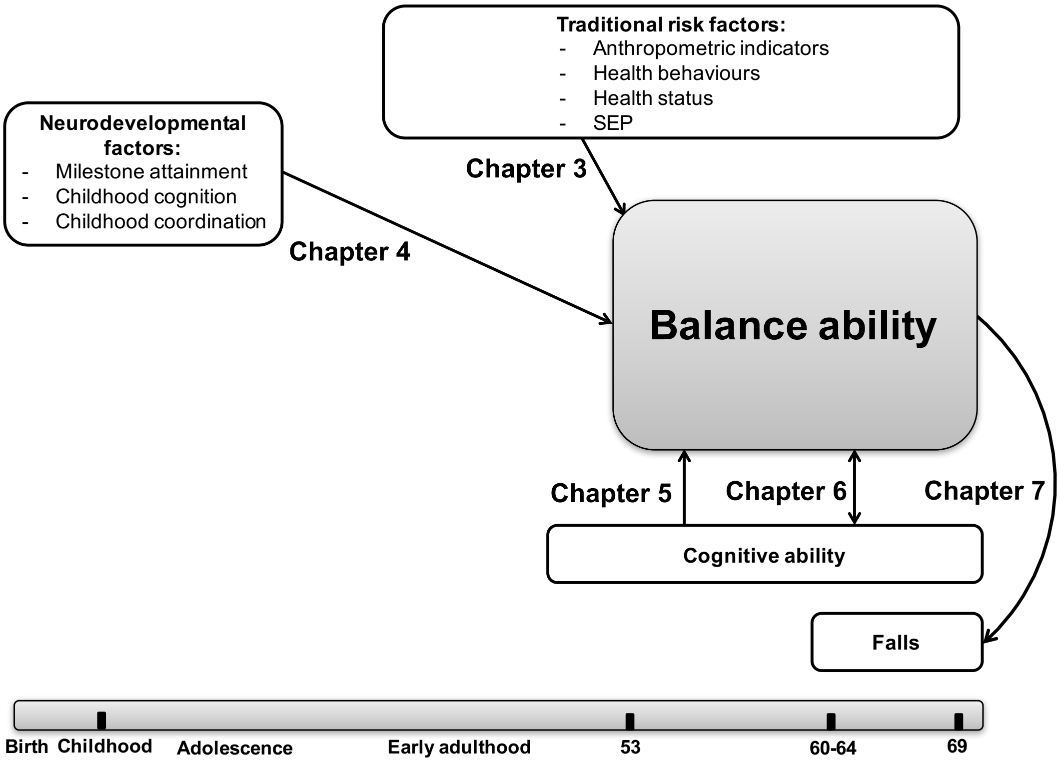


Figure 1.2 Conceptual framework of chapters in the thesis

CHAPTER 2: METHODS

This chapter provides an overview of the methods used throughout the thesis. In order to adequately examine a life course approach to balance, an observational study that follows the same individuals over time is crucial. This enables factors from multiple stages in life to be considered and for repeat measures of balance to be examined. The design of such a study is crucial to high quality life course research as it underlies appropriate research questions, analyses and conclusions [298]. There is a lack of data that has assessed early life factors and repeated measures of balance ability in adulthood. Thus, the MRC National Survey of Health and Development (NSHD) offers a unique opportunity to examine how early and midlife experiences and exposures are associated with the ageing process and specifically with balance in mid and later life.

NSHD, used for all analyses, is first introduced (section 2.1). Next, the assessment of balance ability and all common covariates are described (section 2.2). Subsequently, characteristics of the analytical sample are described (section 2.3) and an overview of analytical strategies (section 2.4) is provided. Chapter-specific variables (i.e. neurodevelopmental factors, cognitive tests and falls) as well as statistical techniques are not discussed in detail here as they are outlined in each of the relevant chapters. Finally, missing data throughout the thesis is described, investigated and the strategies used to deal with missing data are outlined (section 2.5).

2.1 Overview of the MRC National Survey of Health and Development

2.1.1 Origins of the study

All analyses use data from the MRC NSHD, commonly referred to as the 1946 British birth cohort. NSHD began as a maternity survey of all births recorded in England, Scotland and Wales during 3-9 March 1946 (n=13 867 of 15 130 total births in that period) [299]. The aims of this original survey were two-fold; first, to examine why the national fertility rate had been falling consistently since the 19th century and second, to examine how obstetric medical and midwifery services could prevent premature infant death and promote the health of infants and their mothers [300]. NSHD was initially intended to be a single cross-sectional survey, however the potential value of a follow-up study was unmistakeable [301] and additional data collection waves were implemented. It has since developed into a longitudinal study of the members' entire lives.

Of the 13 867 infants recruited to the original maternity survey, 5 362 constituted the original birth cohort sample for longitudinal follow-up. This included all single births to mothers with husbands in non-manual and agricultural employment and a quarter of all comparable births to mothers with husbands in manual employment. Study members remain under active follow-up, having been assessed up to 24 times in infancy, across childhood, adolescence, and adulthood, most recently at age 69 (n=2149) using a combination of questionnaires, interviews and clinical examinations [302]. Until the age of 15, all information was collected using the study members' mothers as proxies with additional assessments provided by school doctors and teachers.

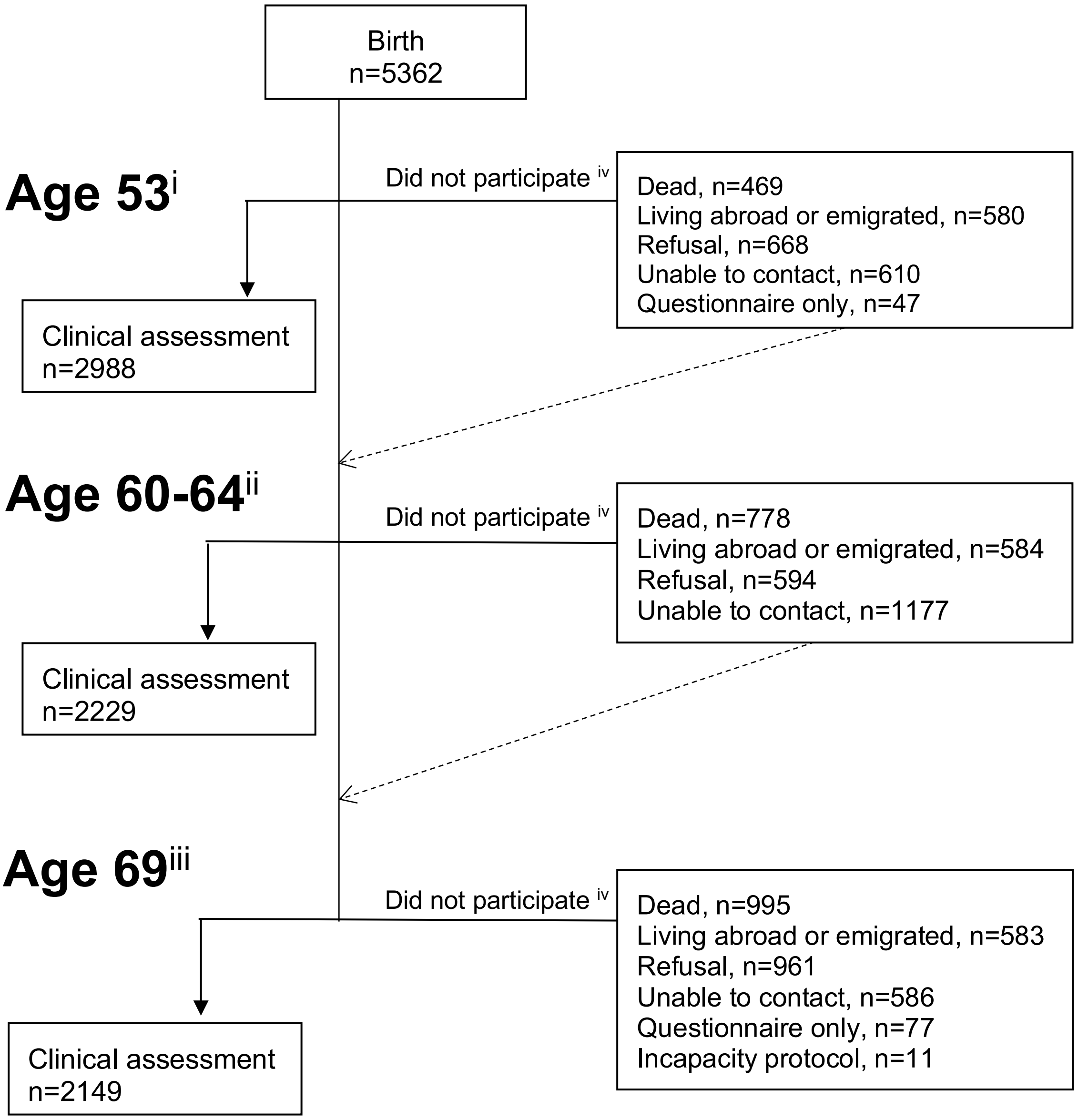
During childhood and adolescence, the main aim of the study shifted from the fertility questions outlined above to investigation of the role of home and school environments on physical and cognitive development. Into mid and later life, the main objective of the study has been to investigate lifetime contributors to adult health and function; recent data collections have focused on ageing outcomes and tests of physical and cognitive capability that may capture the ageing process [303].

2.1.2 Overview of participation rates

NSHD has consistently measured certain domains across the life course including socioeconomic indicators, physical measurements, psychological health, and cognitive ability. As the primary aims of NSHD have evolved over time, there have also been several changes in the types of data collected. In addition, many questions have been added or removed to reflect participant age, study aims and scientific priorities, societal influences of the time and direct recommendations from study members.

A major strength of NSHD has been the maintenance of high participation rates, allowing it to remain as representative as possible of the original sample and the general population born in Great Britain in the late 1940s. The proportion of individuals who participate at each individual data collection remains relatively high compared with other longitudinal studies. More than 75% of the target sample has responded at 22 or more of 24 waves [300]. At the most recent data collection, data was obtained from 2638/2816 (94%) of the target sample from either the postal questionnaire at age 68 or the home visit at age 69. Specific to the home visit, the respondent sample at the most recent data collection (age 69) was 2149/2698, representing 80% of the target sample [302]. Full details on participation rates and patterns at age 68-69 has been previously published [302]. Study members who did not participate in this data collection included those who had already died (n=995), emigrated (n=583), were unable to be contacted due to non-participation or who were untraced (n=586), permanently or temporarily refused (n=961), lacked capacity (n=11) or elected to only receive a postal questionnaire (n=77).

Figure 2.1 provides an overview of those lost to follow up at the nurse clinical assessments (at home or in the clinic) at ages 53 to 60-64 to 69. Minimising attrition is essential in order to minimise risk of bias. It has been well established in several studies, including NSHD, that those lost to follow up tend to have poorer cognitive and physical health and lower adult SEP [247,302,304-306]. As a birth cohort, there is information from earlier waves on all individuals lost to follow up; thus, it is possible to quantify many factors that may contribute to missingness.



[i] *Adapted from Wadsworth et al., 2006* [300]
[ii] *Adapted from Stafford et al., 2013* [303]
[iii] *Adapted from Kuh et al., 2016* [302]
[iv] *At each age, those who participated in clinical assessment and those who did not sums to 5362*

<---------- *individuals who had been living abroad, who had previously chosen not to participate or whose contact details changed had the opportunity to re-enter the study after missing a wave*

Figure 2.1 Flow chart indicating maximum available sample sizes for the clinical assessments at age 53, 60-64 and 69 in the MRC National Survey of Health and Development

2.1.3 Advantages and disadvantages of using NSHD data

In addition to the availability of prospectively ascertained data across life and high participation rates described above, there are several notable strengths in using this dataset to address the research objectives. First, NSHD allows multiple factors across life to be investigated which may help improve understanding of the aetiology and development of various age-related health conditions. The temporal sequence can be more easily investigated, whereas cohort studies with shorter follow-up are limited in their scope to investigate associations between early life factors and age-related health outcomes. In NSHD, there is much less recall bias than in cohorts that rely on retrospective recall of events from early life. Time between data collection waves – particularly in early life – is relatively short, reducing risk of recall bias even further. The readily available, prospectively collected data from every stage across life can provide valuable information on all participants; this enables investigation of confounding and mediating factors that may contribute to the associations of interest.

Second, the quantity and quality of the dataset is exceptional. Data quality is high; research nurses are given intensive training to ensure standardisation and reliability of data, health questions are checked against hospital records and specialists are employed to code disease events as well as clinical and dietary data [300]. Study data have been collected from not only the study members themselves but also by trained nurses, doctors, teachers and study members' mothers using questionnaires and objective measures at multiple time points.

Another advantage of NSHD for the purposes of these analyses is the age homogeneity of the sample. As all study members were born within the same week, any associations identified within the dataset can be examined independent of age. While studies commonly adjust for age, the complex interaction of age, period and cohort effects can still confound relationships when examining age-related outcomes [307].

Finally, the repeat data available within NSHD allows age-associated change to be investigated. This includes multiple measures of balance ability, cognitive ability and other time varying measures assessed throughout adult life. There are very few studies that have examined associations between early and midlife factors and balance, however there are none which have examined changes in balance over time. NSHD is unique in its repeat assessment of balance at ages 53, 60-64 and 69 and thus provide an optimal dataset to examine a life course approach to balance ability.

There are some limitations that must be acknowledged. While inferences can be made about the effect of the exposure variable on the outcome due to temporal sequence, the data are strictly observational with no intervention or controlled environment. Despite continual high participation in the study, those lost to follow-up in adult life were more likely to have lower SEP and poorer health [302]. Further exploration of the representativeness of the sample is explored in section 2.5 below. Finally, the sampling framework of NSHD aimed to select a representative sample of single births to married women that was generalisable to the rest of the population [299]. Although the study sample remains representative of those born in 1946, there are secular changes between generations such as differing family structures, changing ethnic distributions and different societal influences that may make the results less generalisable to younger generations within the United Kingdom (UK) and overseas [308,309].

2.2 Measurement of balance ability and key covariates in the MRC NSHD

Many studies assessing physical capability have examined older samples after decline has already begun to occur (i.e. ≥65). A series of physical performance tests were introduced in NSHD in adulthood at age 53. Measuring physical capability at age 53 enabled midlife balance ability to be captured, thus giving a reference to which subsequent age-related change can be compared.

2.2.1 Measurement of balance ability

Standing balance was assessed during clinical assessments at ages 53, 60-64 and 69. Home visits were conducted at ages 53 and 69, while study members attended a clinical research facility in Manchester, London, Edinburgh, Birmingham or Cardiff at age 60-64. For those unable or unwilling to attend the facility, research nurses conducted home visits (~20%) [305]. Trained nurses followed standardised protocols (see Appendix 2.1) when carrying out the assessment to ensure consistency both between individuals at each data collection point and within individuals over time. Nurses first explained the test procedure; study members were asked to fold their arms and, when indicated by the nurse, to stand on their preferred leg and raise their other foot off the floor. They were instructed to maintain this position for as long as they could or until the nurse told them to stop after 30 seconds. The nurses informed the study member that the test would be conducted with eyes open followed by eyes closed.

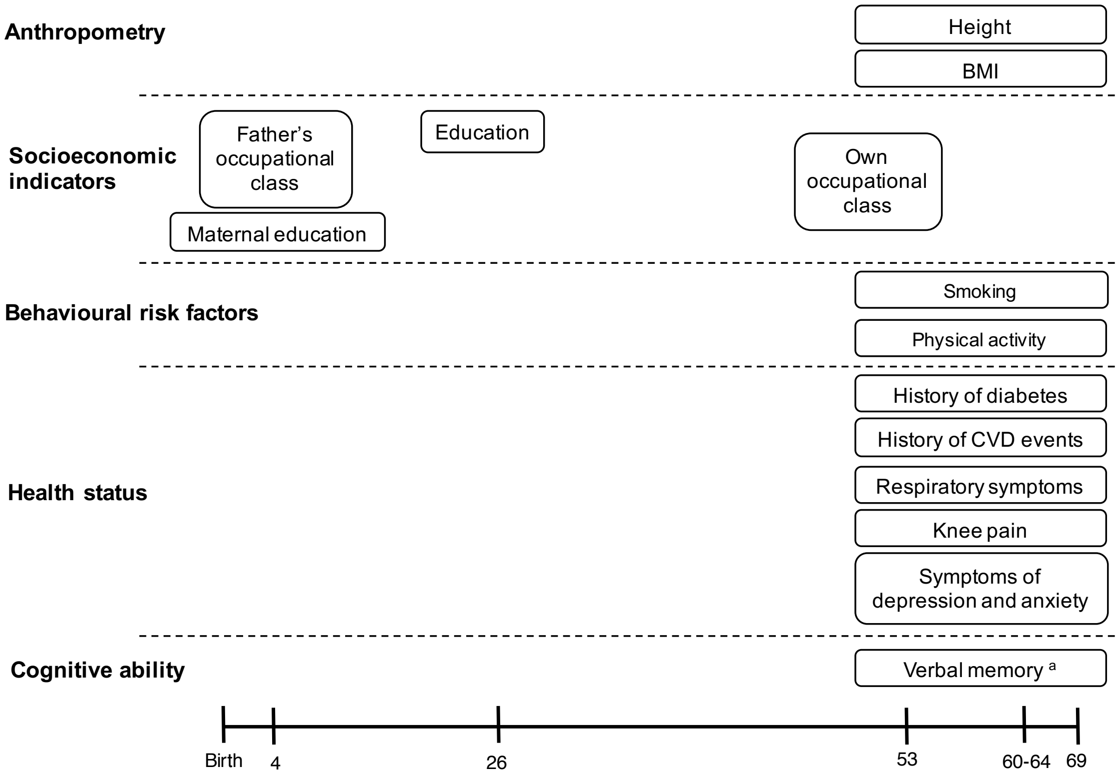
Those who were willing to complete the test were given the opportunity to practice before beginning. The nurse started the stopwatch when the study member's leg was raised off the ground and stopped the stop watch when a) the raised leg touched the ground if the individual lost their balance or b) after 30 seconds. The test was repeated with the study member's eyes closed. Total balance time for each test was recorded; balance was measured in seconds at age 53 and in milliseconds at ages 60-64 and 69.

If study members were not willing or able to do the tests, nurses were asked to report a reason. Reasons for not completing the test included being unable for health reasons, unable for other reasons (time restrictions, timer not functioning, room constraints, etc.) or unwilling (reason not specified). If participants were unable to complete the tests due to health reasons at age 60-64 or 69, the health reason was noted and later coded using International Classification of Diseases 10th Revision (ICD-10) codes [310]. At age 69, the most common reasons were inability or difficulty walking and standing (n=36), dizziness/vertigo (n=9) and musculoskeletal system or connective tissue disease (n=15) (e.g. pain in joint, osteoarthritis). Differences in individuals with and without a valid balance score are extensively explored in section 2.4. As these individuals missing data due to health reasons were conceptually similar – with similar balance times at other ages – to those with the lowest scores, their balance times were imputed with zero. After employing zero imputation, the final maximal available sample size of those who had a balance time at one or more ages was 3111 with eyes closed and 3128 with eyes open.

Due to the recognised ceiling effect of the eyes opened test, the majority of the sample was able to reach the maximum balance time of 30 seconds at all ages (46-69%). This is demonstrated and discussed in further detail in section 2.3. As a result of this, while a preliminary description of both eyes open and eyes closed data are provided in this chapter, subsequent chapters will focus on balance times with eyes closed only.

2.2.2 Measurement of main covariates

Covariates that are hypothesised to contribute to the relationship between the main exposures studied and balance are summarised below. These items were selected *a priori* for potential inclusion in analyses based on the review of the literature provided in Chapter 1 and can be separated into several domains: anthropometric indicators [128,151,251,311], socioeconomic indicators [158,159,251], health behaviours [175,177,204], physical and mental health status, and adult cognitive ability [171]. Figure 2.2 provides a summary of all covariates included throughout the thesis. Descriptions of the main variables of interest are provided in each individual chapter (Chapter 4: childhood cognitive ability; Chapter 5 and 6: adult cognitive ability; Chapter 7: falls), while Chapter 3 investigates how each covariate is associated with balance ability.



[a] *Note: verbal memory is also collected at age 43, but only scores at ages 53-69 will be used as covariates.*

Figure 2.2 Overview of all covariates used throughout the thesis

2.2.2.1 Anthropometric indicators

Height (m) and BMI (kg/m^2) were derived from height and weight measurements taken by nurses at ages 53, 60-64 and 69. BMI and height adequately capture the relevant aspects of body size and it has been recommended that these two measurements are considered together in studies of physical performance [312]. To avoid collinearity, weight was not included in analyses.

2.2.2.2 Socioeconomic indicators

The NSHD has collected data on multiple indicators of SEP in both childhood and adulthood. Examples of childhood indicators include maternal and paternal education, father's occupational class, housing tenure, deprivation of basic household amenities and household crowding, while adult indicators include household tenure, highest level of education at age 26, own occupational class, own income, and household income at several ages. Based on existing literature that has examined life course influences on physical capability [158,159] and preliminary investigation of how each relates to balance within the NSHD dataset, two measures of SEP from childhood and two from adulthood were chosen: maternal education, father's occupational class, own education level attained by age 26 and own occupational class. Each of these SEP indicators has shown reliability and consistency in other NSHD publications and are widely considered to be the most accurate indicators in this cohort. It was important to have multiple indicators of SEP in childhood as maternal education and father's occupational class are thought to demonstrate differing patterns of association with childhood development [313,314]. Furthermore, education and own occupational class are thought to capture two different dimensions of SEP; education is also thought to impact balance ability through a cognitive pathway and as such, these two adulthood SEP indicators are often used in separate stages of adjustment.

Consistent with previous NSHD analysis, paternal occupational class (at age 4) and own occupational class (reported at age 53 years) were classified using the Registrar General's Social Classification and grouped into the following three categories [315]: 1) I Professional and II Intermediate; 2) III Skilled (non-manual) and III Skilled (manual); and 3) IV Partly skilled and V Unskilled [170]. Maternal education was classified into four categories: 1) Primary only; 2) Primary and further education; 3) Secondary only; 4) Secondary and further education.

Participants reported their highest level of educational attainment by age 26; possible responses were 1) degree or higher, 2) General Certificate of Education (GCE) A level or Burnham B, 3) GCE O level or Burnham C, 4) Sub GCE or sub Burnham C, or 5) none attempted [316].

2.2.2.3 Behavioural risk factors

Behavioural risk factors such as smoking and physical activity have been measured multiple times throughout adult life. Contemporaneous indicators of each (at ages 53, 60-64 and 69) are used to represent the current health behaviour at the time of the balance test. Individuals reported the number of times per month that they participated in sports, vigorous leisure activities or exercise (never, 1-4 times/month, ≥5 times/month) and their smoking status (never, past smoker, current smoker). Current and past smokers were those who smoked at least one cigarette a day for 12 months or more; this was corroborated with reports at earlier ages (ages 20, 25, 31, 36 and 43).

2.2.2.4 Health status

Four measures of physical health (history of diabetes, history of cardiovascular events, respiratory symptoms and knee pain) and one measure of mental health (symptoms of depression and anxiety) were ascertained at ages 53, 60-64 and 69. In order to create harmonized health status variables from ages 53 to 69, dichotomous indicators of physical health were derived based on previous work in NSHD at ages 53 [317] and 60-64 [170,247]. These variables were selected *a priori* as they have been identified as health outcomes that may influence physical performance [170,247].

History of diabetes at ages 53, 60-64 and 69 (yes/no) was determined using both self-reported questions and doctor-diagnosed reports of either Type 1 or Type II diabetes. An individual was considered to have a *history of cardiovascular events* if they self-reported having a history of doctor-diagnosed stroke, angina or myocardial infarction at ages 53, 60-64 and 69. For both variables, positive reports of diabetes or cardiovascular events from previous data collection waves were used to populate missing data.

Respiratory symptoms were assessed at all three ages using the MRC Respiratory Questionnaire [318,319]. A study member was considered to have severe respiratory symptoms if they experienced one or more of the following: a wheezy or whistling chest most days or nights; usually bringing up phlegm or coughing in the morning, day or night in winter for at least 3 months each year; or more than one chest illness in the past 3 years that kept them off work or indoors for 1 week or more.

Knee pain was derived using a self-reported question with slight variation at each age. At age 53, study members were asked the following question: “In the last 12 months, have you had pain or stiffness in your left/right knee on most days for at least a month?” At age 60-64, individuals were considered to have knee pain if they answered yes to “In the last 12 months, have you had pain in and around your knees?” At age 69, study members were asked “In the last 12 months, have you had pain in your right/left knee on most days for at least a month?”

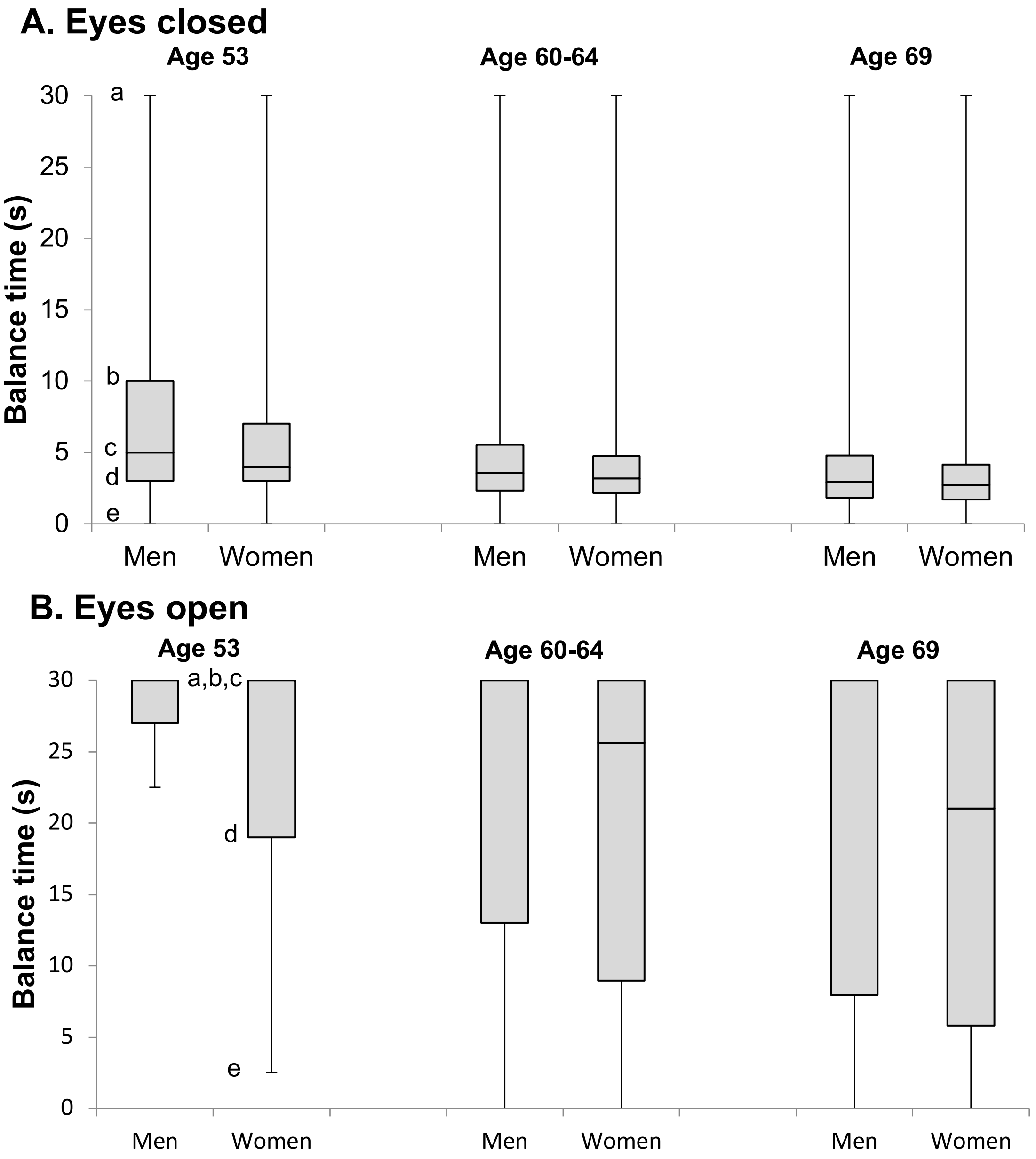
Symptoms of anxiety and depression were measured at ages 53, 60-64 and 69 using the 28-item self-reported General Health Questionnaire (GHQ-28) [320,321]. For each item, study members are asked to identify if they have recently experienced specific symptoms; possible response include ‘not at all’ (0), ‘no more than usual’ (1), ‘more than usual’ (2), ‘much more than usual’ (3). Each item is scored from 0 to 3 and summed giving a total score of 0 to 84, where a higher score indicates higher levels of anxiety and depression.

2.2.2.5 Cognitive ability

Measures of adult cognitive ability within NSHD are explored in further depth in Chapters 5 and 6, which aim to investigate associations between adult cognitive ability and balance. However, adult verbal memory (at ages 53, 60-64 and 69) is used as a covariate in other thesis chapters (Chapter 3, 4, 7) and as such is briefly outlined here. Verbal memory was assessed at ages 43, 53, 60-64 and 69 using three trials of a 15-item word-learning task. Each word was presented for 2 seconds, and study members were then asked to write down all of the words that they could remember (maximum score: 45) [322].

2.3 Characteristics of analytical sample

The following description is based on the maximum sample used in this thesis: 3111 individuals with a balance assessment at one or more age. Derivation of this sample size is provided in section 2.5. Median balance time with eyes closed decreased from 4 seconds (Quartile 1 (Q1), Quartile 3 (Q3): 3, 8) at age 53 to 3.32s (2.22, 5.19) at age 60-64 to 2.85s (1.75, 4.44) at age 69. Median balance ability with eyes open showed a similar trend, slightly decreasing with age from 30s (22, 30) at age 53 to 30s (10.16, 30) at age 60-64 to 25.22s (6.78, 30) at age 69. Wilcoxon signed-rank tests demonstrated that the declining patterns over time were statistically significant ($p<0.001$). When stratified by sex, men had significantly higher balance times than times than women for both eyes open and eyes closed ($p<0.005$); this held true at all ages (see Figure 2.3)



[a] maximum; [b] 75th percentile; [c] median; [d] 25th percentile; [e] minimum

Figure 2.3 Box and whisker plots demonstrating balance performance distributions for A) Eyes closed; B) Eyes open

T-tests were used to examine sex differences in all continuous covariates, while chi-square tests were used to examine sex differences in categorical covariates. Characteristics of the analytical sample (n=3111), stratified by sex, are described in Table 2.1 with means and standard deviations (SD). Men were taller than women at all three ages (p<0.001), however there were no differences in mean BMI. There were no sex differences in father's occupational class or maternal education. Men were more likely to have a higher occupational class (p<0.001) and higher education level (p<0.001) than women. There were no differences in leisure time physical activity at any age between men and women, although men were more likely to have a history of smoking (p<0.001 at all ages). Men were also more likely to have a history of diabetes or cardiovascular events, while women were more likely to have knee pain. There was no difference in prevalence of respiratory symptoms between men and women. At all ages, women had more symptoms of anxiety and depression as well as higher verbal memory scores than men (p<0.001 at all ages).

Table 2.1 Characteristics of total available analytical sample (n=3111), MRC National Survey of Health and Development [a]

	Men (n=1550)	Women (n=1561)	Tests of sex differences (p-value)
ANTHROPOMETRY, mean (SD)			
Height (m)			
Age 53	1.75 (0.07), n=1436	1.62 (0.06), n=1498	<0.001
Age 60-64	1.75 (0.09), n=1062	1.62 (0.06), n=1159	<0.001
Age 69	1.73 (0.09), n=1023	1.61 (0.06), n=1077	<0.001
BMI (kg/m^2)			
Age 53	27.4 (4.0), n=1435	27.4 (5.5), n=1486	0.89
Age 60-64	27.9 (4.1), n=1061	27.9 (5.5), n=1158	0.92
Age 69	28.2 (4.6), n=1040	28.2 (5.7), n=1081	0.91
SOCIOECONOMIC INDICATORS, n (%)			
Paternal occupational class			
I Professional/II Intermediate	407 (27.6)	383 (26.0)	0.56
III Skilled (non-manual/manual)	692 (46.9)	716 (48.7)	
IV Partly skilled/V Unskilled	377 (25.5)	372 (25.3)	
Maternal education			
Secondary and further education	162 (11.74)	169 (12.2)	0.49
Secondary only	167 (12.1)	153 (11.0))	
Primary and further education	213 (15.4)	193 (13.90)	
Primary only	838 (60.7)	873 (62.9)	
Highest household occupational class			
I Professional/II Intermediate	788 (51.6)	559 (36.1)	<0.001
III Skilled (non-manual or manual)	578 (37.8)	659 (42.6)	
IV Partly skilled/V Unskilled	162 (10.6)	329 (21.3)	

		Men (n=1550)	Women (n=1561)	p-value
Educational attainment at age 26				
Degree or higher		212 (14.5)	81 (5.5)	<0.001
GCE A level or Burnham B		408 (27.9)	343 (23.3)	
GCE O level or Burnham C		211 (14.4)	377 (25.6)	
Sub GCE		92 (6.3)	134 (9.1)	
None attempted		540 (36.9)	537 (36.5)	
BEHAVIOURAL RISK FACTORS, n (%)				
Leisure time physical activity				
Age 53	None	693 (47.9)	761 (50.4)	0.18
	1-4 times/month	270 (18.7)	245 (16.2)	
	≥5 times/month	485 (33.5)	503 (33.3)	
Age 60-64	None	681 (65.2)	716 (62.9)	0.52
	1-4 times/month	137 (13.1)	162 (14.2)	
	≥5 times/month	227 (21.7)	261 (22.9)	
Age 69	None	711 (59.9)	777 (61.3)	0.08
	1-4 times/month	135 (11.4)	170 (13.4)	
	≥5 times/month	341 (28.7)	320 (25.3)	
Smoking status				
Age 53	Current	343 (23.6)	339 (22.5)	<0.001
	Previous smoker	737 (50.8)	671 (44.5)	
	Never smoker	371 (25.6)	499 (33.1)	
Age 60-64	Current	137 (12.3)	142 (11.8)	<0.001
	Previous smoker	663 (59.5)	629 (52.1)	
	Never smoker	314 (28.2)	436 (36.1)	
Age 69	Current	123 (10.3)	111 (8.8)	<0.001
	Previous smoker	756 (63.5)	723 (57.2)	
	Never smoker	311 (26.1)	430 (34.0)	
HEALTH STATUS				
History of diabetes, n (%)				
Age 53		57 (3.1)	43 (2.4)	0.18
Age 60-64		129 (10.1)	99 (7.2)	<0.01
Age 69		175 (13.7)	136 (10.0)	<0.005
History of cardiovascular events, n (%)				
Age 53		85 (5.8)	48 (3.2)	<0.01
Age 60-64		131 (11.5)	62 (5.1)	<0.001
Age 69		193 (17.6)	114 (10.0)	<0.001
Respiratory symptoms, n (%)				
Age 53		292 (19.9)	276 (18.2)	0.22
Age 60-64		233 (20.1)	224 (18.2)	0.15
Age 69		264 (24.5)	266 (22.4)	0.23
Knee pain, n(%)				
Age 53		226 (15.5)	310 (20.6)	<0.001
Age 60-64		216 (20.3)	288 (24.6)	0.01
Age 69		190 (18.1)	241 (22.1)	0.02
Symptoms of anxiety and depression, mean (SD)				
Age 53		15.2 (7.3), n=1051	17.8 (8.9), n=1137	<0.001
Age 60-64		15.7 (8.6), n=1407	18.9 (10.3), n=1470	<0.001
Age 69		14.1 (7.5), n=1025	16.2 (8.2), n=1068	<0.001
OTHER Verbal memory, mean (SD)				
Age 53		23.0 (6.2), n=1397	24.9 (6.2), n=1473	<0.001
Age 60-64		23.0 (5.9), n=1023	25.4 (6.1), n=1127	<0.001
Age 69		21.2 (6.0), n=1005	23.1 (6.0), n=1057	<0.001

[a] *Analytical sample is based on 3111 individuals with at least one valid balance time. Thus, total n may not add up to 3111 at each age due to missing covariate data (see section 2.5.4 for investigation of missing covariate data)*

2.4 Analytical strategies

This section provides an overview of the statistical methods used throughout the PhD thesis. Note that the specific methodologies and variables used in each chapter may differ due to the chapter aims and objectives; however, the commonalities in statistical analyses across chapters are outlined below.

2.4.1 Non-normal distribution of data

The distribution of balance times was examined and assessed for deviation from normality. Figure 2.4 demonstrates the distribution of balance times with both eyes closed (Figure 2.4 A-C) and eyes open (Figure 2.4 D-E). Due to the heavy skew of the data, non-parametric statistics were used to model balance data throughout this thesis, while analyses that require Gaussian distributions (e.g. regressions) use log-transformed balance as an outcome [323]. As the mean and standard deviations are not the best measure of central tendency for skewed data, medians and interquartile ranges are used to describe balance times in the sample.

As shown in Figure 2.4, there is a strong ceiling effect in the eyes-open test as the majority of individuals were able to maintain their balance for the maximum time of 30 seconds. The proportion of those able to balance with their eyes open for the maximum time declines with age from 69% to 50% to 46% (Figure 2.4 D-F), but remains high. While men’s median balance time with eyes open at all three ages was 30 seconds, women demonstrate more variability across time with a median balance time of 30, 26 and 21 seconds at ages 53, 60-64 and 69, respectively. The high proportion of individuals able to reach the maximum time with their eyes open indicates that the assessment ability range of the test does not capture the full range of functional ability within the sample. It is for this reason that the analyses in this PhD thesis focus on the eyes-closed test.

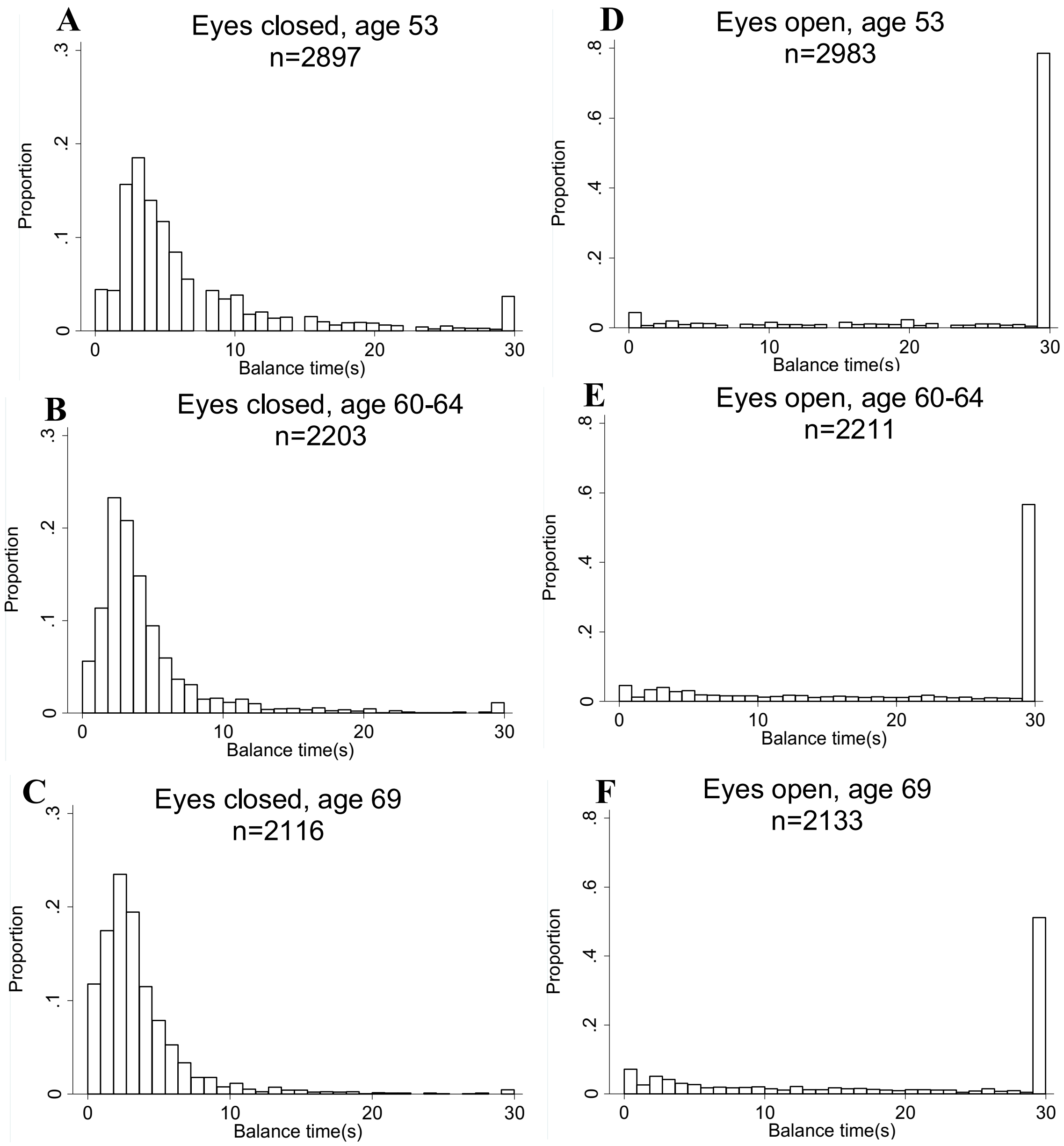


Figure 2.4 Balance distribution times of maximal sample at ages 53, 60-64 and 69 with A-C) eyes closed and D-F) eyes open

2.4.2 Multilevel modelling

Linear regressions are a basic type of regression analysis and are used to investigate the association between an independent variable and a continuous dependent variable [324]. These regressions estimate an outcome at a single time point and do not consider trends over time nor within-individual variation in balance performance over time.

In contrast to traditional regression models that treat each individual score as an independent observation, multilevel models (MLMs) recognise that an individual's outcome scores are correlated over time. Multilevel analyses consider the total variation in the model to be partitioned into variation attributable to individual factors as well as variation attributable to time or ageing. This allows the contribution of individual variation and variation over time to be simultaneously considered within a model. Furthermore, MLMs allow individuals without complete covariate or outcome data at all three ages to still be included in the analyses. This is explored further in section 2.5 on missing data strategies.

For all MLMs, the age intercept is set to zero at age 53. As the sample is age homogenous, the inclusion of age within the model refers to the expected variability in balance performance at different collection waves (i.e. ages 53, 60-64 or 69). Within MLMs, an integer is required for the time variable. As the mean age at the age 60-64 assessment was 63.2 (SD: 1.1), 63 was utilised for age 60-64. Continuous variables, including main exposures and covariates, are centred at the mean value; this allows the parameters to be interpreted in relation to mean scores as well as the time at first observation (i.e. the intercept). The covariance for each age and individual is unstructured, denoting that there are no constraints on the data such that each variance and covariance can be estimated uniquely from the data. As there are only three time points, it is not possible to test for any non-linear trends [35]; as such, no polynomial time terms are evaluated in the models. Potential interaction terms of the main exposure variable with both sex and age are tested to determine if the association between the exposure and outcome variables differs between men and women or across time. Other sex and age interaction terms for covariates are included if they are statistical significant at $p<0.05$. A significant age interaction term suggests that the association either strengthens or weakens with age; interpretation of these terms are explained in further detail in Chapter 3 (section 3.3.1). Tests of linearity are used to assess whether any exposure variables or covariates deviated from linearity in their association with balance. Although MLM are the optimal type of regression analyses employed throughout the thesis, both linear and logistic regression models will be used when time-varying outcomes are not possible (i.e. cross-sectional associations in Chapter 5 and associations between balance and falls in Chapter 7).

2.5 Missing data

This section explores components of missing data that are applicable to the full thesis. It is important to acknowledge and consider many types of missing data both in the modelling and interpretation of results [325-327]. There are several categories of missing data that are considered and discussed in detail below:

1) missing balance data (section 2.4.1);
2) individuals from the original sample (n=5362 at birth) who were lost to follow up before age 53 (section 2.4.2);
3) individuals within the study sample who did not participate in one or more clinical assessments between ages 53 and 69 (section 2.4.3);
4) missing covariate or main variable data (section 2.4.4).

2.5.1 Missing balance data

2.5.1.1 Describing missing balance data

Of the 2988 study members who received a clinical assessment at age 53 in 1999, 2893 completed an eyes open or an eyes closed balance test (96.8%); 2123 of 2229 (95.2%) eligible study members completed a balance test at age 60-64, while 2024 (94.2%) completed a balance assessment at age 69. There were 3023 individuals who had a valid time with eyes closed and 3059 with a valid time with eyes open for at least one age. Of these, 1591 (52.6%) and 1659 (54.2%) participants had a valid time for eyes-closed and eyes-open at all three ages. The participation status of study members on the balance tests at ages 53, 60-64 and 69 including reasons for missingness at each age is outlined in Figure 2.5.

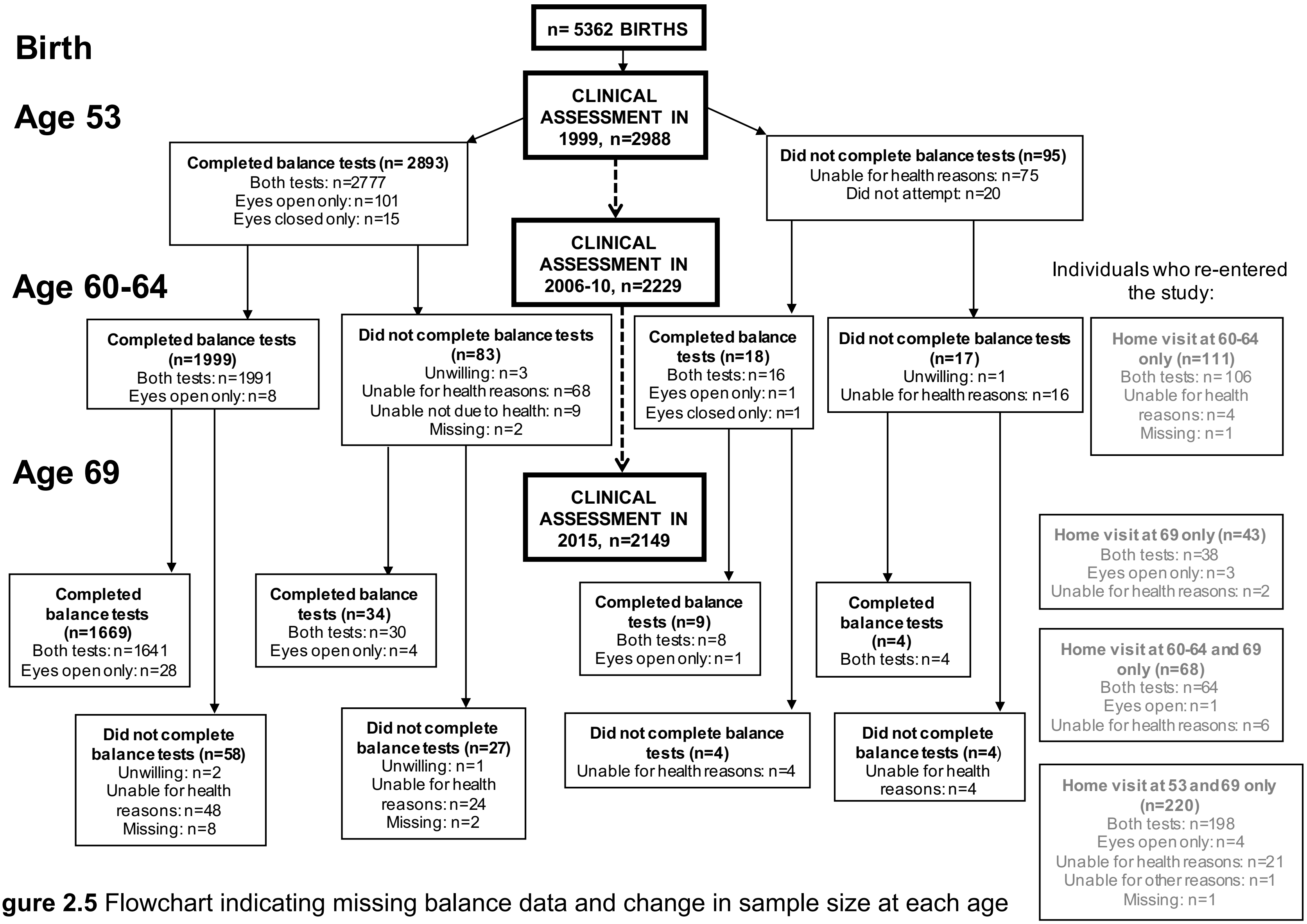


Figure 2.5 Flowchart indicating missing balance data and change in sample size at each age

There are a number of different reasons why, at any one age, individuals may have missing balance data: non-participation in the collection wave, refusal to attempt the test, inability to complete the test due to either health reasons, or other circumstances (e.g. room constraint, time restrictions of data collection, etc.). Refusals, room constraints and time restrictions were quite rare, while health difficulties and non-participation in the collection wave were more common (see Figure 2.5). Collecting information on the reason for not having completed the balance test provides information and an indication of what their balance ability may have been. For example, as identified in section 2.2.1, the most commonly reported health reasons were musculoskeletal, gait or vertigo-related. As many of these health problems impair balance ability [328-331], these individuals can be considered conceptually similar to those who performed worse on the balance test. It was hypothesised that those unable to complete the test due to health reasons would have performed worse than both those who completed the test and those who were unable to complete the test due to non-health related reasons. In the next section, this is tested by comparing the balance ability of different groups with missing data

2.5.1.2 Investigating missing balance data

To investigate if there are systematic differences in those with and without missing balance data, seven groups are considered including: a main reference group with a valid time at all three ages, groups with valid times at age 53 only, at age 60-64 only, at age 69 only, and three groups with a valid time at two of the three time points (ages 53, 60-64 only; ages 53, 69 only; ages 60-64, 69 only). Figure 2.6 outlines a Venn diagram indicating the seven groups of valid and missing balance data.

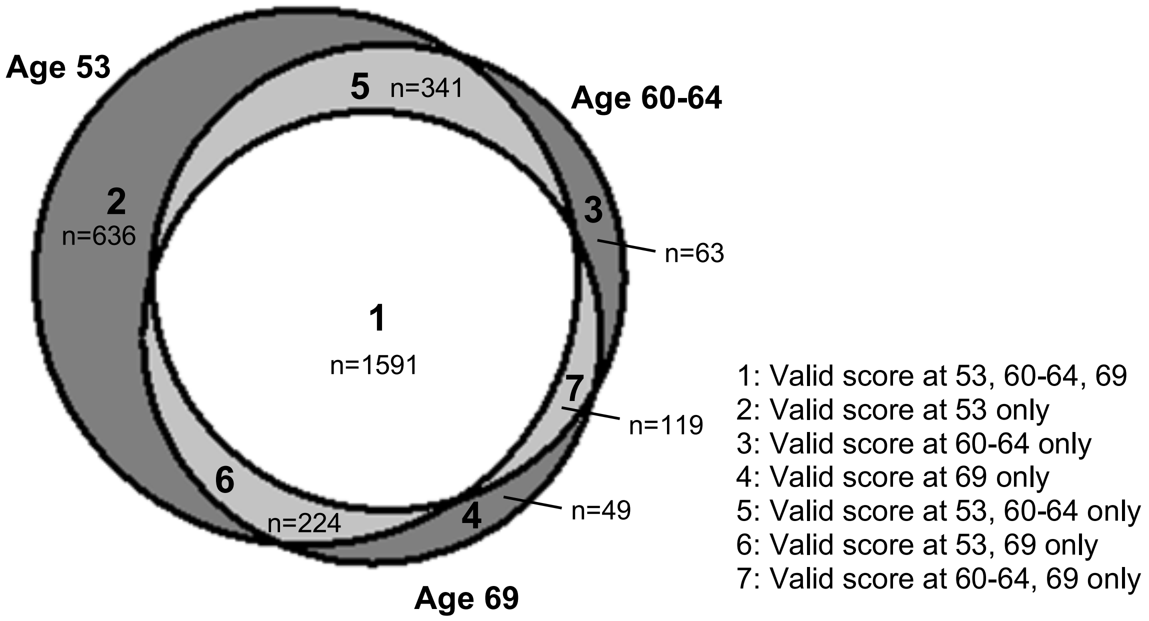


Figure 2.6 Venn diagram indicating valid and missing eyes-closed balance groups at ages 53, 60-64 and 69

Table 2.2 provides the median eyes-closed balance time for each of these groups at ages 53, 60-64 and 69 as well as the proportion of individuals who could maintain the position for 5 or more seconds. Five seconds has commonly been used as a cut-point for impaired balance [25,34]; although balance will not be dichotomised in the thesis, it is helpful to compare at this stage. Kruskal-Wallis and Dunn's tests are used to compare the balance times of each group with the main reference group (Group 1: those with a valid score at all three ages). Those who had an eyes-closed balance assessment at all three ages had significantly higher balance times than those who only underwent a balance assessment at either age 53 only (p<0.001, Table 2.2) or age 60-64 only (p<0.001, Table 2.2) but there were no differences with the group who only completed the test at age 69 (p=0.46, Table 2.2). Furthermore, those with a valid eyes-closed balance assessment at all ages tended to have a higher balance time than the groups with a valid balance measure at only two of the three time points (groups 5,6,7) (Table 2.2). These analyses suggest that those with missing data would have been more likely to have lower performance on the balance tests compared with their peers. The same patterns were observed for missing data in the eyes-open test (see Appendix 2.2).

Table 2.2 Median (Q1, Q3) eyes closed balance times (seconds) and proportion with balance >5seconds (%) by missing data groups at ages 53, 60-64 and 69

Group (n)	Description	Age 53		Age 60-64		Age 69	
		Median (Q1, Q3), % >5sec	p-value[¥]	Median (Q1, Q3), % >5sec	p-value[¥]	Median (Q1, Q3), % >5sec	p-value[¥]
1 (n=1591)	Valid time at 53, 60-64, 69	5 (3, 9) 45.4%		3.59 (2.47, 5.41) 28.9%		3.03 (1.98, 4.70) 21.8%	
2 (n=636)	Valid time at 53 only	4 (2, 6) 31.5%	<0.001	-		-	
3 (n=63)	Valid time at 60-64 only	-		2.84 (1.90, 3.90) 15.9%	<0.001	-	
4 (n=49)	Valid time at 69 only	-		-		2.85 (2.00, 4.77) 24.5%	0.46
5 (n=341)	Valid time at 53, 60-64 only	4 (3, 8) 36.4%	<0.001	3.00 (2.00, 4.83) 23.5%	<0.001	-	
6 (n=224)	Valid time at 53, 69 only	5 (3, 9) 44.2%	0.30	-		2.83 (1.97, 3.99) 18.5%	0.06
7 (n=119)	Valid time at 60-64, 69 only	-		3.37 (2.31, 4.94) 24.4%	0.15	2.69 (1.81, 4.31) 21.3%	0.04

[¥] Dunn's test for statistical differences from Group 1 (those with a valid balance time at all 3 ages)

Q1= quartile 1 (25th percentile); Q3= quartile 3 (75th percentile)

Next, it was assessed if the reason for non-participation at each age could inform why those with missing balance assessments had lower times at other ages. Study members were separated into three groups at each wave: those with a valid balance time, those unable to complete the tests for health reasons, and those who did not complete the test for non-health related reasons (including refusals, timer malfunction, lack of space/time, or no clinical assessment). It was hypothesised that those who were unable to complete the test due to health reasons would be more likely to perform poorly on the balance tests at other ages.

Compared with those with a valid score, those missing balance data at for any reason had lower balance times at all other ages (see Table 2.3). At age 53, this was only statistically significant for those missing data due to non-health reasons; non-significance in health reasons group may be due to a low number of individuals affected (n=32, n=24) or, more likely, because health reasons at age 53 were not specifically collected (i.e. specific health reason not recorded and thus no ICD-10 codes available). The results at age 60-64 and 69 suggest that poorer balance performance at earlier ages may be associated with missing data at later ages ($p<0.001$). As above, the same patterns were observed in the eyes-open balance test (see Appendix 2.3).

Table 2.3 Median (Q1, Q3) eyes closed balance times (seconds) by missing data groups at ages 53, 60-64 and 69

	Age 53		**Age 60-64**		**Age 69**	
	Median (Q1, Q3), n	**p-value¥**	**Median (Q1, Q3), n**	**p-value¥**	**Median (Q1, Q3), n**	**p-value¥**
AGE 53 status						
Valid time at age 53	-	-	3.5 (2.38, 5.33) n=1926	-	3.00 (1.98, 4.66) n=1811	-
Unable to complete due to health reasons	-	-	3.19 (2.23, 3.69) n=32	0.08	2.92 (2.18, 4.89) n=24	0.41
Missing data- unrelated to health reasons	-	-	3.23 (2.15, 4.57) n=156	0.02	2.67 (1.82, 4.30) n=148	0.05
AGE 60-64 status						
Valid time at age 60-64	5 (3, 9) n=1932		-	-	3 (1.97, 4.68) n=1710	
Unable to complete due to health reasons	3 (2, 6) n=66	<0.001	-	-	2.90 (1.41, 3.34) n=26	0.09
Missing data- unrelated to health reasons	4 (3, 7) n=794	<0.001	-	-	2.84 (1.99, 4.37) n=247	0.18
AGE 69 status						
Valid time at age 69	5 (3, 9) n=1815		3.57 (2.47, 5.34) n=1710		-	-
Unable to complete due to health reasons	3 (2, 5) n=102	<0.001	2.25 (1.62, 3.34) n=70	<0.001	-	-
Missing data- unrelated to health reasons	4 (3, 7) n=875	<0.001	3.11 (2.07, 4.83) n=334	<0.001	-	-

¥Dunn's test for statistical differences from Group 1 (those with a valid balance time at all 3 ages)
Q1= quartile 1 (25th percentile); Q3= quartile 3 (75th percentile)

2.5.1.3 Dealing with missing balance data

The above results demonstrate that there are systematic differences in balance times between those with a valid balance measure and those with missing data. These individuals are more likely to have poorer balance at other time points, suggesting that there may be a bias in the remaining sample towards better balance performance. Many imputation methods used for missing data (such as hot deck imputation, mean substitution, last value carried forward) do not fully address non-random reasons for missing data in this situation. This is because the reason for missing balance data provides explanatory information on one's balance ability (i.e. those missing balance scores for health reasons are expected to have lower balance), which would not be addressed using these imputation methods.

Zero imputation offers a simple and appropriate way to deal with missing balance scores. Replacing the missing time with zero for individuals who were unable to complete the test due to health reasons presents a valid alternative as it addresses the reason why they are missing data. This is based on the reasonable assumption that those unable to complete the test due to health reasons would have a very low balance time (as shown above). This approach is thought to minimise bias compared with any bias from excluding these individuals from analyses. Sensitivity analyses that exclude these individuals will replicate all thesis results to confirm that this approach does not alter the findings. Compared with those missing for health reasons, there was not sufficient theoretical justification for imputing missing balance times for non-health related reasons.

Individuals with missing data due to health reasons were given a balance time of 0 seconds at age 53 (n=113), 60-64 (n=89) and 69 (n=133). A total of 335 balance times were imputed in 277 individuals. Of these scores, 224 individuals had their balance time imputed once, 48 had their time imputed twice and five had their time imputed at all three ages. The total analytical sample was 3111 with eyes closed and 3128 with eyes open.

2.5.2 Individuals loss to follow-up before age 53

Previous publications in NSHD have extensively described the characteristics of study members who were lost to follow up before the first clinical visit at age 53. Those lost to follow-up were more likely to be male [303], have lower childhood and adulthood occupational class [302,303], demonstrate unhealthy behaviours (smoking, physical inactivity) [303], have lower verbal memory [303] and have poorer overall health [302]. Many of these characteristics (low SEP, unhealthy behaviours, lower cognition and lower health) are associated with poor physical capability, thus it is hypothesized that those who were loss to follow-up before age 53 may have had poorer balance ability. It is important to acknowledge this bias when interpreting the results throughout the thesis, which will be discussed further in Chapter 8.

There is heterogeneity within this main lost to follow-up group (see Figure 2.5). For example, unavoidable losses through death were high in infancy and, along with refusals, continues to increase with age; conversely, the number of study members who have emigrated or who cannot be contacted have remained relatively stable at ages 53 and 69. There was also some reversibility in loss to follow up, as individuals who were not included in previous waves were given the opportunity to re-enter the study (see sample sizes in Figure 2.5). This is captured in the section below.

2.5.3 Individuals lost to follow-up between ages 53 and 69

In addition to considering the characteristics of those lost to follow-up before age 53, it is also important to consider individuals within the analytical sample who participated in only one or two clinic visits between age 53 and 69. As described in Table 2.2, balance times were highest in those with valid balance assessments at three ages and lowest in individuals with balance assessments at only one age. Thus, individuals with lower balance times may be underestimated. This loss to follow up (due to mortality and other attrition) is a known source of bias for all health-related longitudinal studies [332] and thus must be addressed in analyses.

A major advantage of MLMs is that these individuals can still be included, which subsequently maximises the number of observations that are included in the model. However, MLMs assume that the missing data are missing at random and that censoring is non-informative [36]. As both mortality and attrition are non-random events that are expected to be correlated with balance ability; those lost to follow up are expected to have poorer balance ability than those who remained in the study. One longitudinal approach has suggested that adjusting for attrition and mortality may address this bias [333,334].

Following this approach [333,334], binary indicators for mortality and attrition (not due to death) were created. In 1971 (age 25), all study members were flagged for death notification on the National Health Service Central Register. For the analytical sample, death was dichotomised as alive at age 69 (by March 31st 2015) or died between ages 53 and 69. Attrition was dichotomised as participating in study at age 69 or permanent attrition between ages 53 and 69. The inclusion of separate attrition and death indicators allows for differences in death and non-death attrition to be captured. These indicators are included as the first stage of adjustment for all MLMs throughout the thesis.

2.5.4 Missing covariate and exposure variables

The final category of missing data that must be discussed is missing covariate and exposure data. NSHD continues to yield one of the highest response rates (>80% of target sample at each wave) of longitudinal studies due to the data collection strategies employed by the NSHD team throughout the study period. For example, the study team has continual interaction with study members such as sending annual birthday cards since age 15, holding birthday celebrations on their 65th and 70th birthdays, selective media interviews and public events as well as direct correspondence for clinically important results or individual queries [4, 37]. Furthermore, individuals who participate in a data collection wave have very little missing data at that wave; this is due to the use of research nurses and participant's engagement in questionnaires.

Throughout the thesis, sex-adjusted models in both the maximal available sample size and complete case analyses are presented; this enables comparison of the fully adjusted estimates to the sex-adjusted estimates within the same sample. To consider how missing covariates may impact the results, individuals with complete data were compared to those missing data on one or more covariates at each age. At all ages, individuals with missing data participated in less leisure time physical activity ($p<0.05$ at all ages), had lower educational attainment ($p<0.05$ at all ages) and had lower scores on the verbal memory test ($p<0.01$ at all ages). At age 69, individuals with missing data were also more likely to suffer from knee pain (22.3% vs 18.6%, $p=0.02$) and have higher levels of depression and anxiety (mean (SD): 16.2 (8.9) vs 14.5 (7.2), $p<0.001$). These differences will be considered in the interpretation of chapter findings.

2.6 Summary

This chapter provided an overview of the methods that will be used throughout the remainder of the thesis. The NSHD sample was described in detail including advantages (data quality, longitudinal, prospectively ascertained life course data, repeated measures) and limitations (observational data, loss to follow-up, changing generations). Measurement of balance and all covariates was described. This chapter also examined the biases in missing balance and investigated how best this should be handled. As those who were missing data due to both health reasons and other reasons were more likely to have poorer balance at other ages, zero imputation was deemed to be the best method to minimise missing balance data bias. Finally, the analytical strategies of the thesis were described, followed by a description of the analytical sample. Building on this introduction to the analytical strategy, sample and key variables, Chapter 3 will explore the association of each covariate with balance, specifically testing for sex differences and investigating whether these associations change with age.

CHAPTER 3: ASSOCIATIONS BETWEEN RISK FACTORS ACROSS LIFE AND SUBSEQUENT BALANCE ABILITY

Publication:
Blodgett JM, Cooper R, Kuh D, Davis DHJ, Hardy R. Associations between factors across life and balance ability in mid and later life: evidence from a British birth cohort study. *Frontiers in Sports and Active Living.* Special research topic: Balance and Ageing. 2020, 2:1-28. [see pg 321]

Numerous factors across life are associated with balance ability including anthropometry, socioeconomic indicators, health behaviours, health status, cognitive ability and mental health. A detailed literature review of this evidence was provided in Chapter 1 (section 1.4), while Chapter 2 (section 2.2.2) outlined how these factors were assessed and operationalised in NSHD as the main covariates used throughout the thesis. The aim of this chapter is to investigate the association between these covariates and subsequent balance ability. The introduction section (section 3.1) will briefly summarise the literature reviewed in section 1.4 (Chapter 1), highlight limitations of this research, identify gaps that this chapter will address and outline the objectives and hypotheses of the chapter (section 3.1.1). As in future analytical chapters, the methods (section 3.2), results (section 3.3), discussion (section 3.4) and conclusions (section 3.5) will follow.

3.1 Introduction

As seen in section 1.4 (Chapter 1), men have better average balance ability than women; this finding has been shown across a range of ages [137-140,150,152-154]. Low SEP across life appears to have a negative cumulative association with balance ability [159], with each life period of low SEP conferring an additional risk for poor balance. For example, a systematic review has shown that both childhood and adulthood SEP are separately associated with poorer balance [159,160]. Low levels of physical activity [197-199], smoking history [161], low cognitive ability [171] and higher levels of depression [335] in adulthood are also all associated with poor balance.

These risk factors are hypothesized to partially explain differences in balance ability between individuals. Further variation may be explained by differences in the rate and timing of development in early life, in the peak level achieved in early adulthood, and finally in the onset and rate of decline in mid and later life. The evidence summarised in section 1.4 has explored the association between the specified risk factor and balance at one point in life; no study has examined whether or not these associations change with age. This is particularly important in mid and later life. As described in section 1.1 (Chapter 1), balance is a complex process that relies on sensory input including visual cues, proprioception, vestibular processes as well as muscular strength and cognitive processing. Reliance on these aspects is likely to change with increasing age due to age-related physical and cognitive changes such as a decrease in visual acuity or decline in the musculoskeletal system. Thus, it is important to examine and understand if the role of each risk factor changes with age or if it remains constant over time. This can help establish whether these traditional risk factors play an important role at specific ages or if they are consistently important throughout the life course.

Studies of the associations of risk factors with balance do not commonly report on sex differences. While men have better average balance ability than women, the mechanism behind this is still not fully understood. For example, some studies have shown that these sex differences disappear when anthropometric indicators are included in the model [126,128,149,151] although others suggest there may be sex differences in processing of sensory input required for balance [336]. Section 2.5 (Chapter 2) demonstrated sex differences across the majority of covariates including height, BMI, adult SEP, health behaviours, cognitive ability and symptoms of depression and anxiety. It is therefore important to investigate if the association between each risk factor and balance differs in men and women.

3.1.1 Objectives and hypotheses

The primary objectives of this chapter are:

i) to investigate the associations of each risk factor with balance ability;
ii) to explore whether these associations change with age and sex.

As alluded to above, there are two distinct reasons for this aim. First, there are no investigations into traditional balance ability risk factors demonstrating distinct sex or age-related patterns. Identifying how these risk factors may change with age and sex will contribute novel evidence, particularly when considering a life course approach at different stages of adulthood. Second, each analytical chapter in this thesis investigates main variable(s) of interest and its association with balance. When considering potential mechanisms that may explain these associations, it is important to consider how each covariate may be associated with balance ability and thus how it may confound, mediate or moderate relationships between key exposures and balance.

Based on the literature, it is hypothesized that positive factors such as high SEP, low BMI, participation in healthy behaviours, absence of poor physical and mental health as well as higher adult cognitive ability will be associated with better balance ability. These associations are expected to be similar in men and women, although height and BMI may have different patterns of association. This is supported by evidence that shows that anthropometric indicators explain balance ability variation in women but not in men [150].

Physical and mental comorbidities become more common with age; as such, the associations of diabetes, knee pain, cardiovascular disease (CVD) events and symptoms of depression and anxiety with balance ability are expected to get larger with age. Conversely, as these factors become more important, the relative contribution of SEP in both childhood and adulthood is hypothesized to decrease. Behavioural factors such as physical activity and smoking are expected to demonstrate a constant association with balance ability at all ages.

3.2 Methods

3.2.1 Study sample and measurement of variables.

Individuals are included in analyses if they had a valid balance measurement at one or more age (n=3111, as derived in section 2.2.2 in Chapter 2). In order to maximise the power and available sample size, the maximal available sample size is used for analysis of each covariate, thus sample sizes for each analyses differ slightly.

Measurement of standing balance ability and each covariate were described in Chapter 2 (sections 2.2.1 and 2.2.3). In summary, the following covariates were taken at one time point: father's occupational class (age 4), maternal education (age 4), educational attainment (age 26), and household occupation class (age 53). The following variables were measured at ages 53, 60-64 and 69 and are thus considered time-varying covariates: height, BMI, leisure time physical activity, smoking status, all five indicators of physical and mental health, and verbal memory.

3.2.2 Statistical analyses

Multilevel models are employed to examine the association between each covariate (independent variable) and log-transformed balance ability (dependent variable). An alpha of 0.05 is used as the significance level for all interaction terms in order to parsimoniously build each model. The same steps are followed for analysis of each covariate.

First, all covariates are tested for deviation from linearity. Non-linearity of each continuous variable is assessed by inclusion of a quadratic term in regression models; where significant, it was maintained in all subsequent models. To determine how the categorical covariates (i.e. all indicators of SEP and health behaviours) are modelled, likelihood ratio tests compares the model fit of continuous and categorical versions of each ordinal confounder (i.e. maternal education, paternal occupational class, own occupation class, leisure time physical activity, smoking). If there is no difference in model fit between modelling the covariate as a continuous variable compared with a categorical variable, the covariate is modelled as a continuous variable to maintain parsimony. Where there is a significant difference, it remains modelled as a categorical variable.

This enables the most parsimonious model to be used for the remainder of the thesis.

Second, the presence of a sex interaction with each covariate is formally assessed; if statistically significant, all subsequent models are stratified by sex. If not significant, sex is adjusted for in all subsequent models. Third, interaction terms between age of balance test and each covariate are tested. Any significant age interaction terms are included in all subsequent models in the thesis. Significant interaction terms indicate that the association between the covariate and balance changed with age. Finally, all covariates, quadratic terms and significant interaction terms are included in a combined model in order to identify which variables are independently associated with balance.

3.3 Results

3.3.1 Sex, balance and the interpretation of model estimates

Women had worse balance ability than men (age 53; β=-0.188 [95% CI: -0.239, -0.136], p<0.001, see Table 3.1). As balance is log-transformed for all analyses, it is important to understand that there are two ways to present the model estimates. The two terminologies are outlined here and may be used interchangeably throughout the rest of the thesis. The first is that compared with men, women have 0.188 (95% CI: -0.239, -0.136) poorer balance on a log-transformed scale. The second, equivalent, statement is that women have 18.8% (13.6%, 23.9%) worse balance than men. Although the original estimates (e.g. β= 0.188) will be displayed in tables, the sympercents may be used more commonly in the text in order to ease interpretation for the reader [337].

There was a significant interaction between age and sex (β= 0.007 [95% CI: 0.003, 0.012], p<0.001, see Table 3.1). When the direction of the significant interaction term is opposite to the direction of the main estimate (i.e. positive age interaction term and negative main estimate or negative age interaction term and positive main estimate), this suggests that the association is getting smaller with age. For every additional year, the association between sex and balance decreased by 0.007 on a log-transformed scale or by 0.7%. Thus, at ages 60-64 and 69 respectively, women had 11.4% [-18.8% + (0.7*10)] and 7.0% [-18.8% + (0.7*16)] poorer balance than men. The intercept (estimate at age 53) and slope (age interaction term) for all variables are provided in the main table; estimates at ages 60-64 and 69 for factors that change with age are provided in Appendix 3.1.

For non-time-varying variables (i.e. sex and all SEP indicators), the effect of the age interactions on balance can be interpreted in two different ways. The first approach, as will be used throughout the thesis, suggests that the association between sex and balance decreases with age; this is undoubtedly visible as women have 18.8% poorer balance at age 53, followed by 11.4% at age 60-64 and 7.0% at age 69 (see Table 3.1, Figure 3.1). The second interpretation emphases the effect of sex on the slope; here, men have a steeper decline in balance ability. In Figure 3.1, the steeper decline in balance ability with increasing age in men compared with women can be seen as well as the decrease in the size of the association. For time-varying variables (i.e. body size, health behaviours, health status, verbal memory), MLMs represent cross-sectional associations and thus, no comments on the slope of balance can be made for these. As the main aim is to understand how these associations change with age and as most of the risk factors are time-varying, the focus will remain on the change in strength and size of association throughout the thesis.

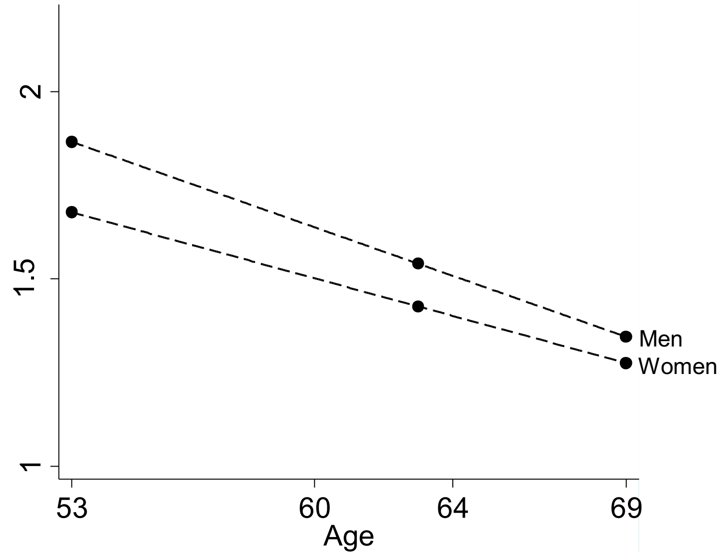


Figure 3.1 Sex differences in balance ability from ages 53 to 69

As the sex-age interaction is significant, this was carried forward in all models. Despite sex differences in balance ability across time, there were no interactions between sex and any of the other covariates. A summary of all sex and age interaction terms as well as non-linearity of covariates is provided in Table 3.2.

Table 3.1 Associations between covariates and log-transformed balance time (sec) at ages 53 to 69 in sex-adjusted multilevel models

			Change in balance time at age 53 per covariate unit (intercept)		**Age (yr)*covariate interaction**	
Covariates [a]		**n participants (n observations)**	**Coefficient (95% CI)**	***p-value***	**Coefficient (95% CI)**	***p-value***
1: Sex (female)		3111 (7216)	-0.188 (-0.239, -0.136)	<0.001	0.007 (0.003, 0.012)	<0.001
2: Height (cm)	linear term	3090 (7144)	0.125 (0.064, 0.187)	<0.001	Not significant	0.11
	quadratic term		-0.0004 (-0.0005, -0.0002)	<0.001		
3: BMI (kg/m^2)		3083 (7150)	-0.028 (-0.031, -0.025)	<0.001	Not significant	0.59
4: Paternal occupational class [b] (per 1 level change)		2947 (6838)	-0.148 (-0.184, -0.111)	<0.001	0.005 (0.002, 0.008)	<0.001
5: Maternal education [c] (per 1 level change)		2768 (6424)	-0.113 (-0.238, -0.088)	<0.001	0.004 (0.002, 0.006)	<0.001
6: Education at age 26 [d] (per 1 level change)		2935 (6830)	-0.111 (-0.129, -0.093)	<0.001	0.003 (0.002, 0.005)	<0.001
7: Own occupational class [b] (per 1 level change)		3075 (7167)	-0.152 (-0.179, -0.126)	<0.001	Not significant	0.14
8: Leisure time physical activity		3094 (6960)				
Ref: None						
1-4 times/month			0.239 (0.173, 0.305)	<0.001	-0.007 (-0.013, -0.0002)	0.08 [h]
≥5 times/month			0.233 (0.180, 0.287)		-0.004 (-0.009, 0.001)	
9: Smoking status (per 1 level change)		3092 (6996)	0.061 (0.033, 0.089)	<0.001	Not significant	0.53
10: History of diabetes		3111 (7214)	-0.180 (-0.244, -0.116)	<0.001	Not significant	0.89
11: History of cardiovascular events		3072 (6895)	-0.191 (-0.254, -0.129)	<0.001	Not significant	0.46
12: Respiratory symptoms		3062 (6634)	-0.086 (-0.127, -0.045)	<0.001	Not significant	0.48
13: Knee pain		3108 (7173)	-0.108 (-0.170, -0.046)	<0.001	-0.007 (-0.012, -0.001)	0.02
14: Symptoms of anxiety/depression (per 1 SD)		3071 (7032)	-0.053 (-0.077, -0.028)	<0.001	0.003 (-0.005, -0.0004)	0.02
15: Adult verbal memory (per 1 SD)		3035 (6979)	0.134 (-0.110, 0.159)	<0.001	-0.004 (-0.006, -0.002)	<0.001

[a] all models adjusted for sex; no sex interactions (see Table 3.2); [b] ref: I Professional or II Intermediate; [c] ref: Secondary and further education; [d] ref: Degree or higher; [e] ref: Current smoker; [f] red: Individuals with no health condition; [g] SD estimates at each age are provided in Table 2.1; [h] although p<0.05 was used as cut-point, p=0.04 for 1-4 times/month and p=0.12 for ≥5 times/month. Therefore, age interaction was included. See Figure 3.5A.

Table 3.2 Summary of tests of non-linearity, sex interactions and age interactions of all covariates with balance

	Description of how variable is modelled	Sex interaction p-value	Age interaction effect on size of association
Sex (female)	n/a[a]	n/a	↓ with age
Anthropometry			
Height	Quadratic term	0.95	Constant with age
BMI	Linear term only	0.08	Constant with age
Socioeconomic indicators			
Paternal occupational class	Continuously [b]	0.95	↓ with age
Maternal education	Continuously [b]	0.68	↓ with age
Education	Continuously [b]	0.53	↓ with age
Own occupational class	Continuously [b]	0.44	Constant with age
Health behaviours			
Leisure time physical activity	Categorically	0.70	↓ with age
Smoking	Continuously [b]	0.06	Constant with age
Health status			
History of diabetes	n/a[a]	0.51	Constant with age
History of cardiovascular events	n/a[a]	0.17	Constant with age
Respiratory symptoms	n/a[a]	0.55	Constant with age
Knee pain	n/a[a]	0.81	↑ with age
Symptoms of anxiety/depression	Linear term only	0.39	↑ with age
Other			
Verbal memory	Linear term only	0.22	↓ with age

[a] *Unable to test non-linearity in dichotomous indicators*

[b] *See Appendix 3.2 for the categorically-modelled estimates*

3.3.2 Anthropometric indicators and balance

Height had a quadratic association with balance ($p<0.001$; Table 3.1), such that taller individuals had better balance than shorter individuals but this effect appeared to plateau after a given height (i.e. 1SD or 177cm) (see Figure 3.2). BMI had an inverse linear association with balance, where every additional kg/m^2 was associated with 2.8% poorer balance ability ($p<0.001$; Table 3.1, Figure 3.3). Note that in Figure 3.2, height was graphed on the x-axis to allow the quadratic association to be visually demonstrated. Neither height nor BMI had an interaction with age suggesting that the cross-sectional associations stayed constant with age.

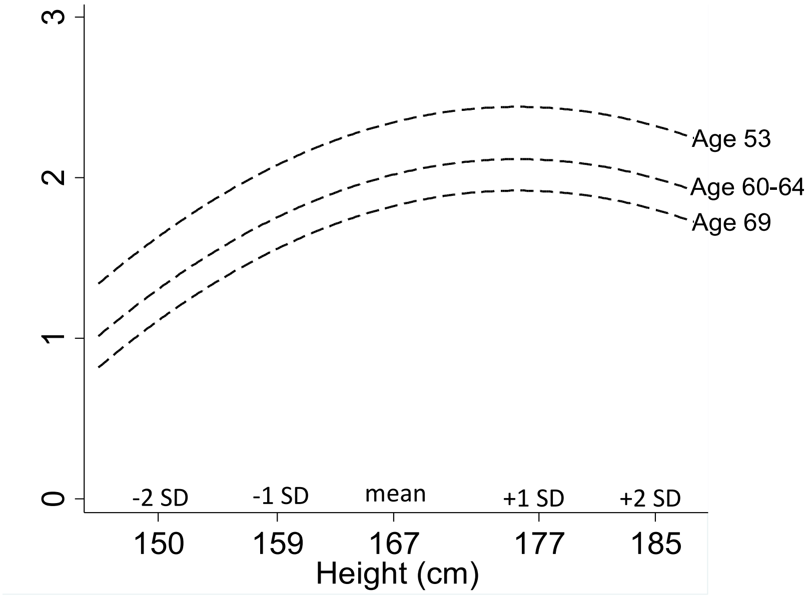


Figure 3.2 Differences in balance ability by height (cm) at ages 53, 60-64 and 69

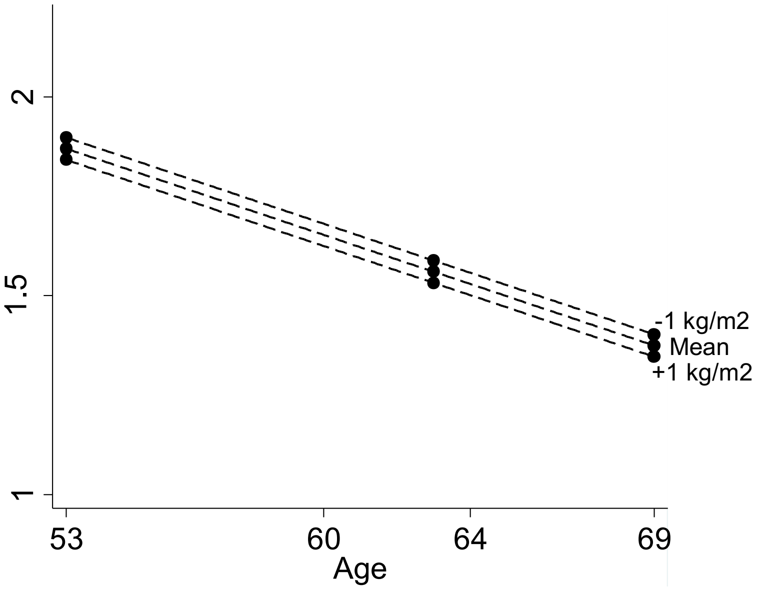


Figure 3.3 Differences in balance ability by BMI (kg/m^2) at ages 53, 60-64 and 69

3.3.3 Socioeconomic indicators and balance

For all four socioeconomic indicators, likelihood ratio tests suggested that there was no statistical difference between a model in which the indicator was modelled continuously and one in which the indicator was modelled categorically. As such each indicator was modelled as a continuous variable. For all models in Table 3.1, the baseline is the highest level of SEP (i.e. I Professional/II Intermediate social class; secondary and further maternal education; degree or higher education), with each unit change representing decreasing SEP levels. Appendix 3.2 provides the estimates for SEP modelled categorically; these estimates confirm that there is a linear decrease in balance ability with diminishing levels of SEP.

Low paternal occupational class was associated with 14.8% (95% CI: 11.1, 18.4%, p<0.001, Table 3.1, Figure 3.4A) poorer balance for each subsequent level. Each decreasing level of maternal education was associated with 11.3% (95% CI: 11.1, 18.4%, p<0.001, Table 3.1, Figure 3.4B) worse balance ability. Lower levels of educational attainment by age 26 were also associated with worse balance ability (p<0.001, Table 3.1, Figure 3.4C); using those with a degree or higher as baseline, each decreasing level of education was associated with an 11.1% (95% CI: 9.3, 12.9%) decrease in balance ability. Finally, having a low occupational class at age 53, was associated with a 15.2 % (95% CI: 12.6, 17.9%, p<0.001, Table 3.1 Figure 3.4D) decrease in balance ability for each decreasing level.

Notably, paternal occupational class, maternal education and educational attainment all had significant interactions with age (all p<0.001, Table 3.1, Figure 3.4), indicating that the association between the socioeconomic indicator and balance became smaller with age. There was no interaction between own occupational class and age (p=0.14).

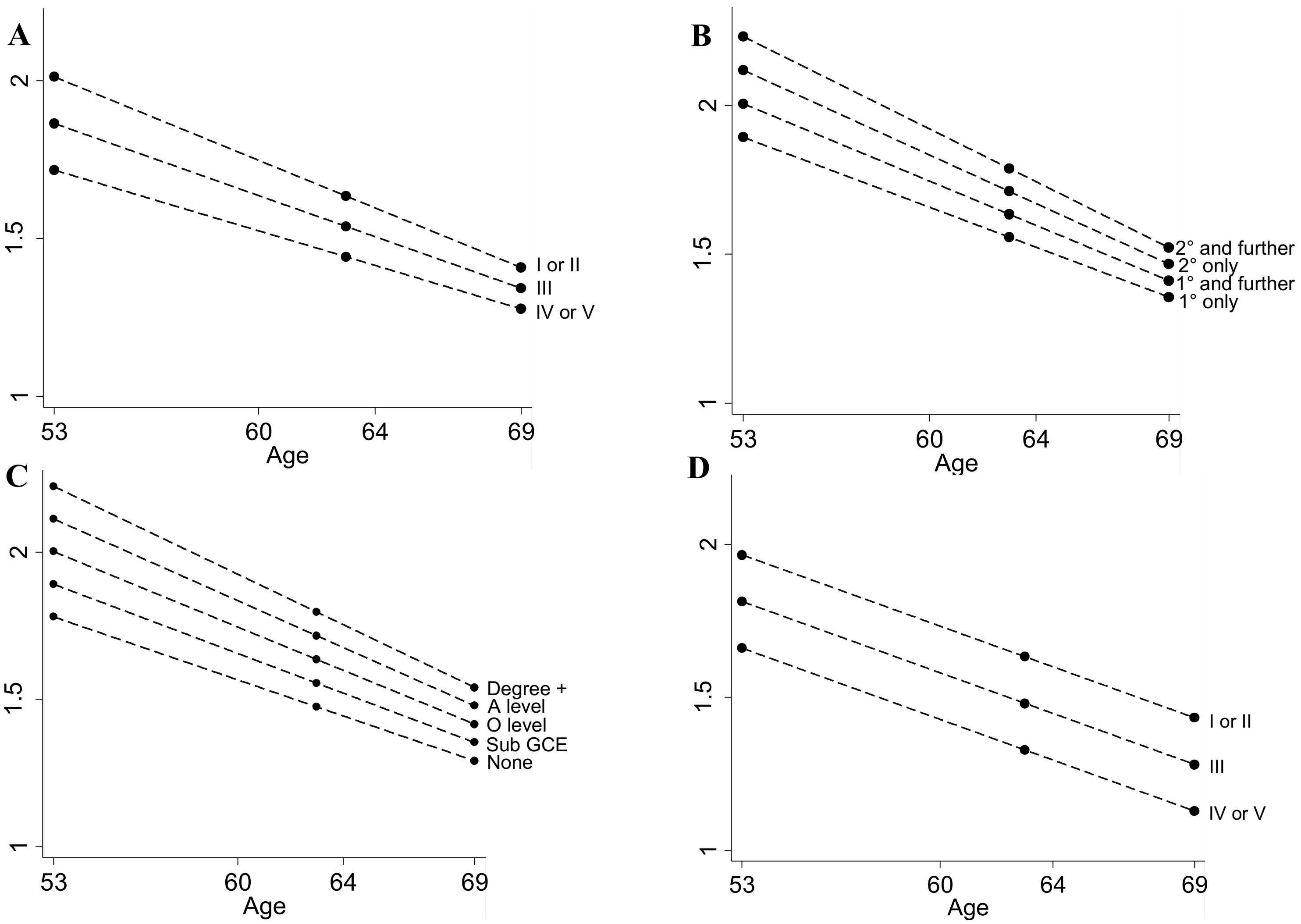


Figure 3.4 Differences in balance ability at ages 53, 60-64 and 69 by A. paternal occupational class, B. maternal education, C. education, and D. own occupational class

3.3.4 Health behaviours and balance

Compared with those who had participated in no leisure-time physical activity in the last four weeks, those who participated 1-4 times (23.9%, 95% CI: 17.3, 30.5%; p<0.001, Table 3.1, Figure 3.5A) and ≥5 times per month (23.3%, 95% CI: 18.0, 28.7%; p<0.001, Table 3.1, Figure 3.5A) had significantly better balance ability. At age 53, there was no difference in balance ability between those who exercised 1-4 times/month and those who exercised ≥5 times/month. However, this association changed with age for the 1-4 times/month group (p=0.04), such that there was a distinct benefit of exercising ≥5 times/month compared to 1-4times/month (see Figure 3.5A). Due to results of the likelihood ratio tests, physical activity levels were modelled categorically for the remainder of the thesis.

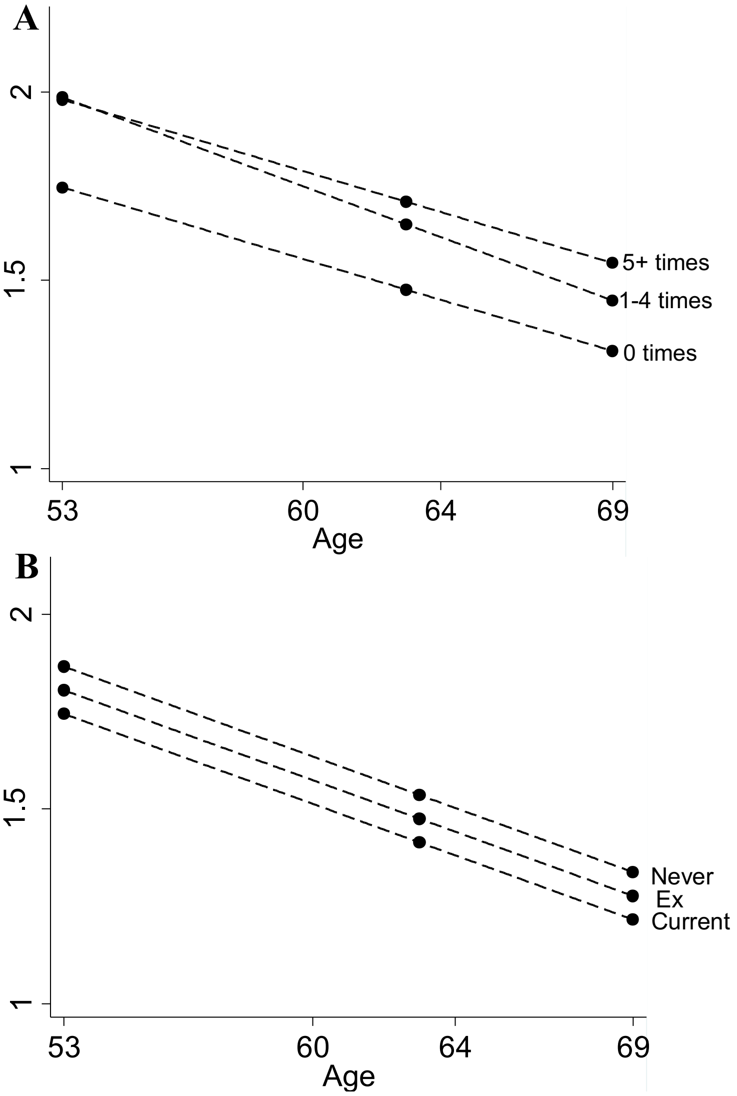


Figure 3.5 Differences in balance ability at ages 53, 60-64 and 69 by A. leisure time physical activity and B. smoking status from ages 53 to 69

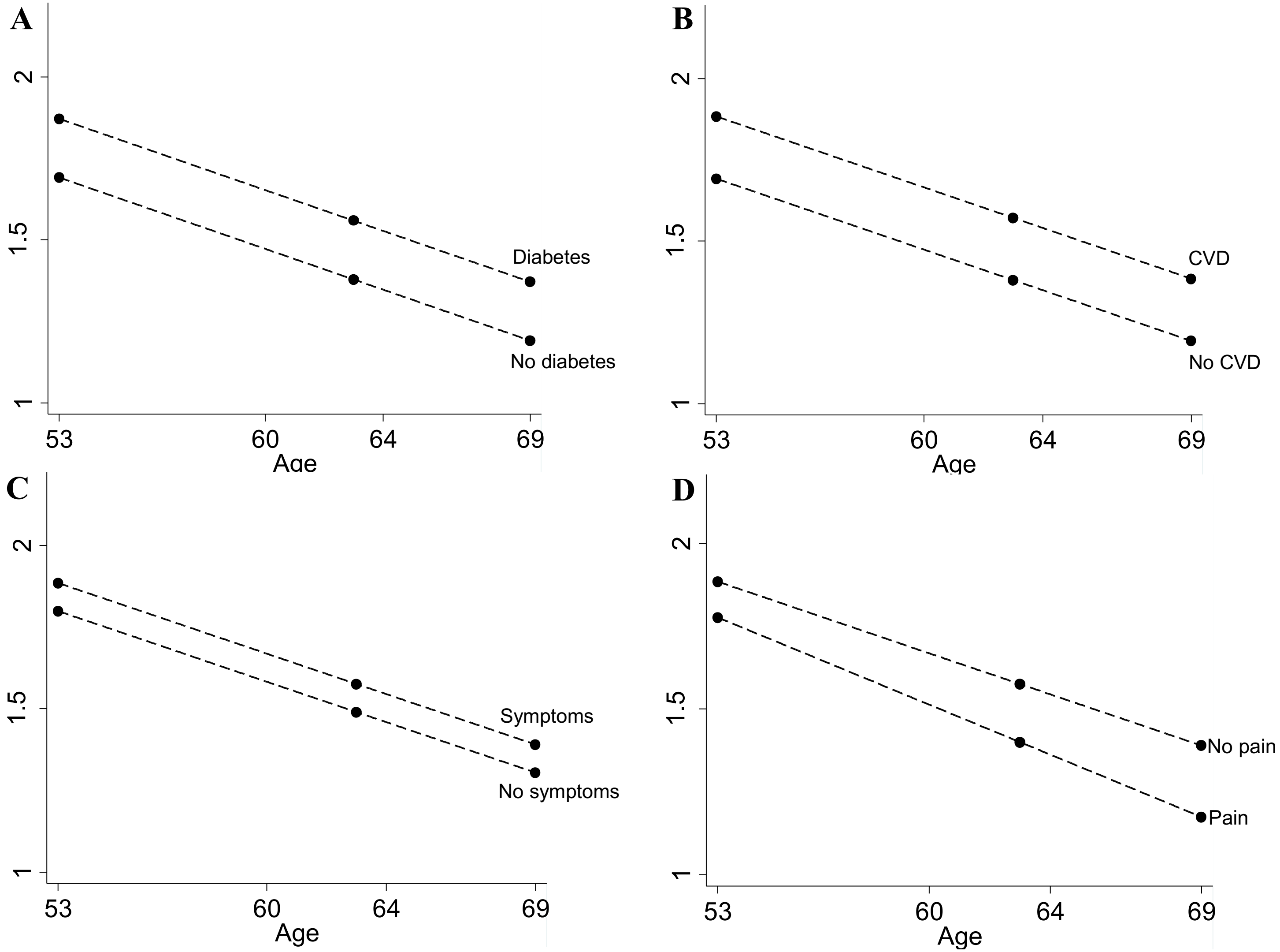
Individuals who had a past history of smoking or who were current smokers had significantly worse balance ability than those who had never smoked (6.1%, 95%CI: 3.3, 8.9%; p<0.001, Table 3.1, Figure 3.5B). There appeared to be a linear increase with the best balance ability in those who had never smoked, followed by those who were ex-smokers and finally those who were current smokers; Appendix 3.2 provides the estimates for categorically modelled smoking. There was no evidence that this cross-sectional association changed with age (p=0.53).

3.3.5 Health status and balance

Individuals who had a history of diabetes, a history of cardiovascular events or current respiratory symptoms had 18.0% (95%CI: 11.6, 24.4%, p<0.001, Table 3.1, Figure 3.6A), 19.1% (95% CI: 12.9, 25.4%; p<0.001, Table 3.1, Figure 3.6B) and 8.6% (95%CI: 4.5, 12.7%, p<0.001, Table 3.1, Figure 3.6C) worse balance ability, respectively. These cross-sectional associations remained constant with age (diabetes interaction: p=0.89, cardiovascular events: p=0.46, respiratory symptoms: p=0.48). Conversely, the association between knee pain and balance ability appeared to get larger with age (0.7% per year, 95% CI: 0.1, 1.2%, p=0.02) such that those with knee pain at age 53 had 10.8% (95% CI: 4.6, 17.0%; p<0.001) worse balance ability, while those with knee pain at age 69 had 21.6% (95% CI: 15.4, 27.8%, p<0.001) worse balance ability than those with no knee pain (Table 3.1, Figure 3.6D).

Every standard deviation increase in depression and anxiety symptoms on the GHQ-28 questionnaire was associated with a 5.2% (95% CI: 2.8, 7.7%, p<0.001, Table 3.1, Figure 3.7) decrease in balance ability at age 53. As with knee pain, this cross-sectional association increased with age by 0.3% per year (95% CI: 0.04, 0.5%). By age 69, 1 SD increase in GHQ-28 score was associated with a 9.5% (95% CI: 7.0, 11.9%, p<0.001) decrease in balance ability.

Figure 3.6 Differences in balance ability by A. history of diabetes, B. history of CVD, C. respiratory symptoms, and D. knee pain



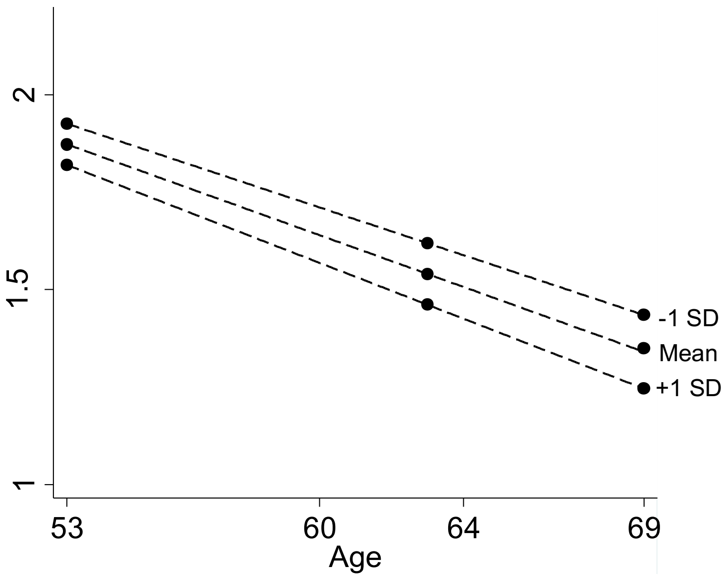


Figure 3.7 Differences in balance ability at ages 53, 60-64 and 69 by symptoms of depression and anxiety

3.3.6 Verbal memory and balance

One standard deviation increase in verbal memory was associated with a 13.4% (11.0, 15.9%, p<0.001, Table 3.1, Figure 3.8) increase in balance ability. Verbal memory was also a time-varying variable and this association got smaller with age (0.5% per year, 95% CI: 0.3, 0.7%, p<0.001). However, it remained significantly associated with balance by age 69 (5.1%, 95% CI: 2.6, 7.5%). This association is only briefly discussed in this chapter, as the association between adult cognitive ability and balance is explored in more detail in Chapters 5 and 6.

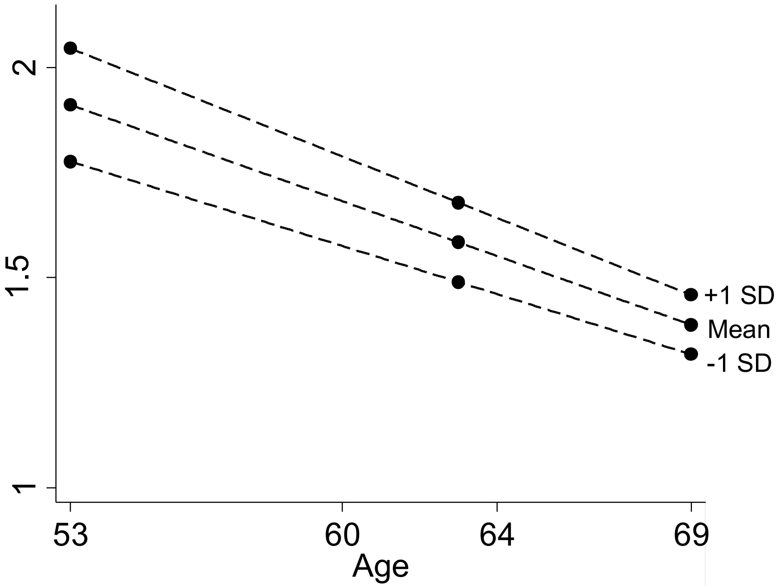


Figure 3.8 Differences in balance ability at ages 53, 60-64 and 69 by adult verbal memory scores

3.3.7 Combined model of all covariates and their associations with balance

Table 3.3 provides the estimates for a mutually-adjusted model of all covariates and the relevant age interaction terms. Notably, being female, higher BMI, lower maternal education, lower educational attainment, lower own occupational class, lower levels of leisure time physical activity, history of CVD events, higher levels of anxiety and depression and lower verbal memory were independently associated with lower balance ability. Nearly all age interactions terms were no longer statistically significant in this model, although there remained evidence that the effect of sex and verbal memory still decreased with age independent of the other covariates. Both attrition and death were included in this final model.

Table 3.3 Combined model demonstrating associations between covariates and log-transformed balance time (sec) at ages 53 to 69 in multilevel models

Covariates [a b]		**Change in balance time at age 53 per unit change (intercept)**		**Age (yr)*covariate interaction**	
		Coefficient (95% CI)	***p-value***	**Coefficient (95% CI)**	***p-value***
Sex (female)		-21.7 (-28.7, -14.7)	<0.001	0.9 (0.4, 1.3)	<0.001
Height (m)	linear term	5.0 (-1.6, 11.6)	0.13	-	-
	quadratic term	-0.02 (-0.04, 0.004)	0.12		
BMI (kg/m^2)		-2.1 (-2.5, -1.7)	<0.001	-	-
Paternal occupational class		-2.7 (-6.8, 1.5)	0.21	0.3 (-0.1, 0.7)	0.11
Maternal education		-3.9 (-6.7, -1.0)	<0.01	0.1 (-0.2, 0.3)	0.51
Education at age 26		-3.8 (-6.2, -1.3)	<0.005	0.2 (-0.1, 0.4)	0.07
Own occupational class		-4.9 (-8.2, -1.7)	<0.005	-	-
Leisure time physical activity					
1-4 times/month		9.1 (1.9, 16.3)	<0.001	0.1 (-0.6, 0.8)	0.28
≥5 times/month		5.8 (-0.2, 11.8)		0.3 (-0.3, 0.9)	
Smoking		1.4 (-1.6, 4.4)	0.36	-	-
History of diabetes		-6.9 (-14.1, 0.5)	0.07	-	-
History of CVD events		-7.1 (-14.0, -0.3)	0.04	-	-
Respiratory symptoms		-2.5 (-7.0, 2.0)	0.28	-	-
Knee pain		-4.5 (-11.2, 2.1)	0.18	-0.2 (-0.8, 0.4)	0.55
Symptoms of anxiety/depression		-3.1 (-5.8, -0.4)	0.02	-0.1 (-0.4, 0.2)	0.46
Verbal memory		5.9 (2.8, 8.9)	<0.001	-0.4 (-0.7, -0.1)	<0.01

[a] *Model is also adjusted for attrition and death;* [b]*n=2465 (obs=5150)*

3.4 Discussion

3.4.1 Main findings

This chapter explored the associations between key covariates and balance at ages 53, 60-64 and 69. Individuals with better balance ability were more likely to be male, be taller, have lower BMI, have higher SEP in both childhood and adulthood, partake in leisure time physical activity and were less likely to smoke. Individuals with better balance ability were also more likely to be healthier (no history of diabetes or CVD, not currently experiencing respiratory symptoms or knee pain), less likely to be experiencing symptoms of depression and anxiety, and have higher verbal memory. There was no evidence to suggest that these associations differed by sex.

Several of these associations weakened with increasing age (sex, socioeconomic indicators, physical activity, and verbal memory), while others stayed constant across the three ages (anthropometric indicators, smoking, and physical health status). Two associations grew larger with age; the associations of both knee pain and symptoms of anxiety and depression with balance doubled from age 53 to 69. In a combined model, the majority of covariates remained independently associated with balance, indicating that the factors across life that contribute to balance are multifaceted and complex. When interpreting the relationship between a single exposure of interest and balance ability, it is important to consider how these covariates may contribute to potential pathways.

3.4.2 Comparison with other studies and explanation of findings

The findings of this chapter are consistent with studies that have identified these covariates as contributing factors to balance. However, the majority of previous studies have focused on balance (or physical capability) at one time point, and have not considered how these associations change with age. This chapter provides novel insight into how these associations differ at different stages of mid and later life.

3.4.2.1 Anthropometric indicators

Height and BMI are commonly used as covariates in physical capability studies due to their known influence on health and capability [138]. Several studies have reliably shown that higher BMI is associated with poor balance [312,338]. Higher body mass can influence the stability of an individual and the motor mechanisms involved in the balance process. Individuals with higher BMI often require more movement in order to maintain their balance and thus frequently demonstrate high levels of postural sway and reduced balance performance [312,339]. Evidence from previous studies has shown that taller individuals perform better on balance tests, which is consistent with the pattern shown in this chapter [45,150]. However, lab-based studies have reported that body stability is inversely related to the height of the centre of gravity and as such, taller individuals demonstrate higher levels of postural sway [312,340,341]. This may explain the non-linear association between height and balance (see Figure 3.2).

3.4.2.2 Socioeconomic indicators

A systematic review and meta-analysis of over 22 000 individuals from 11 separate studies reported that lower childhood SEP was associated with inability to balance with eyes open for ≥ 5 seconds in adulthood in unadjusted models [159]. Similar measures of balance (one-legged stand) and childhood SEP (occupational class, maternal education) from this thesis were used in the study, enabling some comparison of results. Childhood SEP may contribute to balance ability through a number of direct and indirect pathways including cognitive and motor development, health behaviours, education and cognitive ability as well as lifelong health and functional ability that may be impacted by inflammation or cardiovascular mechanisms.

Adult SEP was also associated with balance ability. In the combined model (Table 3.3), maternal education and both indicators of adulthood SEP remained independently associated with balance. Different results were reported in the meta-analysis, where adjustment for adult SEP fully attenuated the effect of childhood SEP. There are several possible explanations for these results. First, although NSHD was included in the meta-analysis, all other cohorts were older; thus, secular changes in the socioeconomic landscape in the UK could explain some differences. Divergent operationalisations of balance ability (continuous vs binary; eyes closed vs eyes open) as well as a low cut-point for impaired balance may have resulted in a less sensitive measure in the meta-analysis. Finally, 9 of 11 studies in the meta-analysis relied upon retrospective reports to report childhood SEP [159], whereas NSHD data was prospectively ascertained and thus not prone to recall bias. That both childhood and adult SEP indicators remained independently associated with balance suggests that accumulation of low SEP across the life course may be a greater risk factor than low SEP at one particular life stage.

Notably, the impact of most SEP indicators on balance weakened with increasing age. This suggests that SEP may influence balance and overall physical capability the most during midlife before substantial decline begins. Note that the association between the most recent measure of SEP (occupational class at age 53) and balance did not change with age. SEP in early childhood and early adulthood may have a diminishing impact on later life health due to temporal proximity, whereas current SEP appears to have a substantial and constant influence at ages 53, 60-64 and 69. The associations examined in this chapter are limited to balance ability at three distinct ages. Next steps should investigate how different indicators of SEP at different ages are associated with other dimensions of balance ability including initial development, peak ability and both onset and rate of decline.

3.4.2.3 Health behaviours

It is well recognised that negative health behaviours (e.g. smoking, sedentary behaviour, heavy alcohol consumption, poor diet, alcohol consumption, unhealthy diet) can have a direct influence on health outcomes [342-346]. Increasing positive health behaviours and decreasing negative health behaviours is an ongoing public health challenge [347]. Low levels of physical activity [344,348-350], current or past smoking [344,351], an unhealthy diet (high fat and sodium, low grain and fruit/vegetable intake) [346] and alcohol consumption above the new suggested threshold of 100g/week [345] have major adverse consequences for an individual's health.

This chapter suggests that participation in leisure time physical activity is associated with better balance performance. At age 53, there was a similar effect when participating either 1-4 or ≥5 times/ month, although a dose-response association emerged by age 69. Previous research has shown a dose-response benefit of increasing physical activity [352], with a recent review reported that there is no upper threshold of physical activity where benefits for numerous health outcomes (e.g. mortality risk, morbidities) begin to plateau [352]. However, there is inconsistent evidence regarding the benefit of high levels of physical activity, compared with moderate levels, on balance. Some studies have shown that there is little difference between moderately active and the most active groups [344], whereas others have shown an increasing benefit of additional time spent doing MVPA [198,353,354]. The impact of physical activity on improving balance acts via improving postural control, lower body strength, confidence and overall health status [355]. As with SEP, no study had considered how the association between physical activity levels and balance changed with time. Once again, the association appeared to weaken slightly with age for 1-4 times/ month but remained constant for ≥5 times/ month.

Findings from this chapter demonstrated that current or ex-smokers had worse balance compared with those who had never smoked, while individuals who were ex-smokers had better balance than those who currently smoked. This is consistent with increasing severity of risk of poor health outcomes seen amongst categories of smoking history [344,356], suggesting that quitting can reduce risk compared with those who continue to smoke. The constant association at all ages is likely due to a lack of variability in smoking status over time. There was limited mobility between the ex and current smoker groups, while only two individuals who had never smoked by age 53 reported being a current smoker at age 60-64 or 69.

3.4.2.4 Health status

The presence of each physical and mental health condition (diabetes, CVD, respiratory symptoms, knee pain, symptoms of anxiety and depression) was associated with poor balance. This is consistent with the literature on how current health impacts an individual's physical capability [74]. Each health condition likely has a direct biological pathway involved in balance ability. For example, diabetes is considered a contributor to both peripheral neuropathy [357] and age-related visual impairment [358,359] while knee pain can have a direct impact on proprioception and musculoskeletal function [360]. Individuals with a history of CVD events or respiratory symptoms often demonstrate shared pathophysiological features common in those with balance impairment; this includes increased postural sway due to physical displacement of breathing [361], decreased blood flow in specific functional areas [362] and decreased musculoskeletal capacity [363]. Finally, individuals with depression also exhibit psychomotor retardation that includes a slowing in both musculoskeletal components as well as cognitive components which could directly influence balance ability by reducing both cognitive and motor functioning [364]. Given that these comorbidities can often occur in combination [365-367], the impact on balance ability could be amplified in those with multiple comorbidities

Notably, the impact of diabetes, CVD and respiratory symptoms on balance ability was constant at all ages. However, the association of both knee pain and symptoms of anxiety and depression with balance became bigger at older ages. Due to their direct involvement with physical health and mental wellbeing, knee pain and symptoms of anxiety and depression may become increasingly important factors in one's balance ability at older ages. This is a rare finding as the other covariates explored in this chapter had a decreasing effect with age or remained constant.

3.4.2.5 Cognitive ability

As expected given previous findings in NSHD [171,368], higher verbal memory was associated with higher levels of balance ability. Cognitive processing of sensory input is an important component of the balancing process. The decreasing effect with age may reflect that cognitive ability may become less important with age, while other factors in the ageing process that influence balance may begin to emerge (for example, knee pain or symptoms of anxiety and depression as described above). Again, this is explored in depth in Chapters 4, 5, 6 and is not discussed in detail here.

3.4.3 Methodological considerations

This section briefly summarises the strengths and limitations and comments on methodological strategies that may impact the remainder of the thesis. Strengths and limitations of the data were discussed in Chapter 2.1.3 and overall strengths and limitations will be explored in section 8.3 (Chapter 8), while considerations specific to this chapter are summarised below.

A major strength of this chapter is the identification of numerous factors across life that are associated with balance ability. The data are all prospectively ascertained which increases accuracy of response and eliminates any recall bias. By considering each of these factors in individual models and in a combined model, the results demonstrated the complexity of risk factors for poor balance, particularly highlighting the benefit of utilising a life course approach. This chapter also provides novel evidence on how the association between these risk factors and balance ability changes with age.

One limitation specific to this chapter is the inability to compare the relative contribution of each covariate in the individual regression models. As the sample size differs for each model due to missing data on covariates and the scale of each covariate differs, estimates cannot be directly compared. Furthermore, it isn’t clear if several interaction terms in the combined model lost significance due to changes in sample size and subsequent reductions in power or due to the adjustments their selves.

A strict threshold of alpha 0.05 was used for all interaction terms. Although some studies utilise higher cut-points such as p<0.10 in order to select interaction terms, <0.05 was intentionally used in order to remain selective and identify the most parsimonious model for the remainder of the thesis. As discussed in section 3.3.1, the interpretation of the age interaction terms warrants discussion. Due to the parsimonious aims of modelling the covariates to be used in subsequent models and to understand how these associations vary at different ages, interpretation of age interaction terms has focused entirely on how the associations change with age. In order to appropriately examine how time-varying covariates are associated with the slope (e.g. steeper or shallower decline), more complex models are required. Further life course research should investigate how these risk factors impact trajectories of balance ability.

3.5 Conclusions and implications for future chapters

The results of this chapter have implications for both broader understanding of public health and for future research conducted in the thesis. First, this chapter demonstrates that a considerable number of risk factors across life are associated with balance ability. That the majority of covariates remained independently associated with balance suggests that the range of risk factors for balance is diverse and complex. When considering appropriate interventions to minimise balance decline and falls risk, a multifactorial approach may have more benefit than focusing on one single risk factor. Several of these risk factors have different associations with balance at different ages. Consequently, different factors should be targeted depending on the age when interventions are taking place. Knee pain and symptoms of depression and anxiety are the two factors that become more important with age and as such, they may represent feasible targets for both early and late intervention. Earlier intervention would allow these factors to be targeted improved before the impact on balance ability increases, whereas intervention at later ages would allow a larger immediate impact compared to risk factors that become less important with age (i.e. SEP, cognition, physical activity)

Second, each of the following analytical chapters in this thesis investigates a main variable of interest and its association with balance. The findings of this chapter directly inform how each covariate is modelled in all subsequent chapters. When considering pathways that may explain main associations in other chapters, understanding how covariates are associated with balance across ages can provide insight into associations identified. This chapter demonstrated the complexity of risk factors across life and how they exhibit different patterns of association with balance at different ages.

CHAPTER 4: NEURODEVELOPMENTAL FACTORS AND BALANCE ABILITY IN MID AND LATER LIFE

Publication:
Blodgett JM, Kuh D, Hardy R, Davis DHJ, Cooper R. Childhood cognition and age-related change in standing balance performance from mid to later life: findings from a British birth cohort. *J Gerontol A Biol Sci Med Sci*. 2020, 75(1): 155-161. [see pg 335]

Despite hypotheses that early life physical development contributes to lifelong physical capability, there are very few available datasets that can examine potential neurodevelopmental pathways involved in mid to later life outcomes. Understanding how divergent pathways of development in infancy and childhood may contribute to balance ability will contribute to the life course approach to balance outlined in section 1.3 (Chapter 1). The aim of this chapter is to explore if neurodevelopmental pathways in infancy and childhood are associated with balance in mid and late life. The evidence on markers of childhood cognitive (section 4.1.1) and physical development (section 4.1.2) and their associations with cognitive and physical health, including balance, in mid to later life are summarised below. The gaps in research exploring neurodevelopmental indicators and their relationship with both single measures of balance as well as age-dependent decline in balance and other measures of physical capability are also identified. Chapter objectives and hypotheses are provided in section 4.1.3.

4.1 Introduction

High-order process, such as cognition or balance, in mid and later life may be dependent on a foundation of basic processes that develop early in life [369]. Several sensitive and crucial periods in early cognitive and motor development have been identified [370-373]. For example, in language development, the ability to perceive and understand phonemes – specific units of sound – is dependent on exposure to languages within an infant's first 12 months [374]. Similarly, the development of basic gross-motor skills is dependent on a critical window between ages one and five [371]. Physical movement in the first two years of life is crucial for the development of neural motor pathways [372,373]. This may be due to the significant development of the cerebellum throughout childhood and adolescence [375], with studies identifying a 240% growth in volume in the first 12 months [376] and continual maturation until approximately 15 years of age [377]. Considering that the cerebellum plays a prominent role in balance and posture [23] (see section 1.1, Chapter 1) as well as neurocognitive development [378], further investigation on neurological development and its contribution to balance is warranted.

4.1.1 Cognitive development

The life course approach to ageing, as introduced in Chapter 1 (section 1.3), suggests that factors across life including childhood experiences, behaviours and abilities may have long-term effects on health, disease risk and function in later adult life [71,379]. There is a strong consensus that childhood cognitive ability is directly associated with cognitive ability throughout adulthood [157,380,381]. Evidence suggests that individuals with higher childhood cognition had slower rates of cognitive decline in adulthood [380-382], lower risk of dementia [383] and fewer several neuropathological indicators of ageing [384,385]. A Swedish study examining inter-individual differences in cognition from age 18 demonstrated that these differences were maintained into older age including eventual cognitive deterioration at age 65, and suggested that the cognitive rank order of individuals remained stable throughout later life [386]. Cognitive ability is still susceptible to change due to varying environments, educational pursuits or employment opportunities; however, it is widely accepted that higher childhood cognitive ability has lasting advantages throughout an individual's life.

Independent of associations with adult cognition, low childhood cognitive ability has been associated with higher risk of premature death [157,387-390] and adverse health outcomes including various morbidities [391], poor lung function [392], cardiovascular risk [393], and diabetes [394,395]. Low cognitive function in early life is also a risk factor for lower well-being [396] and mental health problems in adulthood such as anxiety and depression [397-400] and increased risk of being diagnosed with schizophrenia [397,401,402]. While there is some evidence that SEP mediates these associations [388], the system-integrity hypothesis by Deary and colleagues [403,404] suggests that higher cognitive scores reflect efficiency across multiple physiological systems and that this operates independent of SEP [387,405].

There is considerably less evidence exploring associations between early cognitive ability and physical capability in mid and later life. A series of papers in NSHD by Kuh et al. [156,169,171] reported that better performance on cognitive tests in childhood were associated with higher levels of physical capability at age 53 including balance time, chair rise performance and grip strength. Cognitive performance at ages 8 [156] and 15 [171] were associated with better standing balance and faster chair rise times, while associations with grip strength were weaker and inconsistent [156,171]. Similarly, in a Danish study, Meincke et al. [172] found positive evidence of associations between cognitive ability at age 18 and numerous measures of physical performance at age 50 including chair rises, jumping, balance, grip strength and back force while one study failed to find significant associations between childhood intelligence quotient (IQ) and walking speed or grip strength [406]. A single study by Cooper et al. [170], also in NSHD, identified that those with higher childhood cognitive ability were less likely to experience decline in grip strength and chair rise speed between ages 53 and 60-64. Even so, no study examined how these associations changed with age.

Building on these early studies of balance at age 53 and examination of trends in physical capability in midlife, this chapter will examine how childhood cognition is associated with balance at multiple ages in mid and late life. Associations between childhood cognition and balance performance may be explained by CNS pathways necessary for successful integration of sensory efferent and motor afferent information; section 4.1.3 outlines in further detail possible mechanisms that may explain this relationship. Establishing these neural pathways early in life may have long-term advantages in the face of inevitable age-related decline in the systems underlying physical capability.

4.1.2 Physical development

Common biological processes may underlie cognitive and physical development and as such it is important to consider physical development in addition to the cognitive development discussed above. Studies of motor development in humans and other species have identified associations between onset of walking and cerebellar development and brain mass [407,408] suggesting that cognitive and physical development are intertwined.

Evidence has shown that earlier motor development in infants is associated with better physical and cognitive development in childhood. For example, better postural control [409] and fine motor skills in infancy [162,163], and higher birth weight [164] are directly associated with better cognitive and motor ability in children reaching school age. Positive benefits of early milestone attainment are diverse including socio-emotional [410], cognitive [163,411,412] and future physical development [163,411]. However, the follow-up period of these studies is often short, frequently reporting on further childhood or adolescent outcomes.

Limited longitudinal evidence has shown that the positive association between motor development and cognition is sustained into early adulthood and midlife [412-414]. Likewise, delayed development, which can often identify individuals with educational needs, can be an early marker of lower cognitive performance [165,412,413] or lower educational attainment [166]. There is very little evidence on the associations between attainment of milestones and physical capability in adulthood. Earlier attainment of milestones (i.e. walking and standing) has been associated with greater muscle strength, higher muscle endurance and stronger aerobic endurance in early adulthood in the Northern Finland Birth Cohort 1966 [167], although an NSHD-based study suggested that advanced developmental milestones may not always be advantageous [169]. Kuh et al. [156,169] identified that balance, chair rise performance and grip strength in midlife were, on average, better in those who began standing and walking at 12 months (i.e. around the modal age) compared with those who reached these milestones earlier or later. No study has examined the association between age of first talking – a cognitive developmental milestone – and physical capability in later life. These studies, described above, focused on adult physical capability in early (age=31) [167] and midlife (age=53) [156,169], and will be extended to ages 60-64 and 69 in this chapter.

Motor development is a dynamic process that changes from infancy to childhood to adolescence. Individuals develop at different rates with considerable variability in physical capability across the life course; childhood and adolescence are sensitive periods for physiological and psychological development and the formation of health behaviours. Many studies do not have data from early and later life to test these associations. Studies that have investigated this area have shown that poor physical development in early life may be associated with various health outcomes later in life including worsening physical capability [156,169], obesity [168,415,416], cardiovascular disease risk factors [416] and premature death [417]. Despite evidence of a neurological pathway between coordination, reaction time and standing balance [418], only one study has examined the associations of early life coordination and motor development with balance from midlife. Kuh et al. [169] demonstrated that higher performance on tapping tests at age 15 were associated with better balance and walking speed at age 53.

How exactly physical development may be associated with later physical decline is unknown. Motor skill development in early childhood may positively contribute to later health outcomes via increased physical activity [419,420] and better physiological integrity [419,421,422]. The limited studies that have examined associations of motor development with future health and physical capability did not look at patterns of decline [156,167,169,423]. In summary, there is very little data that can adequately access associations between neurodevelopmental factors and mid to later life balance. Studies who have aimed to understand these associations have not examined how they may change at different ages, nor have they appropriately considered covariates across the life course that explain potential mechanisms.

4.1.3 Objectives and hypotheses

To address the gaps in research identified above, this chapter aims to use longitudinal data from the MRC NSHD:

i) to investigate how ages of milestone attainment, childhood cognitive ability and childhood are associated with balance in mid to late life;

ii) to determine if these associations change with age or sex;

i) to explore how various factors across life (e.g. SEP, health behaviours, etc.) impact these pathways.

It is hypothesised that advantageous neurodevelopment, including higher cognitive ability, earlier motor development and faster performance on coordination, will be associated with better balance ability in later life as well as a slower rate of decline. These neurodevelopmental processes are hypothesized to play both a primary role in neural mechanisms involved in balance and a secondary role in maintaining balance in mid to later life. The secondary pathways through which neurodevelopmental factors may be associated with later life balance are unclear, although factors investigated in Chapter 3 namely contemporaneous body size, health behaviours, health status, adult cognition and socioeconomic position are expected to impact these associations. Figure 4.1 outlines the hypothesised role of these factors.

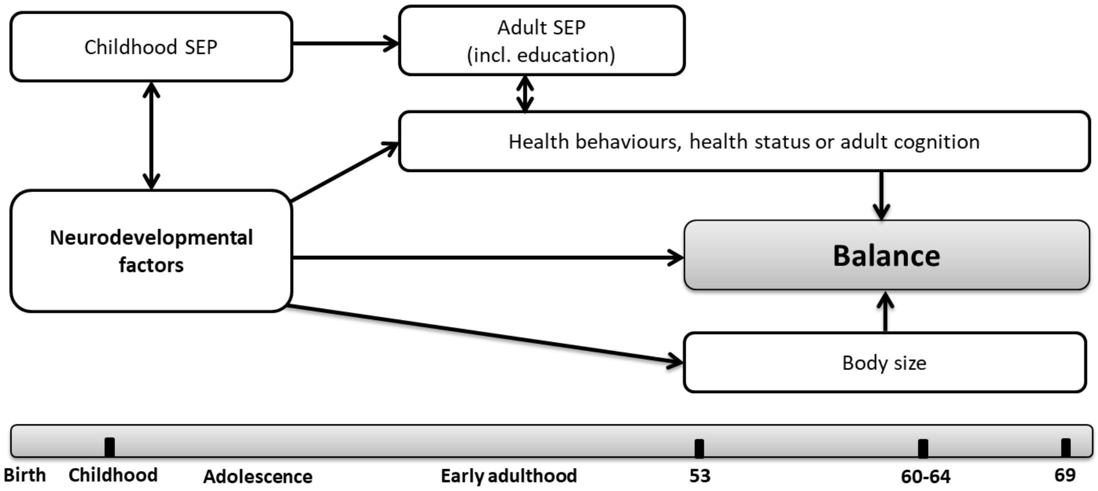


Figure 4.1 Conceptual model of potential pathways between neurodevelopmental factors and subsequent balance

4.2 Methods

4.2.1 Study sample

Individuals are included in analyses if they had a balance measurement at one or more age and one or more of the exposures of interest; this included a valid age of attainment for sitting, standing, walking and talking (n=2605), valid childhood cognitive score at one or more ages (n=2861), and valid tapping measurements at age 15 (finger tapping: n=2448, foot tapping: n=2450).

4.2.2 Measurement of variables

As described in section 2.2.1 (Chapter 2), standing balance was assessed as part of a battery of physical capability tests at ages 53, 60-64 and 69. The literature on the following covariates was explored in section 1.4 (Chapter 1), measurement of these covariates was described in section 2.2.3 (Chapter 2) and their association with balance ability was characterised in Chapter 3: mortality, attrition, height, BMI, diabetes, CVD event, knee pain, and respiratory symptoms, symptoms of depression and anxiety, self-reported smoking, leisure-time physical activity, paternal occupational class, maternal education, own occupational class, education and adult verbal memory.

4.2.2.1 Developmental milestones

Mothers were asked to recall timing of developmental milestones when the study member was aged 2. Mothers reported age (months) of first sitting unassisted, standing unassisted, walking several steps unassisted and talking (said more than “mum”, “dad” or “nan”). Outliers that were not considered to be plausible were recoded as missing; this included those who were reported as walking unassisted earlier than sitting unassisted (n=3) and those who were reported as talking earlier than 4 months (n=9). Individuals who had not reached a milestone by age 2 were assigned a value of 25 months (n=2 for sitting; n=14 for standing; n=25 for walking; n=1 for talking). Similar to the zero imputation for balance, this ensured that these individuals could be included in analyses with a value that was indicative of their late development. In order to compare the estimates of each milestone directly and maintain the same sample size, only individuals with a valid response for all four milestones were included in the study. Each milestone was examined as a continuous variable in the model to maximise information. As ages of milestone attainment are often categorised as early, average (80-90% of individuals) and late developers [89,91,424], the analytical sample is also described in this way. Categories were established based on developmental parameters identified in the literature for age of walking [89,91,424]; cut points for age of sitting, standing and talking were inferred using similar appropriate percentiles (early:

5th-10th percentile, late 90th-95th percentile). See section 4.1.3 or Table 4.1 for cut-points.

4.2.2.2 Childhood cognitive ability

Childhood cognitive ability was measured at ages 8, 11 and 15. At age 8, children completed four tests of verbal and non-verbal ability: reading comprehension, word reading, vocabulary, and picture intelligence [425]. At age 11, tests of verbal and non-verbal intelligence, arithmetic, pronunciation and vocabulary were administered [425]. At age 15, participants completed the Alice Heim (AH4) test of fluid intelligence, the Watts-Vernon reading test, and a study specific test of mathematical ability [381]. At all ages, each test score was standardised and then summed to create an overall score of cognitive ability. Scores were re-standardised to the analytical sample (mean of 0, SD of 1). To obtain a single indicator of childhood cognition for this study and to minimise missing data, cognitive score at age 15 was used. If missing at age 15, cognitive score at age 11 (n=157) was imputed; if missing at age 15 and age 11, score at age 8 (n=79) was used. This was based on past findings in NSHD that demonstrate that children maintained a similar cognitive ranking over time (Pearson correlation coefficients ≥ 0.7) [170,426].

4.2.2.3 Childhood coordination

Childhood coordination was measured at age 15 using finger and foot tapping tests. During a medical examination by the school doctor, study members were asked to tap the back of their left hand with their right finger (and vice versa) as fast as they could for 15 seconds. Study members were then asked to tap the ground with their foot while seated as fast as possible for 15 seconds. Once again, this test was repeated with both the right and left feet. Maximum finger and foot tapping scores were coded into multiples of ten for analyses [169].

4.2.3 Statistical analyses

Sex-stratified mean scores (SD) are presented and sex differences by each developmental factor are examined using t-tests and chi-square tests. Histograms describe the distribution of all developmental factors. The Kolmogorov-Smirnov tests is used to assess whether or not each factor was normally distributed or if transformations or categorisations were needed.

4.2.3.1 Multilevel models

As outlined in section 2.4.2, MLMs provide advantages over a traditional linear regression as they consider balance variation between individuals and within individuals over time. The multilevel models in this chapter will build on the non-linearity, quadratic and interaction terms of all covariates as identified in Chapter 3. Thus, all variables are modelled as continuous variables except for leisure time physical activity, which is modelled categorically, and a quadratic height term will be included. Age-interactions of the following covariates are included in all relevant models: sex, paternal occupation, maternal education, education, physical activity, knee pain, symptoms of anxiety/depression, and verbal memory. Quadratic terms and sex interactions for all neurodevelopmental factors are tested; if a sex interaction is found, all subsequent models are stratified by sex. For each early life factor at each age, the MLMs explore the role of potential covariates in further detail by building the fully adjusted model in several stages. At each stage, changes in the associations between early life exposures and balance are noted to help understand potential pathways or mechanisms. First, sex-adjusted models using the maximal available sample size and complete cases are examined (Model 0). Next, using the complete cases only, the nine stages of adjustment are as follows:

Model 1) sex adjusted;

Model 2) sex, death and attrition adjusted;

Model 3) sex, death, attrition and body size adjusted;

Model 4) sex, death, attrition, body size and health status adjusted;

Model 5) sex, death, attrition, body size and health behaviour adjusted;

Model 6) sex, death, attrition, body size and SEP adjusted;

Model 7) sex, death, attrition, body size and education adjusted;

Model 8) sex, death, attrition, body size and adult verbal memory adjusted;

Model 9) sex, death, attrition, body size, health status, health behaviours, SEP, education, adult verbal memory.

Due to bias introduced by loss to follow up due to death and attrition as well as robust sex and body size differences in balance identified in Chapter 1, these covariates were included in all subsequent stages of analysis. Five main pathways were explored: 1) health status; 2) health behaviours; 3) SEP; 4) education and 5) adult verbal memory. Although educational attainment is commonly used as a marker of SEP, it was examined separately from other indicators of SEP in these analyses because education may play a role in a pathway between childhood and adulthood cognitive ability. As in Chapter 3, estimates are plotted to help visualise associations between each neurodevelopmental factor and balance ability.

4.3 Results

4.3.1 Descriptive statistics

A description of the complete analytical sample was previously provided in Table 2.3. Of 3111 individuals with a valid balance time at one or more ages, 2645 also had valid data on milestones, 2861 for cognitive ability and 2448 and 2450 for finger and foot tapping respectively. The final numbers of observations and individuals for all models are provided with the model estimates. Early life factors mostly demonstrated approximate normal distributions (see Figure 4.2). This normal distribution was more pronounced for childhood cognition and finger and foot tapping, with age of first talking demonstrated the largest spread of data.

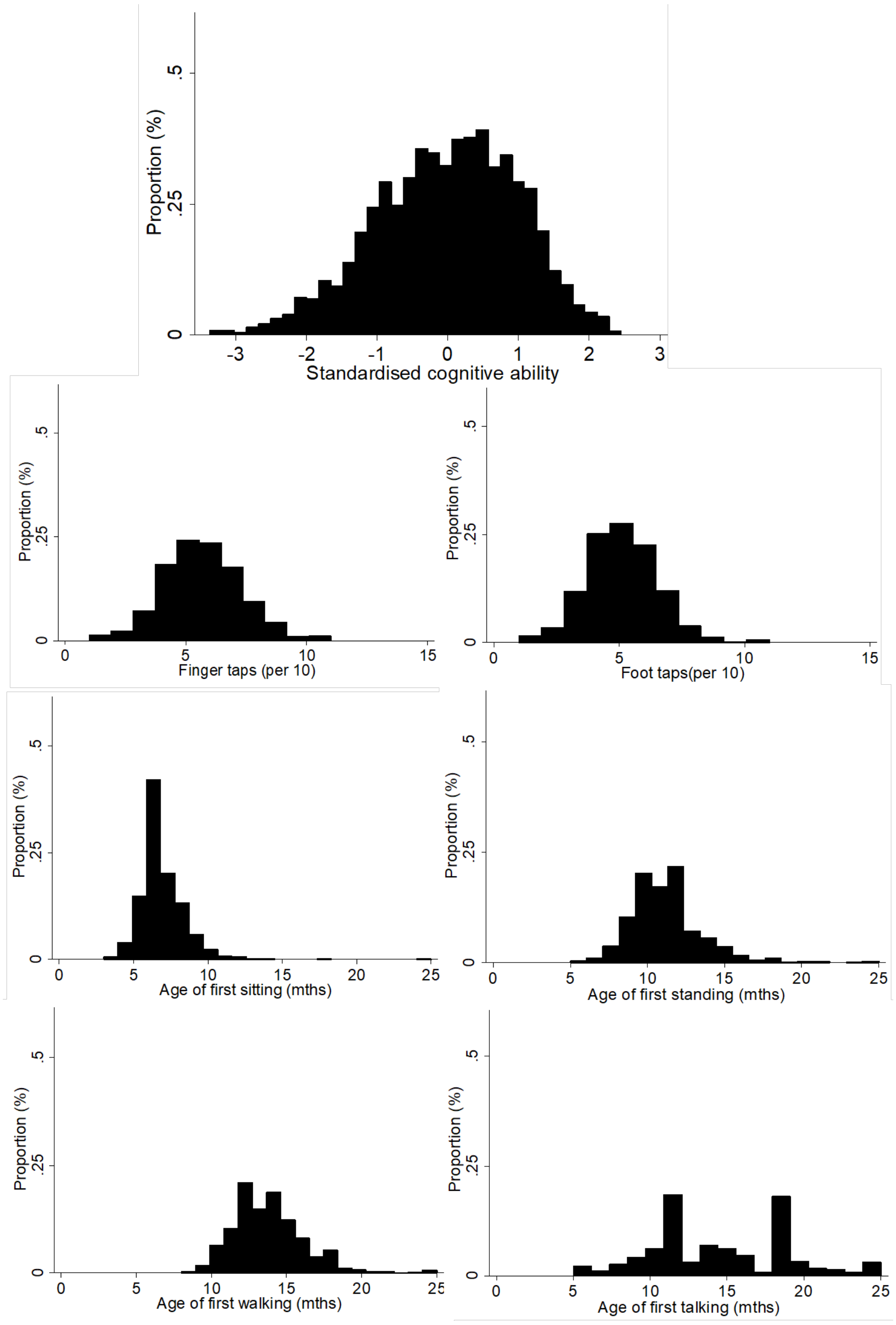


Figure 4.2 Histograms showing distributions of all early life factors

Table 4.1 describes the sample by each exposure. There were no sex differences in continuous ages of walking, standing or sitting, however girls were more likely to talk at an earlier age than boys [mean (±SD): 13.88 (4.15) mths in girls vs 15.04 (4.40), p<0.001], be below average on the standardised cognitive tests [-0.08 (0.97) vs 0.06 (1.04), p<0.001] and score lower on the finger tapping test [5.78 (1.84) [per 10 taps] vs 5.50 (1.72); p<0.001] and the foot tapping test [5.08 (1.64) [per 10 taps] vs 4.96 (1.54); p=0.06].

Table 4.1 Characteristics of each neurodevelopmental marker by sex in the maximal available analytical sample

	n	**Men**	**Women**	**Tests of sex differences (p-value)**
Milestones (cont), *mean (SD)*				
Age of first sitting (mths)	2645	6.62 (1.63)	6.54 (1.48)	0.22
Age of first standing (mths)		11.48 (2.43)	11.36 (2.11)	0.20
Age of first walking (mths)		13.68 (2.60)	13.60 (2.46)	0.44
Age of first talking (mths)		15.04 (4.40)	13.88 (4.15)	<0.001
Milestones (cat), *n (%)*				
Age of first sitting	2645			
Early (<5 mths)		55 (4.15)	58 (4.40)	0.85
Average (5-8 mths)		1143 (86.20)	1141 (86.50)	
Late (≥9 mths)		128 (9.65)	120 (9.10)	
Age of first standing				
Early (<9 mths)		66 (4.98)	68 (5.16)	<0.05
Average (9-15 mths)		1185 (89.37)	1204 (91.28)	
Late (≥16 mths)		75 (5.66)	47 (3.56)	
Age of first walking				
Early (<11 mths)		102 (7.69)	105 (7.96)	0.10
Average (11-17 mths)		1101 (83.03)	1122 (85.06)	
Late (≥18 mths)		123 (9.28)	92 (6.97)	
Age of first talking				
Early (<9 mths)		79 (5.96)	108 (8.19)	<0.001
Average (9-20 mths)		1108 (83.56)	1133 (85.90)	
Late (≥21 mths)		139 (10.48)	78 (5.91)	
Childhood cognitive ability, *mean (SD)*				
(standardised to 0)	2861	0.06 (1.04)	-0.08 (0.97)	<0.001
Adolescent coordination, *mean (SD)*				
Finger tapping (per 10 taps)	2448	5.78 (1.84)	5.50 (1.72)	<0.001
Foot tapping (per 10 taps)	2450	5.08 (1.64)	4.96 (1.54)	0.06

4.3.2 Milestone attainment

Ages of first sitting, walking and standing were each associated with standing balance; these associations were best described using a quadratic function (Table 4.2). Individuals who could sit unassisted at a younger age (i.e. ~8 months; Table 4.2A) had better balance in midlife than later developers. There was little difference amongst those who developed at an average age – 5 to 8 months as described in Table 4.1 –, while the drop-off in balance ability was notably strong in those with well-defined developmental delays (see Figure 4.3). This association remained constant at all ages (p=0.13).

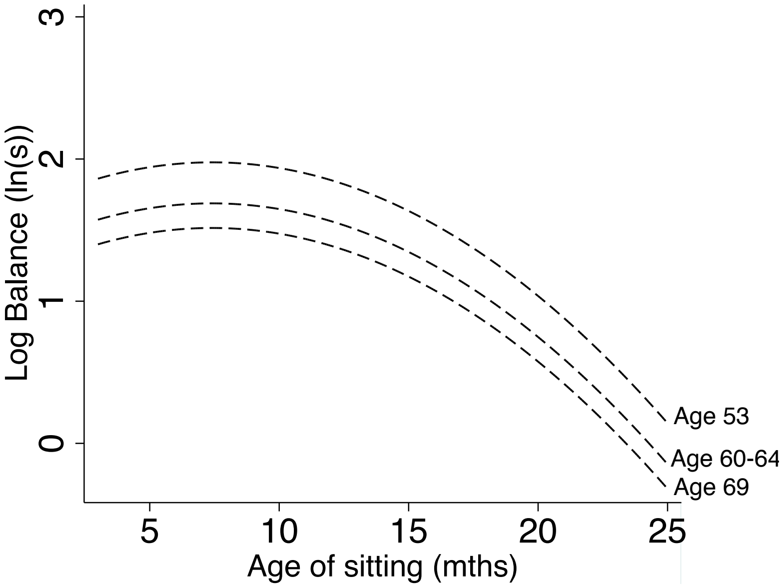


Figure 4.3 Association between log-transformed balance at ages 53, 60-64 and 69 and age of first sitting in sex-adjusted, maximal sample multilevel models

There was a similar association between age of first standing and balance in the maximal available sample (Model 0, Table 4.2), however this association was not present in the complete cases model. To understand these large differences in estimates, the maximal and complete cases samples were explored. There were six individuals in the maximal sample who could not stand by 24 months and each of these individuals had a balance time of 0 (n=5) or 2 (n=1) seconds at age 53. Only one of these individuals remained in the complete cases sample, leading to speculation that the association may be driven by these late developers. To confirm this, when these six individuals were excluded from the maximal sample size and models were re-run, the association was no longer significant (p=0.53, p=0.56 for linear and quadratic terms).

Table 4.2 Associations of age of first sitting and standing (per month) and log-transformed balance time (sec) in multilevel models

		Change in logged balance time at age 53 per month of first sitting [intercept][k]		**Change in logged balance time at age 53 per month of first standing [intercept]**		**Age of first standing (month) *age (year) interaction [slope]**	
Model:		**Coefficient (95% CI)**	***p-value***	**Coefficient (95% CI)**	***p-value***	**Coefficient (95% CI)**	***p-value***
Maximal available sample		n = 2645 (obs= 6157)					
0: age[a], sex[b]	linear term	0.09 (0.04, 0.13)	<0.001	0.12 (0.05, 0.19)	<0.001	-0.006 (-0.012, -0.00003)	0.05
	quadratic term	-0.006 (-0.009, -0.003)	<0.001	-0.005 (-0.012, -0.002)	<0.001	0.0003 (0.00003, 0.0005)	0.03
Complete cases sample		n=2141 (obs **=** 4486)					
1: age[a], sex[b]		0.09 (0.01, 0.18)	0.03	0.01 (0.0003, 0.01)	0.71	Not significant in	0.58
		-0.006 (-0.011, -0.0002)	0.04	-0.0005 (-0.003, -0.002)	0.70	complete cases	0.60
2: model 1+ death + attrition[c]		0.09 (0.01, 0.18)	0.03	0.01 (-0.06, 0.07)	0.81	--	--
		-0.006 (-0.012, -0.0004)	0.04	-0.0004 (-0.003, 0.002)	0.78		
3: model 2 + anthropometric[d]		0.09 (0.01, 0.18)	0.03	0.02 (-0.05, 0.08)	0.60	--	--
		-0.006 (-0.012, -0.001)	0.03	-0.001 (-0.003, 0.001)	0.43		
4: model 3 + health status[e]		0.08 (-0.002, 0.16)	0.06	0.02 (0.003, 0.01)	0.47	--	--
		-0.005 (-0.011, 0.00003)	0.05	-0.0005 (-0.003, 0.001)	0.35		
5: model 3 + health behaviours[f]		0.08 (-0.002, 0.16)	0.06	0.01 (-0.050, 0.070)	0.75	--	--
		-0.005 (-0.011, 0.0001)	0.06	-0.001 (-0.003, 0.002)	0.58		
6: model 3 + SEP[g]		0.08 (-0.001, 0.16)	0.05	0.01 (-0.05, 0.07)	0.78	--	--
		-0.004 (-0.011, -0.0002)	0.04	-0.001 (-0.003, 0.002)	0.53		
7: model 3 + education[h]		0.07 (-0.01, 0.15)	0.09	-0.001 (-0.06, 0.06)	0.97	--	--
		-0.005 (-0.010, 0.0004)	0.07	-0.0003 (-0.003, 0.002)	0.78		
8: model 3 + verbal memory[i]		0.08 (-0.003, 0.16)	0.06	0.02 (-0.04, 0.08)	0.45	--	--
		-0.005 (-0.011, 0.0002)	0.06	-0.001 (-0.0033, 0.001)	0.36		
9: fully adjusted[j]		0.06 (-0.02, 0.14)	0.14	0.01 (-0.05, 0.06)	0.86	--	--
		-0.004 (-0.01, 0.001)	0.11	-0.001 (-0.003, 0.002)	0.63		

[a] Age is centred at age 53 = 0 in all models. [b] Adjusted for age, sex. [c] Adjusted for M1 + death, attrition. [d] Adjusted for M2 + height, height^2, BMI. [e] Adjusted for M3 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression. [f] Adjusted for M3 + smoking history, leisure time physical activity. [g] Adjusted for M3 + maternal education, paternal social class, adulthood social class. [h] Adjusted for M3 + education, age*education. [i]Adjusted for M 3 + verbal memory. [k] Adjusted for all covariates in M1–8· [k] Age*sitting interaction terms: linear, p=0.94; quadratic, p=0.89

Those who began walking around the average age (i.e. ~9=15 months; Table 4.3) had better balance than early or late walkers, however there were both linear and quadratic interactions between age of walking and age of balance test suggesting that these associations attenuated at later ages. Figure 4.4 demonstrates a visual representation of these interactions, with a quadratic relationship at age 53 that fully attenuated at ages 60-64 and 69. Finally, there was no evidence of an association between age of first talking and balance ability (Table 4.3).

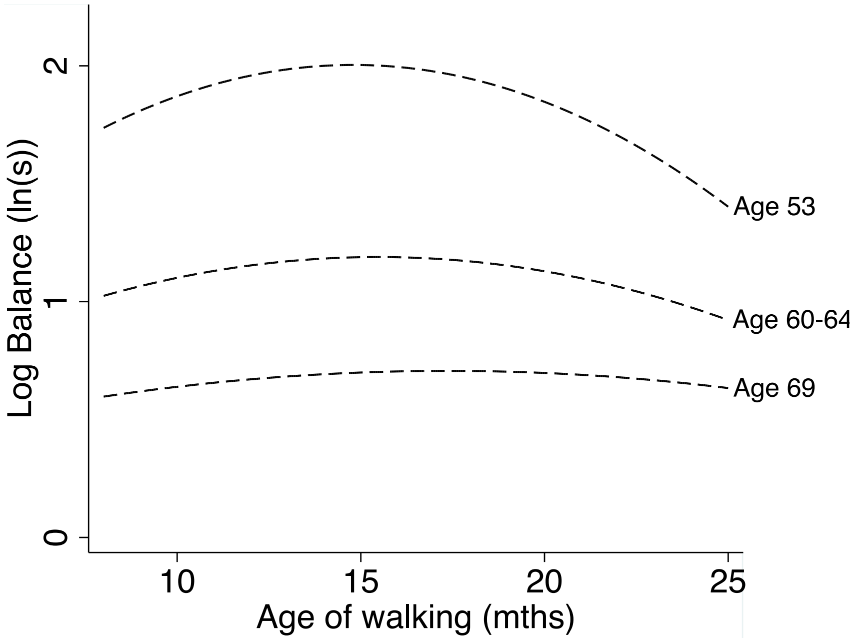


Figure 4.4 Association between log-transformed balance at ages 53, 60-64 and 69 and age of first walking in sex-adjusted, maximal sample multilevel models

Table 4.3 Associations of age of first walking and talking (per month) and log-transformed balance time (sec) in multilevel models

Model:		**Change in logged balance time at age 53 per month of first walking [intercept]**		**Age of first walking (month) *age (year) interaction [slope]**		**Change in logged balance time at age 53 per month of first talking [intercept] [k]**	
		Coefficient (%) (95% CI)	***p-value***	**Coefficient (%) (95% CI)**	***p-value***	**Coefficient (%) (95% CI)**	***p-value***
Maximal available sample		n = 2645 (obs= 6157)					
0: age [a], sex [b]	linear term	0.17 (0.10, 0.25)	<0.001	-0.008 (-0.01, -0.002)	0.01	0.00002 (-0.005,0.005)	0.99
	quadratic term	-0.006 (-0.008, -0.003)	<0.001	0.0003 (0.0001, 0.001)	0.01		
Complete cases sample		n=2141 (obs **=** 4486)					
1: age [a], sex [b]		0.11 (0.01, 0.20)	0.03	-0.008 (-0.02, 0.0002)	0.06	0.001 (-0.005, 0.006)	0.85
		-0.003 (-0.007, 0.00002)	0.05	0.0003 (-0.00002, 0.001)	0.08		
2: model 1+ death + attrition [c]		0.10 (0.004, 0.19)	0.04	-0.007 (-0.02, 0.0004)	0.06	0.0004 (-0.005, 0.006)	0.90
		-0.003 (-0.006, 0.0002)	0.06	0.0002 (-0.00003, 0.001)	0.08		
3: model 2 + anthropometric [d]		0.09 (-0.004, 0.18)	0.08	-0.007 (-0.02, 0.001)	0.08	-0.0002 (-0.005, 0.005)	0.94
		-0.003 (-0.01, 0.0003)	0.07	0.0002 (-0.00004, 0.0005)	0.10		
4: model 3 + health status [e]		0.09 (-0.02, 0.18)	0.06	-0.007 (-0.01, 0.001)	0.08	0.0003 (-0.005, 0.005)	0.92
		-0.003 (-0.006, 0.0002)	0.07	0.0002 (-0.00005, 0.0005)	0.11		
5: model 3 + health behaviours [f]		0.08 (-0.01, 0.17)	0.08	-0.007 (-0.01, 0.001)	0.08	0.0002 (-0.005, 0.005)	0.95
		-0.003 (-0.0004, 0.0004)	0.09	0.0002 (-0.00004, 0.0004)	0.10		
6: model 3 + SEP [g]		0.07 (-0.02, 0.16)	0.15	-0.006 (-0.01, 0.002)	0.12	0.0003 (-0.005, 0.005)	0.91
		-0.003 (-0.01, 0.001)	0.11	0.0003 (-0.0001, 0.0005)	0.12		
7: model 3 + education [h]		0.04 (-0.05, 0.13)	0.37	-0.005 (-0.01, 0.003)	0.20	0.0004 (-0.005, 0.006)	0.89
		-0.002 (-0.005, 0.002)	0.32	0.0002 (-0.0001, 0.0004)	0.21		
8: model 3 + verbal memory [i]		0.07 (-0.02, 0.16)	0.14	-0.006 (-0.01, 0.001)	0.11	0.0003 (-0.005, 0.005)	0.92
		-0.002 (-0.01, 0.001)	0.14	0.0002 (-0.0001, 0.0005)	0.13		
9: fully adjusted [j]		0.03 (-0.06, 0.12)	0.47	-0.004 (-0.01, 0.004)	0.31	0.0004 (-0.005, 0.005)	0.87
		-0.001 (-0.004, 0.002)	0.38	0.0001 (-0.0001, 0.0004)	0.30		

[a] Age is centred at age 53 = 0 in all models. [b] Adjusted for age, sex. [c] Adjusted for M1 + death, attrition. [d] Adjusted for M2 + height, height^2, BMI. [e] Adjusted for M3 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression. [f] Adjusted for M3 + smoking history, leisure time physical activity. [g] Adjusted for M3 + maternal education, paternal social class, adulthood social class. [h] Adjusted for M3 + education, age*education. [i] Adjusted for M 3 + verbal memory. [j] Adjusted for all covariates in M1–8. [k] age*talking interaction terms, p=0.66

4.3.3 Childhood cognitive ability

In the maximal sample, one standard deviation increase in childhood cognition was associated with 16% (95% CI: 14, 19%; Table 4.4) better balance ability at age 53. This association got smaller with age as there was a significant interaction between childhood cognitive ability and age (-0.5% per year (-0.3, -0.7%; p<0.001; Table 4.4). The negative coefficient in the interaction term indicates that the association decreased over time towards the null; once again, a visual representation of this interaction confirms the findings (see Figure 4.5). Despite the decrease in association with age, the overall association remained at ages 60-64 and 69 (see Table 4.4, footnote k).

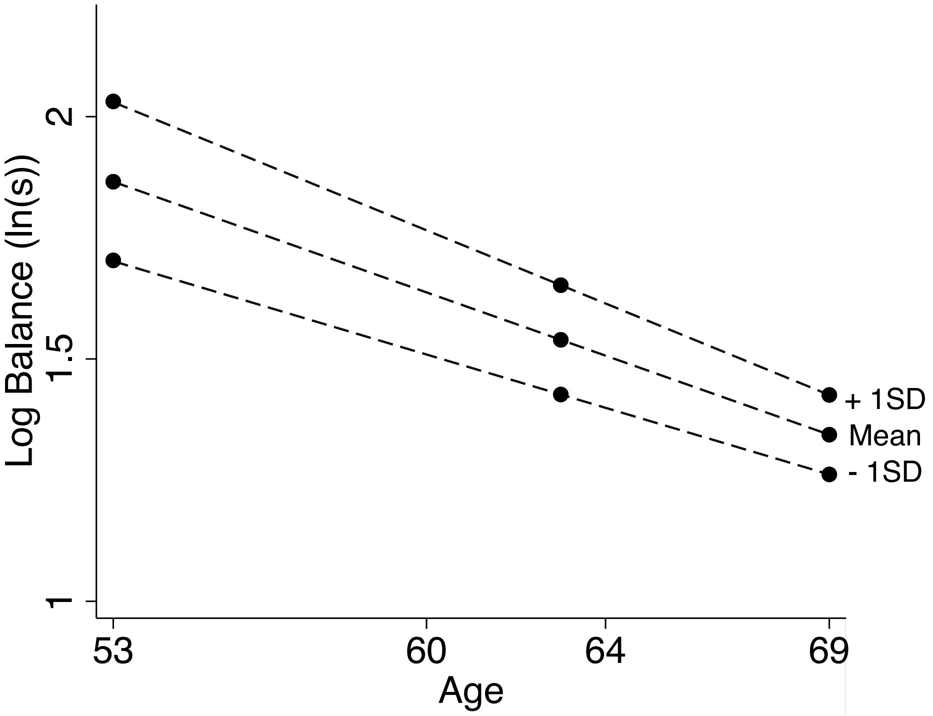


Figure 4.5 Association between log-transformed balance at ages 53, 60-64 and 69 and childhood cognitive ability using unadjusted multilevel models

The association between higher childhood cognitive ability and better balance in mid to late life was slightly attenuated by each category of covariates including body size (Table 4.4, Model 2), health behaviours (Model 3), socioeconomic indicators (Model 4), and educational attainment (Model 5) and did not remain significant in the fully adjusted model (Model 6). Education and socioeconomic indicators explained more of the association between childhood cognitive ability and balance than health behaviours as indicated by greater attenuation of the estimates for both intercept and slope (Table 4.4).

Table 4.4 Associations between childhood cognition (per 1SD) and log-transformed balance time (sec) in multilevel models

	Change in logged balance time at age 53 per SD of childhood cognition [intercept]		**Childhood cognition (SD) *age (year) interaction [slope]**	
Model:	**Coefficient (%) (95% CI)**	***p-value***	**Coefficient (%) (95% CI)**	***p-value***
Maximal available sample	n=2861 (obs **=** 6675)			
0: age[a], sex [b]	0.16 (0.14, 0.19) [k]	<0.001	-0.005 (-0.007, -0.003)	<0.001
Complete cases sample	n=2418 (obs **=** 5032)			
1: age, sex [b]	0.15 (0.12 0.18)	<0.001	-0.005 (-0.008, -0.002)	<0.001
2: model 1+ death + attrition [c]	0.14 (0.11 0.17)	<0.001	-0.005 (-0.007, -0.002)	<0.001
3: model 2 + anthropometric [d]	0.13 (0.10, 0.16)	<0.001	-0.005 (-0.008, -0.003)	<0.001
4: model 3 + health status [e]	0.13 (0.10, 0.16)	<0.001	-0.006 (-0.008, -0.003)	<0.001
5: model 3 + health behaviours [f]	0.12 (0.09, 0.15)	<0.001	-0.005 (-0.008, -0.003)	<0.001
6: model 3 + SEP [g]	0.08 (0.05, 0.12)	<0.001	-0.004 (-0.007, -0.001)	<0.01
7: model 3 + education [h]	0.08 (0.04, 0.11)	<0.001	-0.003 (-0.007, -0.00004)	0.05
8: model 3 + verbal memory [i]	0.10 (0.06, 0.13)	<0.001	-0.006 (-0.009, -0.003)	<0.005
9: fully adjusted [j]	0.03 (-0.01, 0.07)	0.18	-0.003 (-0.006, 0.001)	0.17

[a] Age is centred at age 53 = 0 in all models. [b] Adjusted for age, sex. [c] Adjusted for model 1 + death, attrition. [d] Adjusted for model 2 + height, height^2, BMI. [e] Adjusted for model 3 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression, [f] Adjusted for model 3 + smoking history, leisure time physical activity. [g] Adjusted for model 3 + maternal education, paternal social class, adulthood social class. [h] Adjusted for model 3 + education. [i] Adjusted for model 3 + verbal memory. [j] Adjusted for all covariates in Models 1–8.

[k] β= 0.11 (0.09, 0.13), p<0.001 at age 60-64 and β= 0.08 (0.05, 0.11), p<0.001 at age 69

4.3.4 Adolescent coordination

Quicker finger (β= 2% (95% CI: 0.4, 3.6%; p<0.001; Table 4.5) and foot tapping (β= 2.4% (95% CI: 0.6, 4.1%; p<0.001; Table 4.6) were both associated with better balance ability at age 53. Both associations grew larger with age, nearly doubling in size by age 69 (see Table 4.5, 4.6 footnote ϕ). A visual representation of this is provided in Figures 4.6 and 4.7. The associations and age interaction terms were attenuated after adjustment for covariates. Similar to childhood cognitive ability, education, followed by socioeconomic indicators and then health behaviours appeared to explain the most variation in balance ability when added to the model (Table 4.5 and 4.6).

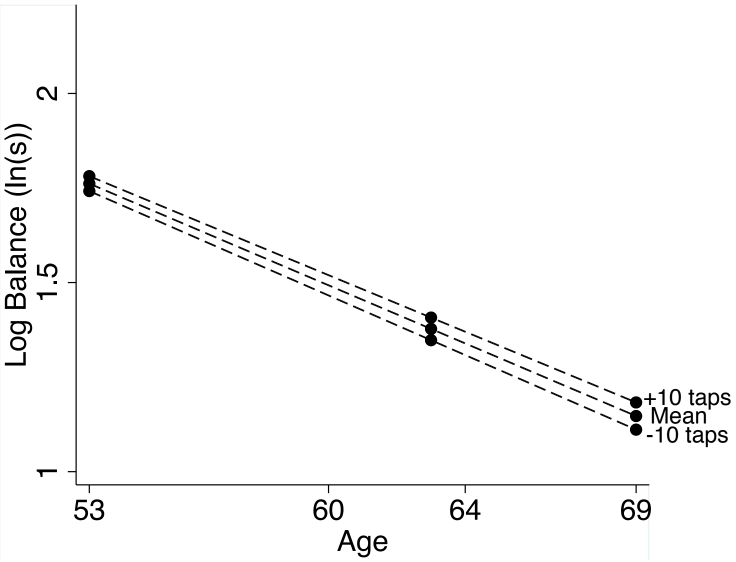


Figure 4.6 Association between log-transformed balance at ages 53, 60-64 and 69 and finger tapping using unadjusted multilevel models

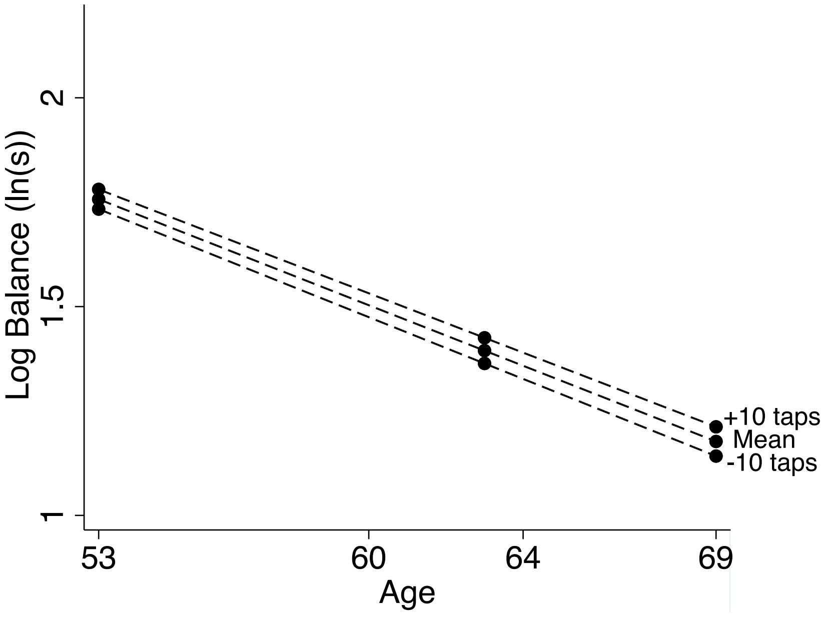


Figure 4.7 Association between log-transformed balance at ages 53, 60-64 and 69 and foot tapping using unadjusted multilevel models

Table 4.5 Associations between finger tapping (per 10 taps) and log-transformed balance time (sec) in multilevel models

	Change in logged balance time at age 53 per 10 finger taps [intercept]		**Finger tapping (per 10 taps) *age (year) interaction [slope]**	
Model:	**Coefficient (%) (95% CI)**	***p-value***	**Coefficient (%) (95% CI)**	***p-value***
Maximal available sample	**Obs =** 5739 (n=2448)			
0: age [a], sex [b]	0.020 [k] (0.004, 0.036)	0.02	0.0010 (-0.0003, 0.0022)	0.12
Complete cases sample	**Obs =** 4408 (n=2108)			
1: age, sex [b]	0.011 (-0.006, 0.028)	0.20	0.0018 (0.0004, 0.0032)	0.01
2: model 1+ death + attrition [c]	0.011 (-0.006, 0.027)	0.23	0.0017 (0.0004, 0.0032)	0.01
3: model 2 + anthropometric [d]	0.012 (-0.005, 0.028)	0.17	0.0014 (0.00004, 0.0028)	0.04
4: model 3 + health status [e]	0.010 (-0.006, 0.027)	0.23	0.0014 (0.00002, 0.0028)	0.05
5: model 3 + health behaviours [f]	0.011 (-0.006, 0.027)	0.20	0.0014 (-0.0005, 0.0028)	0.06
6: model 3 + SEP [g]	0.005 (-0.012, 0.021)	0.58	0.0018 (0.0004, 0.0032)	0.01
7: model 3 + education [h]	0.004 (-0.012, 0.020)	0.62	0.0018 (0.0004, 0.0032)	0.01
8: model 3 + verbal memory [i]	0.006 (-0.011, 0.022)	0.50	0.0017 (0.0004, 0.0031)	0.02
9: fully adjusted [j]	0.001 (-0.015, 0.017)	0.88	0.0018 (0.0005, 0.0032)	<0.01

[a]Age is centred at age 53 = 0 in all models. [b]Adjusted for age, sex. [c]Adjusted for model 1 + death, attrition. [d]Adjusted for model 2 + height, height^2, BMI. [e]Adjusted for model 3 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression. [f]Adjusted for model 3 + smoking history, leisure time physical activity. [g]Adjusted for model 3 + maternal education, paternal social class, adulthood social class. [h]Adjusted for model 3 + education. [i]Adjusted for model 3 + verbal memory. [j] Adjusted for all covariates in Models 1–8. [k] β = 0.031 (0.018, 0.044), $p<0.001$ at age 60-64 and β = 0.035 (0.018, 0.052), $p<0.001$ at age 69

Table 4.6 Associations between foot tapping (per 10 taps) and log-transformed balance time (sec) in multilevel models

	Change in logged balance time at age 53 per 10 foot taps [intercept]		**Foot tapping (per 10 taps) *age (year) interaction [slope]**	
Model:	**Coefficient (%) (95% CI)**	***p-value***	**Coefficient (%) (95% CI)**	***p-value***
Maximal available sample	**Obs =** 5747 (n=2450)			
0: age[a], sex[b]	0.024[k] (0.006, 0.041)	<0.01	0.0007 (-0.0007, 0.0021)	0.32
Complete cases sample	**Obs =** 4408 (n=2108)			
1: age, sex[b]	0.012 (-0.007, 0.031)	0.20	0.0014 (-0.0002, 0.0030)	0.07
2: model 1+ death + attrition[c]	0.011 (-0.008, 0.030)	0.25	0.0015 (-0.0001, 0.0030)	0.07
3: model 2 + anthropometric[d]	0.010 (-0.008, 0.028)	0.28	0.0013 (-0.0003, 0.0028)	0.11
4: model 3 + health status[e]	0.010 (-0.008, 0.028)	0.29	0.0014 (-0.0003, 0.0028)	0.12
5: model 3 + health behaviours[f]	0.010 (-0.008, 0.028)	0.20	0.0011 (-0.0004, 0.0027)	0.16
6: model 3 + SEP[g]	0.005 (-0.013, 0.023)	0.58	0.0015 (-0.00003, 0.0031)	0.06
7: model 3 + education[h]	0.004 (-0.014, 0.022)	0.64	0.0015 (-0.00003, 0.0031)	0.05
8: model 3 + verbal memory[i]	0.005 (-0.013, 0.023)	0.62	0.0016 (0.00001, 0.0031)	0.05
9: fully adjusted[j]	0.002 (-0.016, 0.020)	0.81	0.0016 (0.00004, 0.0031)	0.04

[a] Age is centred at age 53 = 0 in all models. [b] Adjusted for age, sex. [c] Adjusted for model 1 + death, attrition. [d] Adjusted for model 2 + height, height^2, BMI. [e] Adjusted for model 3 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression. [f] Adjusted for model 3 + smoking history, leisure time physical activity. [g] Adjusted for model 3 + maternal education, paternal social class, adulthood social class. [h] Adjusted for model 3 + education. [i] Adjusted for model 3 + verbal memory. [j] Adjusted for all covariates in Models 1–8. [k] $\beta = 0.031$ (0.018, 0.044), $p<0.001$ at age 60-64 and $\beta = 0.035$ (0.018, 0.052), $p<0.001$ at age 69

4.4 Discussion

4.4.1 Main findings

This chapter investigated the association between early life neurodevelopmental factors and balance ability in mid and later life. Individuals who began sitting or walking at an average age and those with higher levels of childhood cognitive ability and coordination (both finger and foot tapping) had better balance in later life. The relationship of age of first sitting with balance ability remained consistent over time, however there was evidence that the associations of age of first walking, childhood cognitive ability and the coordination tests with balance ability changed with age. Age of first walking was associated with balance at age 53, but this association was no longer present at age 60-64 or 69. Childhood cognitive ability was associated with balance at all three ages, however the interaction terms in the multilevel models suggest that higher levels of childhood cognition may have a stronger association with balance in midlife (age 53) compared with later life (age 69). Finally, there was no association between finger and foot coordination and balance ability at age 53, although a positive association emerged by age 69. All associations were slightly attenuated after adjustment for various covariates including anthropometry, socioeconomic indicators and health behaviours, however did not remain in the fully-adjusted models.

4.4.2 Comparison with other studies

As described in the introduction of this chapter (section 4.1.1 and 4.1.2), there are very few longitudinal studies that have investigated early life neurodevelopmental indicators in relation to later life balance and thus, comparisons are limited. Much of the work in this chapter built on previous research in NSHD that examined how these early life factors are associated with balance or other measures of physical capability at age 53 [156,169,171]. These studies reported associations between modal age of first walking [169], higher childhood cognitive ability [169,171], higher childhood coordination [169] and greater balance ability at age 53. As these studies were published before data were collected at ages 60-64 and 69, the authors were unable to investigate how these neurodevelopmental markers are associated with balance at later ages or how these associations change with age.

One other study has examined how infant motor development is associated with balance in adulthood [167], reporting that earlier attainment of walking and standing were associated with better balance performance at age 31 in the Northern Finland Birth Cohort (NFBC). Comparisons between this study and the results presented in this chapter are limited by differences in both the exposure and outcome variables. The age of milestone attainment in the NFBC was reported at 1 year (compared with 2 years in the NSHD). It is likely that many participants still had not reached their developmental milestones by this age; for example, this chapter demonstrated that mean age of attainment of first walking unaided in NSHD was 13.68 months ±2.60 and 13.60 ±2.46 in males and female, while age of first standing was 11.48 ±2.43 and 11.36 ±2.11 respectively (see Table 4.1). The NFBC measured balance ability at age 31; while this may have a better represent peak balance performance, it is not possible to compare balance at age 31 with balance at ages 53, 60-64 and 69 which better represent age-associated decline in balance ability. Outside of the NSHD studies by Kuh and colleagues [156,169,171] discussed above, no associations of early childhood cognition and coordination with later life balance have been investigated.

While this may partly be due to a lack of studies with appropriate data, associations between early neurodevelopmental pathways and other measures of physical capability have been explored. It is unclear whether this is indicative of studies failing to assess balance ability or a publication bias in relation to non-significant balance results. These studies have identified associations between age of first walking [156,167,169], age of first standing [156,167,169], childhood cognitive ability [156,169,170,406] and muscle strength, muscle endurance, aerobic fitness and walking speed. A recent study by Cooper et al. [170] was the first to examine the relationship between childhood cognitive ability and age-related change in physical capability, suggesting that higher childhood cognitive ability may be related to reduced risk of decline in grip strength and chair rise speed in midlife. This chapter therefore presents novel analyses of the relationship between early neurodevelopmental factors and balance in mid and later life. It extends the small body of evidence that consists primarily of research using NSHD data and identifies the need for further research in this area.

4.4.3 Explanation of findings

There are several possible mechanisms that may explain the associations between early neurodevelopmental markers and balance. As previously described, the ability to balance successfully relies on physical and cognitive (sensori-motor integration) components. This section will explore both motor and cognitive pathways, however as these two domains are frequently inter-related, there is considerable overlap.

First, evidence has consistently demonstrated that those with better physical capability in other areas [427-430] have higher balance performance as there is a large musculoskeletal component to balance ability that relies directly on motor ability and physical strength. Overall physical capability, including strength and mobility, in adulthood may be influenced by early motor development and neural connections. Differences in infant motor development are reflective of early variation in the responsible areas of the brain [414]; attaining physical milestones within a time-sensitive window may be fundamental to form initial neural connections required for motor ability. In this chapter, those who began sitting late or walking at the median and modal ages – average developers – had better balance ability in mid and later life. Those with delayed development (Figure 4.2) had notably lower balance ability, which could infer that late development is a disadvantage that persists into mid and later life. It is possible that advantages yielded from structural and functional neural maturation during critical periods in infancy may be sustained throughout life; this would explain continued advantages in motor ability in adulthood [431]. Conversely, late motor development may be a marker of problems across multiple systems [163,432].

Second, balance ability in late life is strongly dependent on the sensori-motor integration of the nervous system (section 1.2, Chapter 1). Those with lower cognition or with known cognitive impairments often have contemporaneous difficulty in balancing; this may be due to reduced ability to successfully integrate sensory information and afferent motor movement [213]. As cognitive ranking remains fairly consistent across the life course [157,380,381,386]; early life advantages of higher cognitive ability may extend past initial formation of neural connections to influence cognitive ability in adulthood. Evidence has consistently demonstrated that those with higher cognitive ability [171,212,433,434] have higher balance performance; Chapters 5 and 6 investigate the role of adulthood cognition further. The stronger strength of the association between early life cognition and balance compared with other physiological measures such as grip strength or walking speed [156,169,170,406] suggests that lifelong cognitive reserve may play an important role in maintaining balance when physical reserve begins to deteriorate. This is particularly important when considering that childhood cognition and coordination demonstrated different patterns of association with age. As balance ability declines with age and relies less on cognitive ability (both childhood cognitive and adult verbal memory (section 3.3.6, Chapter 3)), automated motor processes may play a greater role and thus higher levels of coordination may be important in maintaining balance ability. How well underlying cognitive reserve is able to mitigate the age-related decline of vision, strength and mobility may reflect how well an individual is able to maintain their balance; in turn, this may explain individual variability in patterns of decline.

As education may play a unique role on the pathway between childhood cognitive ability and adulthood cognitive ability, it was separated from other SEP indicators when building the models. The addition of education to the model partially explained some of the association between childhood cognitive ability and balance (see Table 4.4); this is discussed further in Chapter 5.

Third, higher cognitive and physical ability in childhood may play a powerful role in positive health exposures across the life course that subsequently contribute to balance. For example, higher childhood cognition is associated with healthy behaviours such as reduced likelihood of smoking [435-437] and sedentary behaviour [419] as well as greater educational attainment [438,439], higher adulthood SEP [435] and higher levels of leisure time physical activity[419,440]. The Matthews effect, in which early advantages lead to further advantage over time [441], may explain some of the pathways through which those with higher motor and cognitive childhood are more likely to have better balance ability in mid and late life. Better motor skill development – in this case, better coordination – is associated with high participation in physical activity in childhood, adolescence and early adulthood [81,419,421]. Physical activity levels have also been shown to track over time, such that physically active children are more likely to remain physically active throughout life [420,442,443]. These higher levels of physical activity are subsequently associated with better motor skills and better overall strength, mobility and balance ability [173-179]. Similarly, children with better cognitive performance in early school years may receive more encouragement and opportunity, which enables them to progress and thus maintain or even improve their cognitive rank in comparison to their peers.

Next, socioeconomic differences may underlie variability in cognitive and motor development, health behaviours across the life course and health status. A systematic review identified that those with lower childhood SEP had higher balance impairment in adulthood compared with those with higher childhood SEP [159]. Motor and cognitive development in childhood may be heavily influenced by socioeconomic indicators [444,445], although the direction of this association is not always clear. Lower SEP shows a strong association with poor health outcomes including lower physical capability, [159] and increased risk or morbidity and early death [446-449].

This chapter demonstrated that some of the associations between the neurodevelopmental factors and balance ability in mid to later life changed with age. Balance ability is complex, relying on several domains of afferent information including vision, proprioception and vestibular function as well efferent musculoskeletal strength. At older ages, balance ability may rely more on age-related declines in these areas, rather than underlying cognitive and motor neural pathways. Inter-individual differences in balance ability between older adults may, therefore, be due to individual variation in age-related decline across various domains. Understanding how neurodevelopment in early life as well as neurodegeneration in later life may underlie changes in balance ability could help inform interventions targeted at neurodevelopmental pathways, thereby contributing to delay or decreases in declines in balance ability in mid and later life.

4.4.4 Methodological considerations

The overall strengths and limitations of the thesis were discussed in Chapter 2.1.3, while the considerations specific to this chapter are summarised below. Considerations relevant to all chapters are discussed in full in chapter 8.

4.4.4.1 Strengths

There are several major strengths in the analyses and data used in this chapter. The availability of longitudinal data on several major neurodevelopmental markers and multiple measures of balance performance offers a novel opportunity to investigate associations between early life development and mid-later life balance. Further, neurodevelopmental indicators were prospectively collected at several important ages during childhood (ages 2, 8, 11, and 15), thus limiting retrospective recall bias and ensuring higher accuracy of responses. Having multiple measures of balance performance enabled multilevel models to be used in the analyses, thus increasing the statistical power and being able to investigate changes in associations over time. Adjustments were made for a range of covariates that could have explained the associations of interest, enabling a potentially more accurate estimation of the true association. Many studies that investigate physical capability exclude individuals who are unable to complete the test due to physical or health reasons from the analyses. This bias was minimised by including those in the study who were unable to complete the test due to health reasons.

4.4.4.2 Limitations

There are several methodological considerations surrounding missing data that should be taken into account when interpreting these results. Although missing balance data were thoroughly investigated in section 2.4, there remain some inherent limitations. Cognitive tests were conducted using standardised tests to ensure consistency across test collection; however, childhood tests were not identical as the test changed at each age to better reflect concurrent cognitive ability (i.e. a test of picture intelligence at age 8 vs a test of mathematical ability at age 15). Additionally, the age of milestone attainment was reported by the study member's mother; it is hypothesised there may be a social desirability bias in reporting these milestones as factors such as SEP may influence its perceived importance.

4.5 Conclusions and further research

This chapter has shown evidence of an association between early life neurodevelopmental factors – including age of first sitting, age of first walking, childhood cognitive ability and childhood coordination – and balance in later life. The association of balance with childhood cognitive ability decreased with age, while the association with childhood coordination increased. All associations were slightly attenuated by the inclusion of other covariates that may influence balance, indicating that association may be mediated by several different pathways such as health behaviours, socioeconomic position and education. This has implications for future research as well as potential policy implications as it suggests that both early life and midlife factors should be targeted in further studies or possible interventions; this is explored further in section 8.2 (Chapter 8). That some of these neurodevelopmental factors are differentially associated with balance at different ages provides support for the hypothesis that different systems are drawn upon in order to maintain balance in later life. For example, coordination-related reserve may play an important role in balance ability when physical and cognitive decline occurs in later life.

As discussed above, adulthood cognition may directly mediate the association between childhood cognitive ability and balance in mid and later life. Chapter 5 investigates the role of adulthood cognition and educational attainment on balance ability. The associations of age of first walking and sitting with balance were not robust; the associations diminished when the sample size changed. This may reflect a weak overall association of these milestones with balance, given that normal variation in milestone attainment is expected. Age of attainment of motor milestone ages may be useful at identifying specific problems in late developers, while objective assessment of motor ability in infants – in addition to minimising mother's self-report bias – may be more informative for later life physical capability and decline. For example, coordination at age 15 demonstrated increasingly important associations with balance at later ages; further research should assess if coordination, or other motor skills, in infancy show similar patterns. If so, assessment earlier in life could identify individuals who would benefit from interventions during the important childhood development years.

CHAPTER 5: COGNITIVE DOMAINS AND BALANCE ABILITY IN MID AND LATER LIFE

Building on the association between childhood cognition and balance in Chapter 4, this chapter aims to explore the cognitive data available in NSHD from age 43 to 69 and investigate associations between individual domains of cognition and balance. Characterising how distinct cognitive domains are differentially associated with balance, both cross-sectionally and longitudinally, may help improve our understanding of patterns of age-related change in cognitive and balance abilities. As successful balance requires cognitive integration and sensory input from the surrounding environment [450], balance is thought to be one of the domains of physical capability that is most closely linked to cognitive ability.

Following an introduction to cognition (section 5.1.1), the proposed mechanism of the role of cognition in balance is explored in detail (section 5.1.2). The literature review will summarise studies that have considered associations between cognition and subsequent balance ability (section 5.1.3). The gaps in this research are highlighted (section 5.1.4) and the main chapter objectives are described (section 5.1.5). Chapter 6 builds on the results of this chapter by investigating a bidirectional association, thus literature on concurrent trajectories of cognition and balance are summarised in section 6.1.

5.1 Introduction

5.1.1 A brief introduction to cognition

There is no single consensus on classification of cognitive domains, with several different taxonomies proposed. One common classification considers the broader categories of crystallised and fluid intelligence. *Fluid intelligence* refers to the ability to think and reason in order to solve problems, while *crystallised intelligence* reflects an individual's ability to use previous experience and knowledge and relies on long-term memory [451-454]. Additionally, as their names suggest, fluid intelligence can change over time whereas crystallised intelligence tends to remain stable with age [451].

Fluid intelligence consists of cognitive domains involved in processing and manipulation of information such as attention, working memory, and executive function [451-454]. *Attention*, which can include selective, divided or sustained attention, is defined as the capacity to actively process specific information in one's environment [455]. *Working memory* is defined as a short-term facility to store and manipulate information needed to complete the task at hand [456]. Similarly, *prospective memory* is the ability to remember a previous plan at the correct moment [457]. *Executive function* covers a series of higher order processes involved in decision making such as problem solving, organisation, reasoning, inhibition, emotional control, planning, and self-monitoring, amongst others [458,459]. These areas of cognition exhibit gradual age-related decline across adulthood, beginning as early as age 20 in some domains [457,460-462]. Table 5.1 provides an overview of these cognitive domains, their definitions, examples and patterns of change with age.

In contrast to fluid intelligence, crystallised intelligence tends to improve across midlife, plateau later in life before demonstrating slight decline thereafter [461,463]. *Long term memory*, "the process of retaining information over time" [464], can be subdivided into *episodic, semantic, procedural,* and *source memory*. Detailed definitions of each type of memory are provided in Table 5.1. There is some evidence that episodic and source memory decline earlier than procedural or semantic memory [465-470] (see Table 5.1).

Speed of processing contributes to the efficiency of all other cognitive operations

Table 5.1 Summary of cognitive domains: definitions, examples and associations with age

Cognitive domain	Sub-type	Definition	Example	Change with age [a]
Attention	*Selective* [F]	The ability to filter out unimportant stimulus information and focus on a single task	Searching a crowd for a friendly face	Decline from early adulthood
	Divided [F]	The ability to multitask and process multiple points of information at the same time	Processing other cars, traffic lights/signs, and pedestrians while driving	Decline from early adulthood
	Sustained [F]	The ability to maintain concentration on a single task for a sustained period of time.	Reading a book	Inconsistent evidence
Memory	*Working* [F]	Temporarily remembering information available for processing.	Remembering a number before writing it down	Decline from early adulthood
	Semantic	Long term memory of factual information and knowledge	Knowledge of capital cities or understanding of mathematics	Increase with age until late life, slight decline at very old ages
	Episodic [C]	Long term memory of individual-specific experiences including times, places, interactions, emotions or other relevant aspects	Remembering an autobiographical event such as a wedding or an interaction with a friend	Decline from midlife
	Procedural [C]	Long term memory of how to perform a certain skill or activity	Tying a shoelace or riding a bike	Increase or remains with age
	Source [C]	Long term memory of the context of an experience or piece of information rather than the memory of the content itself	Remembering that you were told something on the phone but not what it was	Decline from midlife
	Prospective [F]	The ability to "remember to remember".	Remembering to reply to an email at a later time	Decline from early adulthood
Executive functioning [F]	-	The higher-order processes that govern goal-directed action and adaptive responses to novel, complex, or ambiguous situations.	Problem solving, organising, planning, reasoning, inhibiting, self-monitoring, controlling emotions	Inconsistent evidence, decline from early adulthood or midlife
Processing speed [P]	-	How quickly a person is able to carry out simple or automatic cognitive tasks	Involved in any of the examples above	Decrease from early adulthood

F: fluid intelligence, C: crystallised intelligence, P: processing speed is thought to contribute to both fluid and crystallised intelligence.

[a] References for this column have been referred to in text on previous pages. Specific ages are not provided in this table as there is heterogeneity of the exact age where decline occurs. Early adulthood generally refers to age 20-30, while midlife refers to age 50-65.

including fluid and crystallised intelligence [471]. Slower processing speed can lead to diverted attention, impeded working memory, impaired executive function or slower retrieval of long term memory [471]. Some theoretical models of cognitive ageing consider processing speed to be the driver of cognitive decline [472]. Compared with younger adults, older individuals have reduced cognitive resources available for processing and as a result, there is an obvious decrease in processing speed. This reduced speed may manifest as deficits in attention, memory or executive function [472,473].

5.1.2 How age-related cognitive changes influence balance

The mechanism through which cognitive processes are involved in balance and posture is complex, with contributions from distinct subcortical and cortical areas of the brain as well as neural pathways between both areas. This is explored in further detail below.

5.1.2.1 Subcortical processes involved in balance

Integration of input from visual, vestibular and proprioceptive sources mainly happens at a subcortical level, with important contributions from the brainstem, the cerebellum and the basal ganglia [374,474,475]. The *brainstem* is responsible for the organisation and integration of the major components of balance. It is here that information from visual, vestibular and proprioceptive sources interact with information from the cerebellum and cerebrum [476]. The *cerebellum* is considered the motor coordination centre of the brain. Motor commands of descending pathways pass through the cerebellum, where modifications are made to produce fluid and accurate body movements. This can include postural adjustments, learned motor adaptations and compensation for changes in musculoskeletal burden or positioning [475]. The *basal ganglia* are primarily responsible for regulating motor control, but are also known to play a key role in learning and executive function [477,478]. Similar to the cerebellum, the basal ganglia form iterative synaptic loops with the cerebral cortex [478,479]. Neuronal activity within these loops are involved with both movement and aspects of cognitive function [480].

Connections between subcortical and cortical processes are crucial for maintenance of balance [481], although most neurological studies have focused on brain activity in the subcortical areas of the brain given its role in motor control.

However, communication between upper and lower brain processes is an important part of the cognitive mechanism of balance, as the brainstem continually integrates sensory input with ensuing commands from the cerebral cortex [476]. Studies of neuroplasticity have also shown that stimulation to cerebello-thalamo-cerebral circuits can improve sensation, balance and mobility in patients with acquired or traumatic brain injuries [482-484]. The importance of communication between subcortical and cortical parts of the brain may be partially due to the role of higher order actions involved in balance ability. This is explored further below.

5.1.2.2 Cortical processes involved in balance

The role of cortical processes and higher order thinking in maintaining successful balance is not as well established, although it has been suggested that poor functioning in areas of the cortex responsible for attention, memory, executive function or processing speed may partially explain poor balance impairment [450,485]. Subcortical processes innately contribute to overall cognitive performance and efficiency [486], there is benefit in exploring how measurable cognitive domains may be associated with physical balance. Below, the role of specific higher level cognitive domains in balance ability is explored in greater detail below.

Depending on the complexity of the desired task, *attention* can play a large role in maintaining balance. In controlled laboratory scenarios – such as the one-legged stand – individuals are able to focus their complete attention on balancing whereas in everyday situations, different stimuli are continually competing for attention. Selective attention can be important to filter out unimportant stimulus information (e.g. distracting visual cues), while divided attention allows an individual to carry out more than one task at a time (e.g. walking and talking) [471]. Dual task paradigms, that include simultaneous physical and cognitive tasks, have demonstrated the importance of attention in balance [487]. With increasing complexity of multiple tasks, the human individual will reach a threshold of both cognitive and balance performance. Even in healthy adults, this commonly results in declining performance in one or both tasks compared to doing a single task, as there is competition and prioritisation for attention [450].

Memory and *executive function* can play short and long-term roles in balance. For example, memory of unstable surfaces (e.g. stepping off a curb or walking on ice) can minimise balance instability by allowing the individual to make necessary changes to maintain an upright position. These expectations about the impact of the surrounding environment on balance relies heavily upon previous experience. This can be particularly valuable for older adults as it can assist them in correctly interpreting and responding both proactively and reactively [488].

Action inhibition and task switching are two major components of executive function that are involved in balance performance [458]. Action inhibition is the ability to suppress a tendency to react to irrelevant stimuli [458]. This can include avoiding cognitive distractions or avoiding inappropriate motor responses. Task-switching is similar to divided attention and requires working memory in order to achieve the goals of each task [489]. There is strong evidence in dual task paradigms that older adults are less able to divide their attention and working memory between multiple tasks than younger adults [490]. This could translate to difficulties maintaining balance in a situation with competing cues. There remains considerable uncertainty in how different neural pathways involved in balance are related to one another particularly when one considers how reliance on these pathways may change across the life course.

5.1.2.3 Indirect pathway between cognition and balance

In addition to this direct mechanism whereby cognition contributes to balance ability, a secondary pathway is proposed: cognition may act indirectly on balance via a socio-economic, behavioural and health pathway. Figure 5.1 provides a conceptual model of both of these pathways. Education, adult cognition and SEP are all highly inter-correlated [491,492], as those with higher levels of adult cognition are more likely to have higher educational attainment and a higher SEP. These individuals are also more likely to partake in healthy behaviours, more likely to have positive health outcomes and less likely to demonstrate physical impairments (including balance ability) [160,448,493,494].

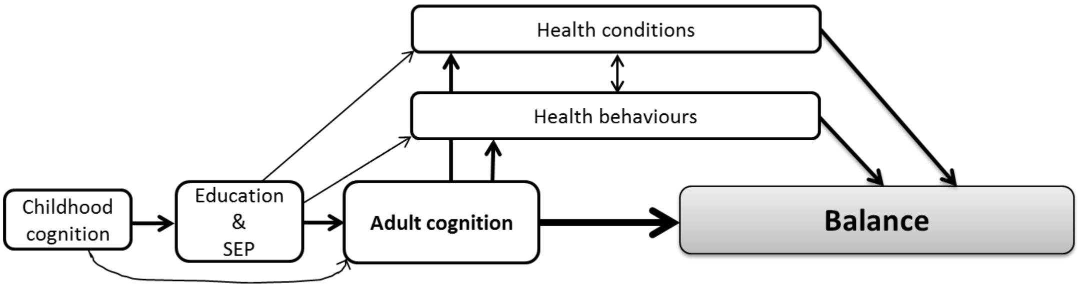


Figure 5.1 Conceptual model theorising pathways of association between adult cognition and balance

5.1.3 Evidence of associations between cognition and subsequent balance ability

Evidence from both cross-sectional and longitudinal studies have consistently demonstrated positive associations between cognition and balance in mid and later life. While a pathway of association was outlined in section 5.1.2, it is important to recognise that the direction of the association between cognition and balance ability has not been fully established. However, the majority of evidence has focused on associations between cognition and subsequent balance ability (as described in Chapter 1, section 1.4.4). Thus, this literature review summarises associations of balance ability with cognitively impaired groups such as dementia (section 5.1.3.1), aggregate cognitive scores (section 5.1.3.2) and specific domains of cognition (section 5.1.3.3). Literature on bidirectional associations is explored in Chapter 6 (section 6.1).

5.1.3.1 Clinically diagnosed cognitive impairments

Many cross-sectional studies have demonstrated that individuals with diagnosed cognitive impairments – such as Alzheimer's disease (AD) or mild cognitive impairment (MCI) – have poorer balance than non-cognitively impaired individuals [270,288,289,495,496]. Balance difficulties appear to increase with increasing severity of cognitive impairment; for example, those with AD have even poorer balance than those with MCI [289,495,496]. These findings have been found across age, sex, county and even amongst different components of balance control (as measured with the Balance Evaluation Systems Test (BEST)) [495]. The BEST assesses six components of balance including biomechanical constraints, stability limits, anticipatory postural adjustments, postural responses, sensory orientation and stability in gait. All components of balance control decreased with increasing severity of cognitive impairment and that these associations were strongest in those with moderate AD as compared to mild AD, MCI or subjective cognitive impairment (SCI) [495].

No studies examined longitudinal follow-up of balance ability amongst cognitively impaired samples. This may be due to the cross-sectional evidence that shown that balance impairments are already present in these baseline populations. However, several longitudinal studies have investigated baseline balance as a potential marker of future cognitive impairment. Several studies of adults over the age of 65 assessed the impact of balance ability on dementia risk with follow-up ranging from 1 year (n=180) [497] to 2.6 years (n=578) [291] to 12 years (n=381) [292]. One study reported that in fully-adjusted models, each misstep on a figure of 8 balance and gait task was associated with 1.06 (1.03–1.10) increased risk of cognitive impairment at follow-up [497]. The other two studies demonstrated that – after adjustment for education, chronic health conditions and other covariates – individuals with impaired balance were 1.90 [291] to 2.86 [292] times more likely to develop dementia than those with no balance impairment. One of these studies – which investigated those aged ≥90 – reported that balance ability was more strongly associated with incident dementia than walking speed, grip strength or chair stands [291]. With strong evidence of poor balance in cognitively impaired individuals, there is a need for a more in-depth investigation of the temporality of cognitive and balance impairments. For example, it is unclear whether these results suggest that balance ability can indicate future cognitive impairment or if the poor balance ability is a result of cognitive decline that precedes a dementia diagnosis.

5.1.3.2 Overall cognitive scores

This association between cognition and balance ability is also present in cognitively healthy, community-dwelling individuals. Several cross-sectional studies demonstrated associations between better balance ability and higher performance on the Mini-Mental Status Examination (MMSE) [498-500]. The MMSE is a screening tool for cognitive impairment and is used in both clinical and research settings [501]. Similar to above, this association remains after adjustment for anthropometric, socioeconomic, behavioural and comorbidity covariates [498] and across multiple types of balance measurements including semi tandem, tandem and one-legged stands [499]. While many studies have examined cognition and physical function (e.g. SPPB) longitudinally, longitudinal studies that have specifically examined balance ability and cognition are rare. A study of high functioning Americans aged 70-79 reported that both baseline and decline in overall cognitive ability (an aggregate score of five cognitive factors) was associated with subsequent poorer balance performance after a seven year follow-up [433]. No comparable study of baseline balance ability and subsequent overall cognitive ability was found.

5.1.3.3 Specific domains of cognition

In addition to studies focusing on overall cognition, several studies have demonstrated cross-sectional associations between specific domains of cognition and balance ability [7,212,498,499]. Balance ability was primarily considered the dependent variable, with studies reporting different patterns of association across different domains. For example, a US-based cohort of older adults (≥65) reported that better performances on working memory and processing speed tasks were cross-sectionally associated with better standing balance ability [498]. A similar cross-sectional UK study of middle aged adults (mean age: 44.5) [212] reported that higher scores of executive functioning, processing speed and both visual and verbal memory were associated with higher balance performance on the Berg Balance Scale. There were several null associations as well, with several studies demonstrating no association of verbal memory [499], verbal fluency [499] and IQ score [212] with balance ability. While it has been suggested that fluid measures of cognition may be more strongly associated with balance than crystallised measures [212], conflicting findings across studies do not support this.

Differences in study findings may be partially explained by heterogeneity in the standing balance test (e.g. Berg Balance Scale [212] vs one-legged stand [498,499]). A cross-sectional study of community-dwelling adults aged ≥60 suggested that distinct cognitive domains may play dissimilar roles in different types of balance [7]. The authors reported an association between dynamic balance (measured using the functional reach test) and tests of processing speed, perceptual reasoning, visuospatial ability and executive functioning. Notably, there was no association between static balance (measured using a two-legged stand on a balance board) and any of these measures, supporting the hypothesis that dynamic balance may require more cognitive processing than static balance [7]. This finding lends support to the importance of motor and sensory coordination in physical ageing processes but further understanding of the mechanisms involved in both types of balance are needed.

Only one longitudinal study of distinct cognitive domains and balance ability was found. In an earlier publication in NSHD, Kuh et al. [171] reported that higher cognitive ability at ages 15, 43 and 53 was associated with better balance performance at age 53. Separate cognitive domains including verbal memory (ages 43, 53), processing speed (ages 43, 53), verbal fluency (age 53) and reading ability (age 53) were each strongly associated with balance performance [171]. This provides support for associations of both fluid and crystallised cognition with balance performance. In addition to looking at concurrent cognitive or balance ability, Kuh et al. [171] also assessed cognitive decline, reporting that slower decline in memory and processing tasks between ages 43 and 53 was associated with better balance at age 53.

5.1.4 Summary and gaps in the literature

The studies summarised above largely provide for an association between higher cognition function and better balance ability. These associations were present cross-sectionally and longitudinally and in both cognitively impaired and cognitively healthy samples. Balance ability was associated with global measures of cognition as well as specific cognitive tests of executive function, working memory, verbal memory, processing speed and reasoning. Different strengths of associations suggest that specific components of cognition may play greater roles in maintaining balance. For example, fluid measures of cognition may be more strongly associated with balance than crystallised measures although the evidence is not always consistent. Furthermore, there is high correlation between many cognitive tests which can present a challenge when assessing their independent contribution to balance.

There are several limitations of the current evidence. First, most of the evidence on associations between cognition and balance relies on cross-sectional data. As both cognitive and balance abilities demonstrate age-related changes, it can be difficult to infer the direction of association. Studies that have examined longitudinal associations have fairly short follow-up (<3 years). In longitudinal studies with a short follow-up, it can be difficult to establish temporality; an association between balance and cognition could indicate reliance of one construct on the other or it could indicate a concurrent decline with ageing.

Second, most of the studies summarised above have age-heterogeneous samples or consider older samples (aged ≥65 only). Adjusting for age may not be sufficient to avoid age confounding as cohort differences could underlie age-related differences in cognitive functioning [502]. The age homogeneity of NSHD can eliminate the contribution of age to any association; this can address gaps in some of the previous studies that may have been confounded by age. Furthermore, examining this association during midlife can provide evidence of when decline in these areas begins and assess if decline occurs earlier in certain domains.

Third, the direction of association tested often depends on the authors' hypotheses and how the analyses are modelled (e.g. cognition to balance or balance to cognition). This was seen in cross-sectional studies, where balance was often chosen as the dependent variable, and in longitudinal studies, where only balance ability was examined as outcome despite the availability of longitudinal assessments of cognition.

Fourth, these studies have often considered an aggregate measure of cognition or are limited in comparison of cognitive domains. This is particularly true for longitudinal evidence, where only one study examined longitudinal associations in different cognitive domains. This study used NSHD data until age 53 [171] and did not consider how the associations changed with time. A major strength of NSHD is the availability of ten different cognitive tests across four different ages (ages 43 to 69) with two tests being repeated at all four ages. Initial investigation of the associations between each cognitive test in NSHD and balance can identify 1) specific cognitive domains involved in balance and 2) determine if these associations are similar at all ages or change with age.

Finally, the majority of studies that assessed this association have considered very few mediating or confounding variables in their models. By examining potential pathways through which cognition and balance are related, one can better understand the mechanism through which these two constructs are associated. For example, as proposed in section 5.1.2, education and health behaviours could influence this association while the inclusion of other covariates in analytical models could minimise confounding.

In summary, there is consistent evidence of an association between cognition and balance ability. This association appears to differ across cognitive domains, but there has been no longitudinal investigation of this across mid and later life. The direction of association has not been well investigated nor established, with the majority of evidence examining how cognition may influence balance ability. Due to the supporting literature as well as the conceptual model (see section 5.1.2) proposing that balance ability relies on cognitive processes, this chapter investigates how cognitive ability may be associated with subsequent balance ability. Chapter 6 explores the bidirectional nature of the association in further detail, hypothesising how balance ability could directly influence cognition.

5.1.5 Objectives and hypotheses

To address the gaps in research identified above, this chapter aims to utilise all of the available cognitive data in NSHD to test how different domains of cognition are associated with subsequent balance in mid and later life. The specific objectives are:

i) to examine cross-sectional associations between different cognitive domains and balance ability in mid to later life;
ii) to investigate longitudinal associations between midlife cognitive domains and subsequent balance ability;
iii) to explore if individual cognitive domains in midlife are independently associated with balance ability;
iv) to investigate how adjustment for sex, anthropometric, socioeconomic, behavioural and psychosocial factors influences the associations described in objectives i, ii and iii.

NSHD has many cognitive measures assessed at ages 43, 53, 60-64 and 69. Analyses may differ depending on available data (age of test, repeated measure, continuous vs categorical data) as this chapter aims to better understand initial associations with balance.

Based on the review of the literature of the cognitive domains and an understanding of the cognitive tests in NSHD, there are several hypotheses for each objective. First, higher performance on each cognitive test is hypothesised to be associated with better balance ability. Cognition plays an essential role in the balance process by integrating various sensory input cues (visual, vestibular, proprioceptive) with the motor output involved in balance and as such, this association is expected to be present across all domains.

Second, cross-sectional associations may also weaken with increasing age as proximal age-related factors (e.g. visual impairment, sarcopenia, reduced proprioception) begin to impact balance in later life. Longitudinal associations of midlife cognition with balance may also weaken with age due to both more proximal age-related factors as well as the temporal proximity of the cognitive test to the balance performance.

Third, cognitive tests that assess working memory or processing speed are expected to be more strongly associated with balance than crystallised measures of cognition such as reading ability or semantic knowledge. This is because balance can require flexible cortical processes to adapt, interpret and coordinate external sensory input. Crystallised measures of cognition should also be associated with balance; however, this is hypothesised to be driven by an overall association of cognition with balance rather than specific processing skills involved in these tasks. Independent associations of multiple measures of cognition with balance would suggest that specific components of cognition play distinct roles in maintaining balance.

Finally, it is hypothesised that the association between each cognitive domain and balance will be mainly attenuated by socioeconomic position and education. As proposed in Figure 5.1, higher SEP and education may influence balance ability and this may transpire through participation in healthy behaviours and higher overall health [160,448,493,494].

5.2 Methods

5.2.1 Study sample

Up to 3111 participants are included in the chapter analyses (as described in Chapter 2). Individuals are included in analyses if they had a valid balance measurement at one or more age and at least one score on any of the cognitive tests.

5.2.2 Overview of cognitive tests in NSHD

All cognitive tests between ages 43 and 69 are described below; Figure 5.2 provides an overview of the ages of each cognitive test. The distribution of each cognitive test is examined. Skewed cognitive variables are categorised while normally distributed continuous cognitive variables are standardised such that the mean is 0 and SD is 1.

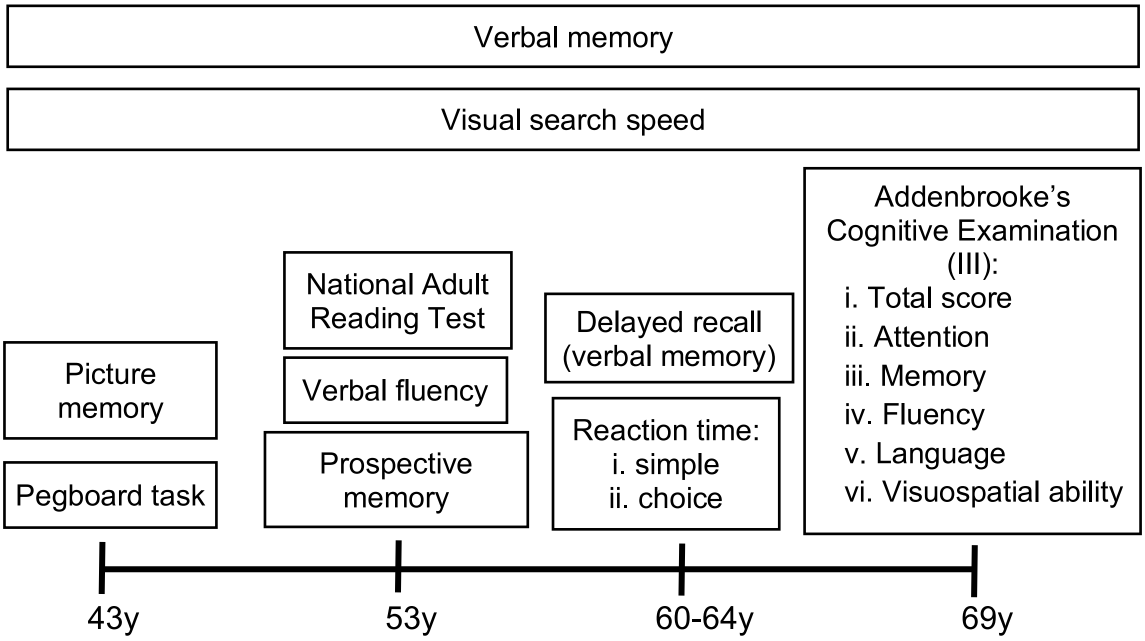


Figure 5.2 Summary of cognitive test battery examined at ages 43, 53, 60-64 and 69

Verbal memory word list (ages 43, 53, 60-64, 69):

As described in section 2.2.2.5 (Chapter 2), verbal memory was assessed at ages 43, 53, 60-64 and 69 using a 15-item word-learning task. Each word was presented for 2 seconds, after which participants were asked to write down all of the words that they could remember, in any order. The total score (maximum 45) represents the total number of words correctly recalled over three identical trials. To minimise any practice effects, two different word lists were rotated between follow-ups [322].

Verbal search speed (ages 43, 53, 60-64, 69):

Visual search speed was assessed at ages 43, 53, 60-64 and 69. Study members were given a grid of letters and were asked to cross out as many “P”s and “W”s as they could, as quickly and as accurately as possible, in 1 minute. The score represents the total number of letters correctly searched (maximum: 600).

Picture memory test (age 43):

Study members were shown five pictures for 30 seconds and were asked to remember what was on them. Due to distribution and skew, scores were categorised as five correct, four correct and three or less correct for the analyses.

Pegboard (age 43):

Study members were asked to move ten pegs from the top row to the bottom row as fast as they could. Five trials were administered for each hand and the mean time taken to complete the task was calculated. If a peg was dropped or there was an external distraction, the trial started again. Study members were advised not to speak while moving the pegs as this could slow their performance and increase their time. The pegboard task is considered a joint motor and cognitive task; this is addressed further in the discussion (section 5.4.2 and 5.4.3.1).

National Adult Reading Test (age 53):

The National Adult Reading Test (NART) is commonly used to assess general verbal ability [503]. NART score has been widely recognised as a measure of crystallised cognition that remains relatively constant across mid and later life [438] and is commonly used in as a measure of premorbid cognition [171,438]. Study members were asked to pronounce a set of 50 words. Responses were scored as correct or incorrect (maximum score: 50). These words are all atypical in grapheme-phoneme correspondence, such that these irregular words are only likely to be pronounced correctly if the study member has previous knowledge of the word. Thus, this is a test of acquired verbal knowledge, an aspect of ‘crystallised’ ability. Examples include ‘hiatus’, ‘syncope’ and ‘placebo’.

Verbal fluency test (age 53):

Study members were asked to name as many animals as possible within one minute. Species (e.g. bird, snowy owl, blue jay, etc.), sex and generation-specific names (e.g. bull, cow, calf) all counted as different names. Repetitions and redundancies (e.g. black cow, brown cow) were not included. Total score is the number of different animals named.

Prospective memory test (age 53):

Study members were told that they would be given an envelope at some point later in the session and would be asked to write a specified name and address on the envelope. After writing this, the task was to turn the envelope over, seal it and write their initials on the back without being prompted. Scores were categorised as both actions correct, one action correct or no actions correct.

Verbal memory, delayed recall (age 60-64):

At age 60-64, a 4th trial of the verbal memory task (described above) was conducted to measure delayed word recall. After the individuals had completed the verbal memory test and the search speed test, they were asked to write down as many words as they could remember from the words used in the verbal memory test (max: 15).

Reaction time (age 60-64):

Simple reaction time required the individual to press a single button as quickly as possible if the number 0 or 8 appeared on the screen. The individual began with their finger on the button to minimise physical reaction time. Eight practice trials were given and any errors during the practice trials were corrected. The test consisted of 20 trials with a variable delay of 1-3 seconds between each signal to avoid anticipation. Reaction time was calculated as the mean time (ms) across the correct responses in the 20 trials.

Choice reaction time required participants to press one of four buttons as quickly as possible that corresponded to the number (between 1 and 4) on the screen. Similar to above, the individual's fingers were already on the keys (1st and 2nd fingers of each hand were on keys 1 to 4). Eight practice trials were given for this task followed by 40 real trials. Reaction time was calculated as the mean for the correct responses in the 40 trials. As with the pegboard task at age 43, the reaction time tests have both cognitive and motor components.

Addenbrooke's Cognitive Examination (age 69):

The Addenbrooke's Cognitive Examination (version III) (ACE-III) is a measure of global cognition, capturing five domains: attention (0-18), memory (0-26), fluency (0-14), language (0-26) and visuospatial skills (0-16). Total score is out of 100.

In the *attention* component, participants were asked for the date (day of week, day, month, year, season), current location (house number, street, town, county, country), three- word immediate recall, and a verbal mathematical question (begin with 100 and serially subtract 7). In the *memory* component, participants were tested on their immediate and delayed recall of a name and address, delayed recall on the three words from above, and semantic memory (current prime minister, female prime minister, current president, president who was assassinated in the 1960s). Participants were given notice that there would be delayed recall tests at a later point and as such were asked to remember the address or words. To test *fluency*, participants were asked to name as many words as they could that began with the given letter (e.g. 'P') in one minute. Similar to the animal naming test in NSHD, they were then asked to name as many animals as possible in one minute. The *language* component consists of the following commands: instructions to pick up the pencil and paper objects, writing two complete sentences, repeating four multisyllabic words and two idioms, naming twelve different objects shown in pictures, matching objects to a description (e.g. "point to the one which has a nautical connection") and reading five words out loud. In the fifth component, *visuospatial ability* was measured by copying two diagrams, clock drawing, counting the number of dots in four figures without pointing, and identifying four incomplete letters.

5.2.3 Covariates

Several categories of covariates are included in analyses. The literature investigating associations between these categories and balance ability was explored in Chapter 1 and assessment of each measure in NSHD was described in Chapter 2: mortality, attrition, height, BMI, diabetes, CVD event, knee pain, and respiratory symptoms, symptoms of depression and anxiety, self-reported smoking, leisure-time physical activity, paternal occupational class, maternal education, own occupational class, education and adult verbal memory.

5.2.4 Statistical analyses

Mean or median scores for each cognitive test by sex are described and differences assessed using t-tests or Kruskal-Wallis tests for continuous variables and chi square tests for categorical variables. Sex-stratified histograms demonstrate the distribution of each test. Pearson correlation coefficients are used to examine i) correlations between balance and cognitive tests at the same age and ii) correlations between the same cognitive tests at different ages (e.g. visual search speed, verbal memory). With the exception of categorical and skewed continuous variables, all cognitive variables are standardised (mean: 0, SD: 1) to directly compare regression estimates.

Analyses are performed in three main stages. In the first stage of analyses (objective i), both linear regressions and multilevel models are used to assess cross-sectional associations between each cognitive test and balance at the same age (at ages 53, 60-64, 69). As the verbal memory and search speed were administered at each age where balance ability was assessed (age 53, 60-64, 69), MLMs could be used to assess the cross-sectional association and whether it changed with age. Linear regressions are employed for the remaining cognitive tests that were administered at one time point.

In the second stage of analyses (objective ii), MLMs are used to assess longitudinal associations between baseline cognitive scores in midlife (each cognitive test at ages 43 or 53) and balance ability at ages 53, 60-64 and 69 and determine whether these associations changed with age. Finally, in the third stage (objective iii), mutually-adjusted models are used to investigate if different cognitive domains in midlife are independently associated with balance ability. Here, cross-sectional associations at age 53 are explored because it presents the best opportunity to mutually adjust given the availability of data at this age, in terms of both quantity and quality. For each fluid cognitive measure (verbal memory, search speed, verbal fluency, prospective memory), the model was mutually adjusted for NART score at age 53. As stated in section 5.2.2, the NART score is recognised as a stable measure of crystallised cognition [438].

For each analytical model, sex*cognition interactions and quadratic terms of each cognitive variable are tested. Where sex*cognition interactions are significant, models are stratified by sex. In multilevel models, age*cognition interactions are also assessed. Inclusion of sex and age interactions as well as quadratic terms for all covariates was previously determined in Chapter 3. Covariates are added to the model in the following stages (objective iv):

Model 1) sex adjusted;

Model 2) sex, death and attrition adjusted;

Model 3) sex, death, attrition and body size adjusted;

Model 4) sex, death, attrition, body size and health status adjusted;

Model 5) sex, death, attrition, body size and health behaviour adjusted;

Model 6) sex, death, attrition, body size and adult social class adjusted;

Model 7) sex, death, attrition, body size and education adjusted;

Model 8) sex, death, attrition, body size, health status, health behaviours, SEP, education adjusted.

Note that in non-longitudinal individual regression models, death and attrition are not adjusted for in order to avoid over adjustment as the attrition or death may not have occurred yet. Sex-adjusted (maximum sample and complete cases) and fully-adjusted model estimates are provided in results. Adjustments made for each category of covariates in turn (objective iv) are presented in the appendices.

5.3 Results

5.3.1 Sex differences in cognitive tests

Histograms of all cognitive scores are provided in Figure 5.3. Continuous scores were mostly normally distributed, except for individual domains in the ACE-III test at age 69. Due to a strong ceiling effect and skewed distribution, total ACE (III) score (range: 0-100) is dichotomised as <88 and ≥88 according to the upper end of the recommended clinical cut-off of 82-88 [79, 80]. This clinical

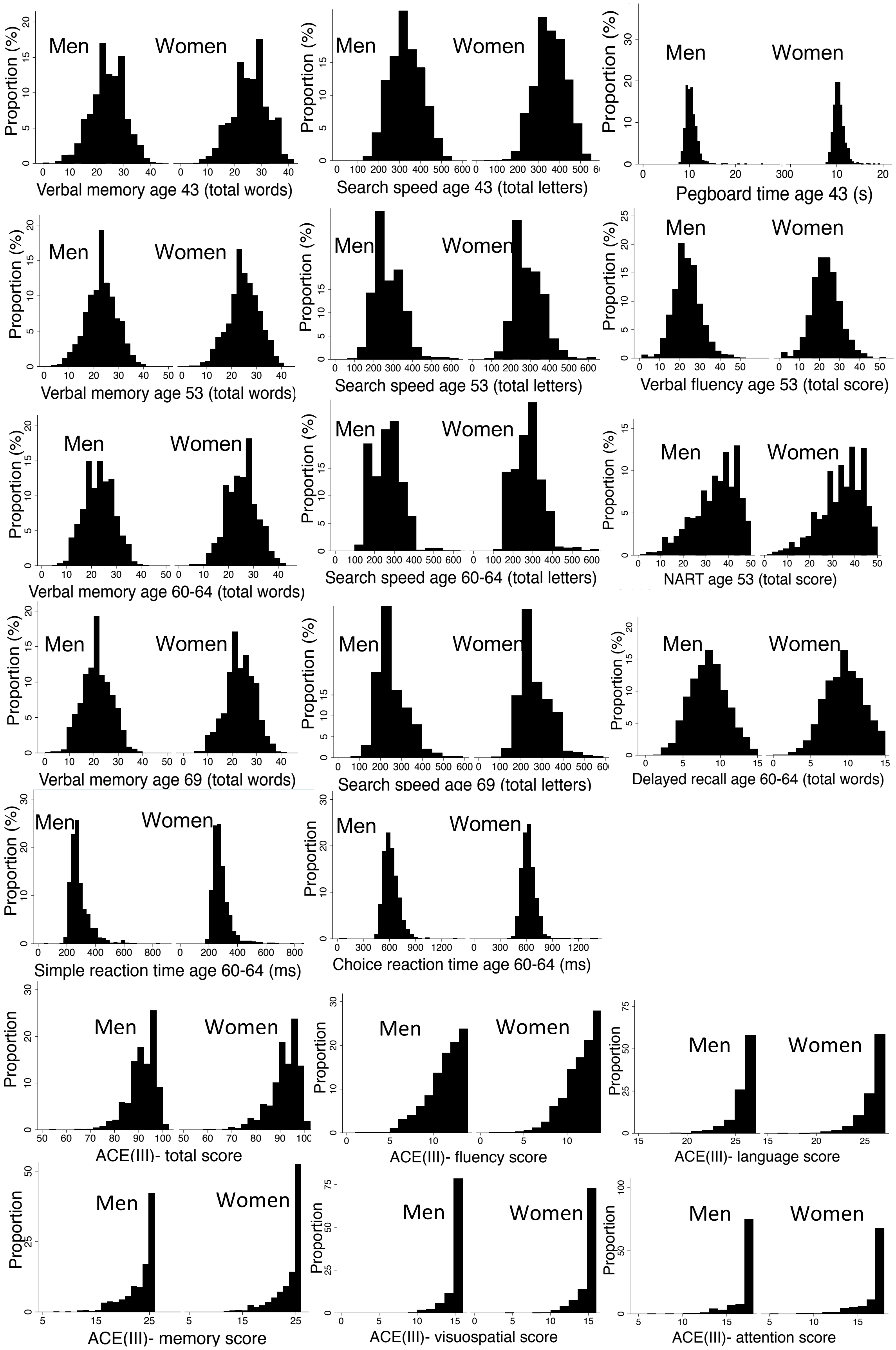


Figure 5.3 Histograms showing distributions of all continuous cognitive tests at ages 43, 53, 60-64 and 69

cut-off for early onset dementia has high sensitivity (1.0) and specificity (0.96). As there are no validated cut-points for each domain of the ACE-III, these scores are categorised using quartiles, or tertiles where quartiles were not possible due to limited range of scores (see Table 5.2). Chi square tests were used to assess sex differences in all categorical variables while t-tests assessed sex differences in all continuous variables. Sex-stratified mean (SD) or frequencies (%) scores for each cognitive test are reported in Tables 5.2 & 5.3.

Women outperformed men on the majority of cognitive tests including the visual search speed and verbal memory tests at all ages, picture memory at age 43, prospective memory at age 53, delayed verbal memory recall at age 60-64, and both the fluency and memory components of the ACE-III at age 69 (Tables 5.2 and 5.3). Men outperformed women on the attention and visuospatial components of the ACE-III. There were no sex differences in verbal fluency scores at age 53, in NART scores at age 53 or in language or total ACE-III scores. Finally, there were no sex differences in simple reaction time; however, men had faster choice reaction time as well as slightly faster performance than women on the pegboard task.

Table 5.2 ACE (III) categorical scores at age 69 by sex in maximal analytical sample

		Men n (%)	**Women** n (%)	**Tests of sex difference (p-value)**
Total score	≥88 correct	658 (77.5%)	726 (79.5%)	0.30
	<88 correct	230 (22.5%)	187 (20.5%)	
Fluency	13-14 correct	245 (23.8%)	300 (28.0%)	0.04
	12 correct	214 (20.8%)	228 (21.2%)	
	10-11 correct	329 (32.0%)	341 (31.8%)	
	≤9 correct	240 (23.4%)	204 (19.0%)	
Language	All 26 correct	493 (58.1%)	536 (58.3%)	0.35
	25 correct	220 (25.9%)	215 (23.5%)	
	≤24 correct	136 (16.0%)	165 (18.0%)	
Attention	All 18 correct	442 (51.1%)	425 (46.2%)	<0.01
	17 correct	207 (23.9%)	203 (22.0%)	
	≤16 correct	216 (25.0%)	293 (31.8%)	
Memory	All 26 correct	212 (24.5%)	300 (32.5%)	<0.01
	25 correct	153 (17.7%)	184 (20.0%)	
	23-24 correct	223 (25.8%)	216 (23.4%)	
	≤22 correct	277 (32.0%)	222 (24.1%)	
Visuospatial	All 16 correct	440 (51.1%)	445 (48.5%)	0.02
	15 correct	237 (27.5%)	225 (24.5%)	
	≤ 14 correct	184 (21.4%)	247 (26.9%)	

Table 5.3 Mean cognitive scores by sex for all tests within the main analytical sample

	Men	Women	Tests of sex difference (p-value)
Visual search speed (range: 0-600), ages 43-69			
Age 43, mean (SD)	328.9 (76.6), n=1568	354.9 (73.6), n=1563	<0.001
Age 53, mean (SD)	272.6 (75.4), n=1439	289.2 (75.8), n=1493	<0.001
Age 60-64, mean (SD)	261.1 (71.4), n=1039	271.8 (71.7), n=1143	<0.001
Age 69, mean (SD)	256.4 (74.3), n=1038	268.0 (73.6), n=1073	<0.001
Verbal memory (range: 0-45), ages 43-69			
Age 43, mean (SD)	23.9 (6.3), n=1528	25.5 (6.4), n=1531	<0.001
Age 53, mean (SD)	23.0 (6.2), n=1409	24.8 (6.3), n=1478	<0.001
Age 60-64, mean (SD)	23.0 (5.9), n=1023	25.4 (6.1), n=1127	<0.001
Age 69, mean (SD)	21.1 (6.0), n=1011	23.1 (6.0), n=103	<0.001
Picture memory (range: 0-5), age 43			
Categorical, n (%) 5 correct	827 (51.4%)	970 (60.0%)	<0.001
4 correct	571 (35.5%)	475 (29.4%)	
3 correct	162 (10.1%)	145 (9.0%)	
2 correct	38 (2.4%)	20 (1.2)	
1 correct	6 (0.4%)	3 (0.2%)	
0 correct	5 (0.3%)	3 (0.2%)	
Pegboard test (s), age 43 (range: 76.5-280)			
Mean (SD)	1.04 (1.3), n=1574	1.05 (1.3), n=1587	0.07
Verbal fluency (range: 0-62), age 53			
Mean (SD)	23.7 (6.7), n=1443	23.4 (7.1), n=1506	0.18
NART reading score (range: 0-50), age 53			
Mean (SD)	34.4 (9.7), n=1370	34.2 (9.4), n=1455	0.58
Prospective memory, age 53			
Both actions correct, n (%)	1144 (80.3%)	1287 (85.7%)	<0.001
One action correct, n (%)	171 (12.0%)	139 (9.3%)	
No actions correct, n (%)	109 (7.7%)	75 (5.0%)	
Delayed recall (range: 0-15), age 60-64			
Mean (SD)	7.9 (2.5), n=1021	9.0 (2.6), n=1126	<0.001
Reaction time (range: 19-1378ms), age 60-64			
Mean (SD) simple reaction	288 (71), n=1033	286 (68), n=1134	0.36
Mean (SD) choice reaction	619 (91), n=1030	628 (91), n=1128	0.02

5.3.2 Correlations

Sex stratified correlation coefficients between all cognitive tests at each age can be found in Appendix 5.1. Both search speed (all r >0.45) and verbal memory (all r >0.60) scores at ages 43, 53, 60-64 and 69 were highly correlated at all ages, suggesting that cognitive ranking on these tests remained relatively stable over time (see Appendix 5.1i). Scores on different cognitive tests at each age were weakly correlated with one another (see Appendix 5.1ii-iv) [504], with verbal memory demonstrating the strongest correlations with the other tests at all ages. Balance times were weakly correlated with cross-sectional cognitive scores across all ages (<0.20); these correlations were strongest at age 53 and were smaller at older ages.

5.3.3 Cross-sectional associations between cognitive scores and balance ability

5.3.3.1 Cross-sectional associations: verbal memory and search speed at ages 53, 60-64 & 69

Higher verbal memory scores were associated with better balance performance at all ages. In sex-adjusted models, a one standard deviation increase in verbal memory score was associated with a 12% (95% CI: 10, 14%; p<0.001) increase in balance time at age 53 (Table 5.4). The negative coefficient in the interaction between verbal memory and age (-0.5% [-0.7, -0.3%], p<0.001) indicates that the cross-sectional association became smaller with age. Thus, in sex-adjusted models at ages 60-64 and 69, one SD increase in verbal memory was associated with 7% (6, 9%; p<0.001) and 4% (2, 7%; p<0.001) increases, respectively (Table 5.4, footnote [a]).

Adjustment for attrition, anthropometric indicators, health status, health behaviours and adult SEP had little to no effect on the estimates (Appendix 5.2, Models 1-6); rather, the association was attenuated most strongly by adjustment for education (Appendix 5.2, Model 7). In the fully-adjusted model, a 1 SD increase in verbal memory score was associated with a 6% (3, 9%; p<0.001) increase in balance ability at age 53. This association decreased to 4% (2, 6%) at age 60-64 but was no longer statistically significant at age 69 (p=0.10) (see Table 5.4, footnote [b]).

Due to an interaction between sex and search speed, multilevel models were stratified by sex. At age 53, higher search speed was associated with 8% (5, 10%; p<0.001) and 4% (2, 6%; p<0.001) better balance times in men and women, respectively (see Table 5.4). In contrast to verbal memory above, there was no interaction between search speed and age (men: p=0.52; women: p=0.12) suggesting that the association remained constant. In men, the association was partially attenuated by adjustment for covariates (Appendix 5.2) but remained significant in the fully-adjusted model (4% [2, 7%]; p<0.001). In women, the association was fully attenuated in the fully-adjusted model (1% [-1, 4%] p=0.20). As with verbal memory, education largely explained attenuation of estimates (Appendix 5.2).

Table 5.4 Cross-sectional associations of verbal memory and search speed (per SD change) with log-transformed balance time (sec) in multilevel models

	Change in balance time at age 53 per 1SD change in cognition [intercept]		**Age (yr)*covariate interaction**	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
VERBAL MEMORY				
Sex-adjusted (max) n=2969 (obs=6712)	0.12 [a] (0.10, 0.14)	<0.001	-0.005 (-0.007, -0.003)	<0.001
Sex-adjusted (ccs) n=2696 (obs=5533)	0.12 (0.10, 0.15)	<0.001	-0.005 (-0.007, -0.003)	<0.001
Fully-adjusted [cd] n=2696 (obs=5533)	0.06 [b] (0.03, 0.09)	<0.001	-0.003 (-0.005, -0.0001)	0.04
SEARCH SPEED - men				
Sex-adjusted (max) n=1496 (obs=3335)	0.08 (0.05, 0.10)	<0.001	-	-
Sex-adjusted (ccs) n=1372 (obs=2756)	0.07 (0.04, 0.09)	<0.001	-	-
Fully-adjusted [cd] n=1372 (obs=2756)	0.04 (0.02, 0.07)	<0.001	-	-
SEARCH SPEED - women				
Sex-adjusted (max) n=1507 (obs=3467)	0.04 (0.02, 0.06)	<0.001	-	-
Sex-adjusted (ccs) n=1354 (obs=2846)	0.03 (0.01, 0.05)	<0.01	-	-
Fully-adjusted [cd] n=1354 (obs=2846)	0.01 (-0.01, 0.04)	0.20	-	-

max = maximal available sample; ccs = complete cases sample

[a] *β= 0.07 (0.06, 0.09), p<0.001 at age 60-64 and β= 0.04 (0.02, 0.07), p<0.001 at age 69*

[b] *β= 0.04 (0.02, 0.06), p<0.001 at age 60-64 and β= 0.02 (-0.004, 0.05), p=0.10 at age 69*

[c] *Adjusted for sex, death, attrition, height, weight, CVD events, diabetes, respiratory symptoms, knee pain, symptoms of depression and anxiety, smoking history, leisure time physical activity, adult social class, education*

[d] *Estimates for covariate adjustments in stages are provided in Appendix 5.2*

5.3.3.2 Cross-sectional associations: other cognitive tests at age 53 and 60-64

The final three cognitive tests at age 53 were positively associated with balance ability at age 53 in both sex and fully-adjusted linear regression models (see Table 5.5a-c). First, 1SD higher performance on the verbal fluency was associated with 11% (8, 13%) better balance ability. Next, individuals who did no actions correct on the prospective memory test had 16% (5, 27%) worse balance ability than those who did both right. Those who did one action correct did not have different balance ability than those who did both right. NART scores demonstrated a positive quadratic association with balance ability, with a stronger association at higher levels of cognition. As above, the estimates for each cognitive test were mainly attenuated by adjustment for education level and adult social class (see Appendix 5.3) but remained in fully-adjusted models.

Higher performance on the delayed recall at age 60-64 was associated with better balance ability at age 60-64 in sex-adjusted models (5% (3, 8%) per 1SD in sex adjusted models; see Table 5.5d), however adjustment for education and social class fully explained this association (see Appendix 5.4). Slower performance on both the simple and choice reaction tests was associated with lower balance ability (see Table 5.5e-f). In fully-adjusted models, the association with choice reaction time was attenuated (Table 5.5f) but remained for simple reaction time (Table 5.5e).

Table 5.5 Cross-sectional associations of cognitive tests at ages 53 and 60-64 with log-transformed balance time (sec) using linear regression models

	Change in balance time at age 53 per change in cognition					
	Sex-adjusted (max)		**Sex-adjusted (ccs)**		**Fully-adjusted [a,b]**	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
AGE 53						
a. Verbal fluency (n)	n=2774		n=2507		n=2507	
Linear term (per SD)	0.11 (0.08, 0.13)	<0.001	0.10 (0.07, 0.12)	<0.001	0.05 (0.02, 0.08)	<0.001
b. Prospective memory (n)					n=2499	
Ref: Both correct	n=2759		n=2499		n=2499	
One action correct	-0.08 (-0.16, -0.001)	<0.001	-0.10 (-0.18, -0.01)	<0.01	-0.06 (-0.14, 0.02)	0.04
No actions correct	-0.17 (-0.27, -0.06)		-0.16 (-0.27, -0.05)		-0.09 (-0.19, 0.02)	
c. NART (n)	n=2669		n=2423		n=2423	
Linear term (per SD)	0.14 (0.11, 0.17)	<0.001	0.14 (0.11, 0.17)	<0.001	0.05 (0.02, 0.09)	<0.005
Quadratic term	0.03 (0.01, 0.05)	<0.005	0.03 (0.01, 0.05)	0.01	0.01 (-0.01, 0.03)	0.30
AGE 60-64						
d. Delayed recall (n)	n=2056		n=1567		n=1567	
Linear term (per SD)	0.05 (0.03, 0.08)	<0.001	0.04 (0.02, 0.07)	<0.005	0.01 (-0.02, 0.04)	0.43
e. Simple reaction (n)	n=2071		n=1576		n=1576	
Linear term (per SD)	-0.05 (-0.07, -0.02)	<0.001	-0.05 (-0.08, -0.02)	<0.005	-0.03 (-0.06, -0.0005)	0.05
vi. Choice reaction (n)	n=2063		n=1569		n=1569	
Linear term (per SD)	-0.06 (-0.09, -0.04)	<0.001	-0.04 (-0.07, -0.01)	<0.005	-0.02 (-0.05, 0.01)	0.25

max = maximal available sample; ccs = complete cases sample

[a] *Adjusted for sex, death, attrition, height, weight, CVD events, diabetes, respiratory symptoms, knee pain, symptoms of depression and anxiety, smoking history, leisure time physical activity, adult social class, education*

[b] *Estimates for covariate adjustments in stages are provided in Appendix 5.3 (for age 53) and Appendix 5.4 (for age 60-64)*

5.3.3.3 Cross-sectional associations of ACE (III) scores at age 69

Linear regressions were also used to assess associations between ACE (III) scores and balance ability at age 69. Those who demonstrated impaired ACE (III) performance (<88) had worse balance performance compared with those with no impairment (≥88) (see Table 5.6). Better performance on the fluency, memory, visuospatial and attention subcomponents was also associated with better balance ability in sex-adjusted models, however there was no evidence of an association with language performance (see Appendix 5.5). Each association was attenuated at every stage of adjustment, although there remained some evidence that there may be an association between both visuospatial ability and attention and balance ability in the fully adjusted model (see Appendix 5.5).

Table 5.6 Cross-sectional association of ACE (III) impairment at age 69 and log-transformed balance time (sec) in linear regressions

	Change in balance time at age 69 if <88 correct on ACE (III) (95% CI)	**p-value**
Sex-adjusted (max), n=1634	-0.09 (-0.16, -0.02)	0.01
Sex-adjusted (ccs), n=1260	-0.09 (-0.17, -0.01)	0.03
Fully-adjusted (ccs), n=1260 [a b]	-0.04 (-0.13, 0.04)	0.32

max = maximal available sample; ccs = complete cases sample; Ref category: ≥88 correct

[a] *Adjusted for sex, death, attrition, height, weight, CVD events, diabetes, respiratory symptoms, knee pain, symptoms of depression and anxiety, smoking history, leisure time physical activity, adult social class, education*

[b] *Estimates for covariate adjustments in stages are provided in Appendix 5.5*

5.3.4 Longitudinal associations between cognitive scores and balance ability

Consistent with the cross-sectional models, higher performance on cognitive tests at age 43 – including verbal memory, search speed, and pegboard task – was associated with better balance performance from age 53 to age 69 (see Table 5.7). Associations remained in fully adjusted models. While search speed (p=0.07) and pegboard task (p=0.53) demonstrated a constant pattern of association with balance ability by age, an age interaction in the verbal memory model implied that the association became smaller at later ages. Verbal memory at age 43 remained associated with balance at 60-64 and 69 in sex-adjusted models (p<0.001) but not in fully-adjusted models (see Table 5.7 footnote). Men who performed better on the picture memory task also had better balance performance – this was constant at all ages (p=0.46) –, however there was no association in women.

Table 5.7 Longitudinal associations of cognitive tests at age 43 with log-transformed balance time (sec) using multilevel models

	Change in balance time at age 53 per change in cognition					
	Sex-adjusted (max)		**Sex-adjusted (ccs)**		**Fully-adjusted (ccs)** [d]	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
a. Verbal memory (n)	n=2665 (obs=6213)		n=2451 (obs=5155)		n=2451 (obs=5155)	
Linear term (per SD)	0.10 (0.08, 0.13)	<0.001	0.11 (0.08, 0.13)	<0.001	0.03 (0.005, 0.06)	0.02
Age interaction (per SD/year)	-0.004 (-0.006, -0.002)[b]	<0.001	-0.004 (-0.007, -0.002)	<0.001	-0.002 (-0.028, -0.018) [c]	0.17
b. Search speed [a] **(n men)**	n=1339 (obs=3062)		n=1248 (obs=2550)		n=1248 (obs=2550)	
(n women)	n=1375 (obs=3253)		n=1250 (obs=2687)		n=1250 (obs=2687)	
Men Linear term (per SD)	0.06 (0.04, 0.09)	<0.001	0.07 (0.04, 0.10)	<0.001	0.05 (0.02, 0.07)	<0.005
Women Linear term (per SD)	0.03 (0.01, 0.05)	0.02	0.04 (0.01, 0.06)	0.01	0.02 (-0.01, 0.04)	0.20
c. Pegboard task [a] **(n)**	n=2743 (obs=6385)		n=2521 (obs=5289)		n=2521 (obs=5289)	
Linear term (per SD)	-0.08 (-0.10, -0.06)	<0.001	-0.08 (-0.11, -0.06)	<0.001	-0.06 (-0.09, -0.04)	<0.001
d. Picture memory [a] **(n men)**	n=1367 (obs=3130)		n=1273 (obs=2605)		n=1273 (obs=2605)	
(n women)	n=1421 (obs=3346)		n=1289 (obs=2764)		n=1289 (obs=2764)	
Ref: All 5 correct						
Men 4 correct	-0.05 (-0.11, 0.003)	<0.001	-0.05 (-0.11, 0.01)	<0.001	-0.02 (-0.08, 0.04)	<0.01
3 correct	-0.20 (-0.28, -0.12)		-0.20 (-0.29, -0.11)		-0.14 (-0.23, -0.05)	
Women 4 correct	-0.01 (-0.06, 0.04)	0.13	-0.03 (-0.08, 0.03)	0.09	-0.01 (-0.06, 0.04)	0.86
3 correct	-0.07 (-0.28, 0.01)		-0.07 (-0.16, 0.02)		0.004 (-0.08, 0.09)	

max = maximal available sample; ccs = complete cases sample

[a] As there was no significant age interaction, coefficients estimates are the same at ages 60-64 and 69.

[b] Verbal memory, sex-adjusted: β= 0.07 (0.05, 0.08), p<0.001 at age 60-64 and β= 0.04 (0.01, 0.06), p<0.01 at age 69

[c] Verbal memory, fully-adjusted: β= 0.02 (-0.01, 0.04), p=0.16, p<0.01 at age 60-64 and β= 0.005 (-0.03, 0.03), p=0.76 at age 69

[d] Adjusted for sex, death, attrition, height, weight, CVD events, diabetes, respiratory symptoms, knee pain, symptoms of depression and anxiety, smoking history, leisure time physical activity, adult social class, education

Higher performance on all cognitive tests at age 53 was also associated with better balance performance at age 53 in both sex and fully-adjusted models (see Table 5.8). Notably, search speed was only associated with balance ability in men but not women. The association remained constant at all ages for prospective memory (p=0.15); however, for search speed, verbal memory, verbal fluency and NART score, all associations became smaller with age. Estimates at age 60-64 and 69 are provided in Appendix 5.6. Sex-adjusted associations of all cognitive tests with balance ability remained at ages 60-64 and 69. However, in the fully-adjusted models, only verbal memory and verbal fluency remained associated with balance ability at age 60-64; all other associations were attenuated.

Table 5.8 Longitudinal associations of cognitive tests at age 53 with log-transformed standing balance time (sec) using multilevel models

	Change in balance time at age 53 per change in cognition [a]					
	Sex-adjusted (max)		**Sex-adjusted (ccs)**		**Fully-adjusted (ccs) [b]**	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
i. Verbal memory (n)	n=2812 (obs=6574)		n=2595 (obs=5453)		n=2595 (obs=5453)	
Linear term (per SD)	0.12 (0.10, 0.14)	<0.001	0.12 (0.10, 0.15)	<0.001	0.06 (0.03, 0.09) [b]	<0.001
Age interaction (per SD/year)	-0.005 (-0.007, -0.003)	<0.001	-0.005 (-0.008, -0.003)	<0.001	-0.003 (-0.006, -0.001)	0.02
ii. Search speed (n men)	n=1402 (obs=3223)		n=1248 (obs=2550)		n=1248 (obs=2550)	
(n women)	n=1448 (obs=3412)		n=1319 (obs=2816)		n=1319 (obs=2816)	
Men Linear term (per SD)	0.09 (0.06, 0.13)	<0.001	0.09 (0.05, 0.13)	<0.001	0.05 (0.01, 0.09) [d]	0.02
Age interaction (per SD/year)	-0.004 (-0.007, -0.001)	<0.01	-0.004 (-0.007, -0.001)	0.02	-0.002 (-0.005, 0.001)	0.22
Women Linear term (per SD)	0.06 (0.02, 0.09)	<0.005	0.04 (0.01, 0.08)	0.02	0.02 (-0.01, 0.05) [f]	0.21
Age interaction (per SD/year)	-0.003 (-0.006, -0.0003)	0.03	-0.002 (-0.005, 0.001)	0.12	-0.002 (-0.005, 0.001)	0.23
iii. Verbal fluency (n)	n=2859 (obs=6648)		n=2633 (obs=5506)		n=2633 (obs=5506)	
Linear term (per SD)	0.10 (0.08, 0.13)	<0.001	0.10 (0.07, 0.12)	<0.001	0.05 (0.02, 0.08) [h]	<0.001
Age interaction (per SD/year)	-0.004 (-0.006, -0.002)	<0.001	-0.004 (-0.006, -0.002)	<0.001	-0.002 (-0.005, -0.0001)	0.05
iv. Prospective memory [a] (n)	n=2843 (obs=6633)		n=2625 (obs=5502)		n=2625 (obs=5502)	
Ref: Both correct						
One action correct	-0.04 (-0.10, 0.02)	<0.005	-0.05 (-0.11, 0.01)	<0.005	-0.03 (-0.09, 0.03)	0.08
No actions correct	-0.10 (-0.18, 0.03)		-0.12 (-0.20, 0.04)		-0.06 (-0.18, 0.02)	
v. NART (n)	n=2751 (obs=6442)		n=2543 (obs=5361)		n=2543 (obs=5361)	
Linear term (per SD)	0.13 (0.11, 0.16)	<0.001	0.14 (0.11, 0.16)	<0.001	0.06 (0.02, 0.09) [j]	<0.005
Quadratic term (per SD)	0.02 (0.01, 0.04)	<0.005	0.02 (0.01, 0.04)	<0.005	0.01 (-0.01, 0.02)	0.29
Linear*age interaction (per SD/year)	-0.005 (-0.007, -0.003)	<0.001	-0.006 (-0.008, -0.004)	<0.001	-0.004 (-0.007, -0.001)	<0.01

max = maximal available sample; ccs = complete cases sample

[a] *Re-centred estimates at age 60-64 and 69 are provided in Appendix 5.6*

[b] *Adjusted for sex, death, attrition, height, weight, CVD events, diabetes, respiratory symptoms, knee pain, symptoms of depression and anxiety, smoking history, leisure time physical activity, adult social class, education*

5.3.5 Mutual adjustment for NART score at age 53

Building on cross-sectional models at age 53 (Tables 5.4 and 5.5), all models were mutually adjusted for crystallised cognition (NART at age 53). Higher performance on each cognitive test (verbal memory, search speed, verbal fluency and prospective memory) remained significantly associated with better balance ability (see Table 5.9). Within every model, NART score also demonstrated independent associations with balance. In fully-adjusted models, estimates were slightly attenuated although the patterns of association remained the same (see Table 5.9).

Table 5.9 Mutually-adjusted cross-sectional associations of NART and other cognitive tests at ages 53 with log-transformed balance time (sec) using linear regression models

	Change in balance time at age 53 per change in cognition					
	Sex-adjusted (max)		**Sex-adjusted (max)**		**Fully-adjusted (ccs)** [a]	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
i. Verbal memory, age 53 (n)	n=2642		n=2397		n=2633	
linear term	0.08 (0.05, 0.11)	<0.001	0.09 (0.05, 0.12)	<0.001	0.05 (0.02, 0.09)	<0.005
NART age 53 linear term	0.10 (0.06, 0.13)	<0.001	0.09 (0.06, 0.13)	<0.001	0.04 (-0.003, 0.07)	0.07
quadratic term	0.03 (0.01, 0.05)	<0.005	0.03 (0.004, 0.05)	0.02	0.01 (-0.01, 0.03)	0.24
ii. Search speed: men, age 53 (n)	n=1303		n=1204		n=1204	
linear term	0.07 (0.03, 0.10)	<0.005	0.06 (0.02, 0.10)	<0.005	0.04 (-0.001, 0.08)	0.06
NART age 53 linear term	0.14 (0.09, 0.18)	<0.001	0.13 (0.09, 0.18)	<0.001	0.07 (0.01, 0.12)	0.02
quadratic term	0.01 (-0.02, 0.05)	0.38	0.01 (-0.02, 0.05)	0.41	-0.002 (-0.03, 0.03)	0.93
ii. Search speed: women, age 53 (n)	n=1358		n=1212		n=1212	
linear term	0.05 (0.01, 0.08)	<0.005	0.03 (-0.0003, 0.07)	0.05	0.02 (-0.01, 0.06)	0.15
NART age 53 linear term	0.12 (0.08, 0.16)	<0.001	0.13 (0.09, 0.17)	<0.001	0.03 (-0.02, 0.08)	0.29
quadratic term	0.04 (0.01, 0.07)	<0.005	0.04 (0.01, 0.06)	0.02	0.02 (-0.01, 0.05)	0.16
iii. Verbal fluency, age 53 (n)	n=2633		n=2419		n=2419	
linear term	0.06 (0.04, 0.09)	<0.001	0.06 (0.03, 0.09)	<0.001	0.04 (0.01, 0.07)	<0.005
NART age 53 linear term	0.12 (0.09, 0.15)	<0.001	0.12 (0.09, 0.15)	<0.001	0.04 (0.01, 0.09)	0.02
quadratic term	0.03 (0.01, 0.05)	<0.005	0.03 (0.005, 0.05)	0.02	0.01 (-0.01, 0.03)	0.29
iv. Prospective memory, age 53 (n)	n=2664		n=2420		n=2420	
Ref: Both correct						
One action correct	-0.03 (-0.11, 0.05)	0.06	-0.05 (-0.13, 0.04)	0.03	-0.04 (-0.12, 0.05)	0.11
No actions correct	-0.10 (-0.21, 0.01)		-0.11 (-0.22, 0.0001)		-0.08 (-0.19, 0.03)	
NART age 53 linear term	0.14 (0.11, 0.16)	<0.001	0.13 (0.10, 0.16)	<0.001	0.05 (0.01, 0.09)	<0.001
quadratic term	0.03 (0.01, 0.05)	<0.005	0.03 (0.01, 0.05)	<0.05	0.01 (-0.01, 0.03)	0.28

max = maximal available sample; ccs = complete cases sample

[a] *Adjusted for sex, death, attrition, height, weight, CVD events, diabetes, respiratory symptoms, knee pain, symptoms of depression and anxiety, smoking history, leisure time physical activity, adult social class, education*

5.4 Discussion

5.4.1 Main findings

Higher cognitive performance across all domains was associated with higher balance ability in mid and later life. In sex-adjusted models, both cross-sectional and longitudinal associations were strongest at age 53 followed by age 60-64 and then age 69. Similarly, in fully-adjusted models, associations were strongest at age 53, but estimates were often attenuated by age 69. Education and SEP had the largest impact on estimate attenuation across all models. Mutually-adjusted models at age 53 suggest that different domains of cognition are independently associated with balance performance. Associations of verbal memory, search speed, verbal fluency, NART score and simple reaction time with balance were robust across most models, while delayed recall, choice reaction time and prospective memory were only associated with balance ability in sex-adjusted models. Minor, albeit inconsistent, sex differences emerged, with associations of picture memory and search speed with balance observed among men but with not in women. Table 5.10 provides a summary of all cognitive associations examined in this chapter.

Table 5.10 Summary of associations between cognitive domains and balance ability

Cognitive test	Cross-sectional association		Longitudinal association		
	Sex-adjusted	Fully-adjusted [a]	Sex-adjusted	Fully-adjusted [a]	Change with age
AGE 43					
Verbal memory	-	-	✓	✓	↓ with age
Search speed	-	-	✓	✓♂	✗
Picture memory	-	-	✓♂	✓♂	✗
Pegboard task	-	-	✓	✓	✗
AGE 53					
Verbal memory	✓	✓	✓	✓	↓ with age
Search speed	✓	✓♂	✓	✓♂	↓ with age
Verbal fluency	✓	✓	✓	✓	↓ with age
Prospective memory	✓	✓	✓	✗	✗
NART	✓	✓	✓	✓	↓ with age
AGE 60-64					
Verbal memory	✓	✓	-	-	-
Search speed	✓	✓♂	-	-	-
Delayed recall	✓	✗	-	-	-
Simple reaction time	✓	✓	-	-	-
Choice reaction time	✓	✗	-	-	-
AGE 69					
Verbal memory	✓	✗	-	-	-
Search speed	✓	✓♂	-	-	-
ACE (III), total	✓	✗	-	-	-
Attention	✓	✗			
Memory	✓	✗			
Fluency	✓	✗			
Language	✗	✗			
Visuospatial	✓	✗			

✓ Higher score on cognitive test = better balance performance, significant at $p<0.05$

✗ no association or no change with age ($p>0.05$)

♂ only in men

[a] Adjusted for sex, death, attrition, height, weight, CVD events, diabetes, respiratory symptoms, knee pain, symptoms of depression and anxiety, smoking history, leisure time physical activity, adult social class, education

5.4.2 Comparisons to other studies

The findings of this chapter are consistent with studies summarised in section 5.1.3 that demonstrated overall associations between cognition and balance ability [4,433,498,499,505]. Much of the comparable evidence is cross-sectional, although chapter findings are consistent with a previous longitudinal study in NSHD [171]. Few studies have examined the associations between specific components of cognition and balance, and as such, comparisons to other studies are limited. Specifically, no study has examined how these associations change with age, considered mutual adjustment of multiple cognitive domains nor reported any sex stratified results and as such, several of the chapter findings are novel.

In a previous NSHD study of balance and cognition, Kuh et al. [171] demonstrated that verbal memory (ages 43 and 53), search speed (ages 43 and 53), verbal fluency (age 53) and reading ability (age 53) were all associated with balance at age 53. This chapter extended this evidence by examining associations with balance at ages 60-64 and 69 as well as investigating the association with other cognitive tests. However, longitudinal and cross-sectional associations between each of verbal memory, search speed, verbal fluency and reading ability with balance became smaller at subsequent ages. The association of ACE (III) score at age 69, both total and by individual component, with balance was weak. This may be because the ACE (III) is commonly used as a clinical tool to indicate those with cognitive impairment and the power to detect an association in a relatively healthy cohort at age 69 is expected to be low [79, 80].

The findings in this chapter are also consistent with studies that have examined distinct cognitive domains. This includes evidence of positive associations of balance with several domains of fluid cognition such as verbal or visual memory [212,498], processing speed [7,498], or fluency [212]. Although Kuh et al. [171] identified associations between reading ability and balance, there is a scarcity of evidence examining measures of crystallised cognition. Won et al. [7] reported no association between IQ score and balance, and suggested that only fluid measures of cognition are associated with balance. However, this chapter demonstrated an association between reading ability (NART score) and balance that was robust to adjustment for relevant covariates including other domains of cognition. This suggests that both crystallised and fluid cognitive domains have distinct associations with balance.

Both the reaction time tests and the pegboard task are considered integrated cognitive-physical tasks due to the cognitive processing and manual dexterity involved. The association of these tasks with balance should be interpreted with caution as other studies have categorised them as physical tasks [506]. No previous study has assessed the association between pegboard performance and balance, while evidence has shown that slower reaction time is also associated with poorer balance ability [507,508]. Notably, the association of reaction time and pegboard task with balance ability was not particularly different than the association with other cognitive domains; this was expected due to correlations between physical function tasks (e.g. balance ability with pegboard or reaction time).

5.4.3 Explanation of findings

As hypothesised in section 5.1.2, the association between cognition and balance likely acts via two main pathways (see Figure 5.1). First, it is evident that cognition plays an important role in the balance mechanism due to the complex integration of the central nervous system. Second, cognition may act indirectly on balance via a socio-economic, behavioural and health pathway. These pathways are examined in further detail below.

5.4.3.1 Direct association between cognition and balance ability

It is well established that successful balance requires the complex integration of sensory input from vestibular, visual and proprioceptive sources and motor output. As outlined in section 5.1.2, the cerebellum and cerebrum both play important roles in the balance process. For example, the cerebellum is important for coordinating movement while the cerebrum, specifically the prefrontal cortex, governs more complex movements requiring higher cognitive functioning. It follows that balance ability and cognitive processing are complexly integrated [509], both at the clinical and neural level.

Processing speed is considered as an underlying domain of cognition that has an impact on the efficiency of all other cognitive operations [471], with slower processing speed leading to slower attention, impeded working memory and impaired executive function [471]. In this chapter, slower search speed was associated with poorer balance. Slower processing speed is linked to reduced activity in the prefrontal cortex and dopamine deficiency, both of which are thought to impact balance and motor abilities [510-513]. Notably, this association was stronger in men than in women, suggesting that men and women may rely, to some extent, on different cognitive mechanisms in order to balance. Although some sex differences in balance have been attributed to body compositions differences [149], cognitive processing mechanisms could also underlie these differences in balance.

Verbal memory, verbal fluency, prospective memory and delayed recall tests all assessed working memory, which draws on a temporary storage system that utilises information needed in the present moment [456]. There was an association between higher performance on these tasks – in particular verbal memory – and better balance performance. Working memory is an important component of balance as it allows one to utilise cognitive resources to maintain postural stability [514]. This is supported by the fully-adjusted results, where both memory tasks remained associated with balance, independent of covariates.

The verbal fluency test relies on both working memory as well as executive functioning skills and as such, performance is tied closely to the working memory and search speed tasks. This task relies heavily on the dorsolateral prefrontal cortex [515], which may explain its direct association with balance ability. Higher performance on the reaction time and pegboard tasks is directly related to the speed of neural transmission [516]. Individuals who are able to quickly process, react and provide an integrated motor response are expected to demonstrate higher balance ability as similar mechanisms are involved.

Finally, the visuospatial score of the ACE (III) demonstrated show the strongest association with balance. Visuospatial deficits are common in individuals with gait impairment [517,518], those at higher risk of falling [517,519] and individuals with Parkinson’s disease [520]. The findings in this chapter add to this evidence by suggesting that visuospatial cognition, particularly within working memory, is important when controlling balance.

5.4.3.2 Indirect association between cognition and balance ability

In addition to this direct mechanism whereby cognition contributes to balance ability, a secondary pathway is proposed: cognition may act indirectly on balance via a socio-economic, behavioural and health pathway. Figure 5.1 provides a conceptual model of both of these pathways. Education, adult cognition and SEP are all highly inter-correlated [491,492], as those with higher levels of adult cognition are more likely to have higher educational attainment and a higher SEP. In turn, these individuals often participate in healthier behaviours and have fewer chronic health conditions than those with a lower SEP or with lower education [160,448,493,494]. Adjusting for SEP and education partially attenuated all of the associations in this chapter suggesting that they may play an important role in the pathway between cognition and balance. However, the associations remained after adjustment suggesting that there are also distinct, direct associations between cognitive domains and balance performance.

5.4.3.3 Weakening of associations with age

Within the cross-sectional results, the associations were strongest at age 53 and weakened with age. For example, the association between verbal memory and balance ability declined from 12% to 7% to 4% from age 53 to 60-64 to 69, respectively. In longitudinal models, there were negative age interactions with verbal memory (ages 43 and 53), search speed (age 53), verbal fluency (age 53) and reading ability (age 53), suggesting that the associations also weakened with age.

This is hypothesised to be due to 1) the emergence of other age-related factors that may contribute to balance; and 2) decreased proximity of cognitive test in midlife to balance outcome in mid or later life. As individuals age, it could be that reliance on cognitive mechanisms may dissipate as more age proximal factors such as visual impairment, muscular atrophy and reduced vestibular functioning emerge. For example, as seen in Chapter 3, knee pain and symptoms of depression and anxiety demonstrated stronger associations with balance ability at older ages. As individual cognitive ability stays relatively constant (i.e. strong correlations between each of verbal memory and search speed between ages 43 and 69), longitudinal associations may also be a reflection of previous cross-sectional associations.

5.4.3.4 Mutually-adjusted associations

Mutual adjustment for different aspects of cognition provided insight into the independent role that each may play in balance. Mutually-adjusted cross-sectional models at age 53 considered the NART score, a proxy for general intelligence [521], in the same model as each cognitive test. In all sex-adjusted models, both the NART and each of the other cognitive domains tested remained significantly associated with balance. This suggests an independent role of specific cognitive domains in the balance process. In fully-adjusted models, verbal memory, verbal fluency and search speed (men only) remained robust to adjustment. The mechanisms through which working memory, processing speed and executive function influence balance were described above; these results confirm that balance relies on integration of multiple distinct domains of cognitive processing.

5.4.4 Methodological considerations

The overall strengths and limitations of the thesis were discussed in section 2.1.3 (Chapter 2), while the considerations specific to this chapter are summarised below. Considerations relevant to all chapters are discussed in full in Chapter 8.

5.4.4.1 Strengths

As previously discussed in section 2.1.3, the availability of longitudinal data in NSHD is a major strength of these analyses. In particular, the cognitive data in NSHD allow greater investigation into a wide range of cognitive domains across a longer follow-up than previous evidence. In this chapter, there are more than 10 different cognitive tests and four different ages at which cognitive data were collected. This spans a 25-year period beginning in midlife, whereas previous studies have tended to examine balance-cognition associations in those aged ≥65. The analyses also considered a large range of potential covariates that were prospectively ascertained across life, allowing exploration of probable factors that could confound or mediate the associations.

5.4.4.2 Limitations

There are several limitations that should be considered. While the availability of multiple cognitive domains is a major strength, the analyses remain restricted by the cognitive tests available. Only verbal memory and search speed were assessed at multiple ages, with the majority of other tests only being assessed at one age. There is also substantial overlap between several of the measures. It can be difficult to isolate single cognitive domains from others; however, the mutual adjustment of differing cognitive domain suggests that distinct facets of each have been appropriately captured. Having three different measures of balance throughout midlife is a strength of this study, as very few other studies have measured balance at these ages. Meaningful variation in balance ability as early as age 53 was demonstrated in Chapters 2, 3 and 4. However, there was no balance assessment at age 43, where the in-depth cognitive testing began and as such, analyses could not be extended to early midlife.

This chapter has unidirectionally modelled the association between cognition and subsequent balance throughout this chapter. This direction was chosen as there is more convincing argument (see section 5.1.2) and stronger evidence (see section 5.1.3) for an association plausibly operating in this direction. However, it is possible that balance ability may also be associated with subsequent cognition as demonstrated by limited evidence summarised in section 5.1.3.

5.5 Conclusions and further research

This chapter has shown evidence of distinct associations between individual cognitive domains - most notably verbal memory, search speed, verbal fluency and reading ability - and balance ability. This has important research and clinical implications. As the first of two main chapters examining adult cognition and balance in NSHD, it has identified cognitive domains that have the strongest associations with balance (i.e. verbal memory, search speed, verbal fluency and reading ability). Using the results of this chapter as preliminary evidence, Chapter 6 investigates bidirectional associations. Verbal memory and search speed are carried forward into this next chapter as 1) they represent optimal data due to repeated measures from age 43 to 69 and 2) they demonstrated robust associations with balance.

As clinicians consider key health domains associated with ageing, cognitive and physical capability are crucial areas. It is well established that both cognitive and physical capabilities decline with age, but there is a gap in understanding how they are associated and how this contributes to healthy ageing. Understanding that low cognitive performance early in life may be a risk factor for subsequent poor balance ability could also help identify individuals at risk of poor or accelerated ageing. Furthermore, interventions aimed at improving balance and mobility or to minimise falls risk could target specific cognitive exercises in addition to a physical training program [517]. Testing if these cognitive interventions improve balance ability beyond physical interventions could contribute to causal inference about the direction of this association. As different domains of cognition appear to independently contribute to balance ability, this training should look to target multiple cognitive domains, including but not limited to memory, attention, processing speed and executive function.

CHAPTER 6: BIDIRECTIONAL ASSOCIATIONS BETWEEN COGNITIVE ABILITY AND BALANCE ABILITY IN MID AND LATER LIFE

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Chapter 5 established associations between distinct cognitive domains and balance in mid and later life. These associations were strongest cross-sectionally, with larger effect sizes at younger ages (i.e. age 53). Although the direction of association in Chapter 5 focused on cognition and subsequent balance ability, there is some indication that balance may contribute to subsequent cognition and as such, the association may be bidirectional.

The main aim of this chapter is to explore bidirectional associations between balance ability and cognitive ability in mid and later life. First, the introduction section explores potential mechanisms through which balance may be associated with subsequent cognition (section 6.1.1). Next, it examines, in detail, studies that have considered bidirectional associations between balance and cognition (section 6.1.2) and provides a summary of the bidirectional associations between cognition and other measures of physical capability (section 6.1.3). Finally, limitations of the current evidence are summarised (section 6.1.4) and specific objectives and hypotheses of the current chapter are outlined (section 6.1.5).

6.1 Introduction

6.1.1 Balance ability as a contributor to subsequent cognitive ability

As discussed in detail in Chapter 5 (see section 5.1.2), cognitive functioning is a key process involved in balance; the brain must integrate sensory and motor information as well as anticipate changes, filter information and react to disturbances that may alter posture and affect balance. A systematic review on the bi-directional relationship between physical capability and cognitive function identified that cognitive functioning at baseline was associated with subsequent changes in physical capability, including balance [211]. Conversely, there is little investigation into how poor balance ability may contribute to subsequent decline in cognitive ability [522]. Indeed, within the same review, the authors noted that only a few studies had examined cognition as an outcome of physical capability and thus evidence of a reciprocal association lacked strength [211].

Conceptually, there are several conceptual models that may explain how balance ability could be associated with subsequent cognitive ability. First, there may be a common aetiology that underlies age-related decline in physical and cognitive domains. This has been termed the “common cause hypothesis” by Christensen et al. [523], which suggests that a common underlying factor (i.e. a third factor), or a set of shared risk factors, drives decline in both cognitive and balance abilities [523]. For example, age-associated brain atrophy, specifically of white matter, is known to play direct roles in both cognitive decline [524] as well as decline in physical performance including balance and gait [525,526]. Most of the support for this hypothesis is based on cross-sectional data, with very limited evidence from longitudinal data [211]. See Figure 6.1A for a conceptual model of this mechanism.

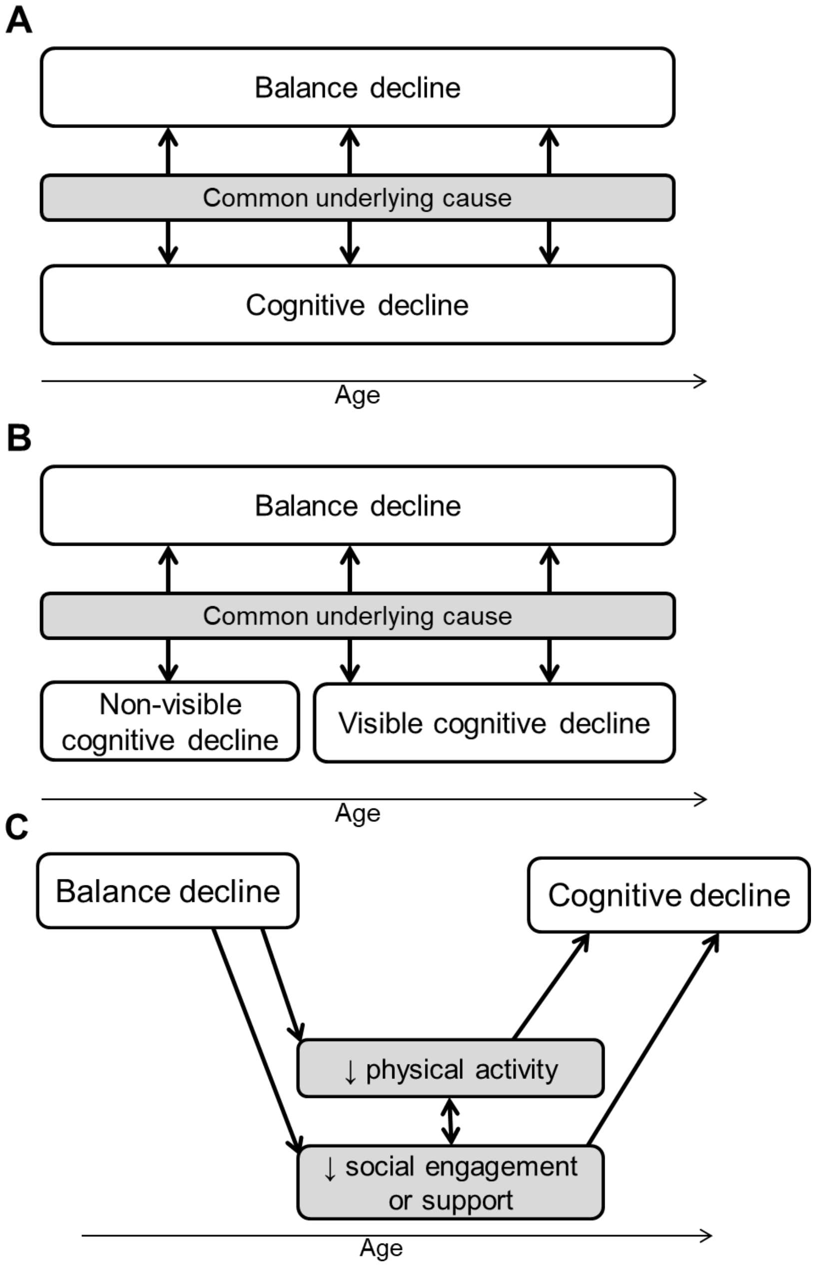


Figure 6.1 Conceptual models for possible mechanism of the association between balance decline and subsequent cognitive decline. A) Common cause hypothesis; B) Common cause hypothesis with balance as a marker for non-visible cognitive decline; C) Indirect pathway via physical activity and social engagement or support.

Building on the common cause hypothesis, a second hypothesis posits that balance impairment may be a marker of cognitive impairment that has not yet become clinically manifest [76,290] (see Figure 6.1B). Several studies have demonstrated that baseline balance impairment was associated with global cognitive decline in several different populations including healthy individuals [4], those with incident dementia [291,497] and those diagnosed with Alzheimer's disease [290]. Although these studies all had relatively short follow-up of one [4,290,497] to three years [291], they suggest that balance impairments at baseline could be indicative of early stages of brain atrophy or white matter change that has not yet exhibited cognitive consequences.

A third and final hypothesis posits that there may be an indirect pathway through which impaired balance influences cognition. This hypothesis is novel to this thesis as no known study has proposed such a pathway. Impaired balance could act indirectly by impacting cognition via decreased social activity or increased activity restriction [233,527,528] (see Figure 6.1C). For example, impaired balance ability may inhibit individuals from being actively involved in everyday physical activity as well as reduce participation in social events or interactions. This combination of low activity and lack of social support and social participation is hypothesised to result in higher levels of cognitive decline [529]. For example, participation in social activities (community memberships, visiting friends, volunteering), size of social network, frequency of social engagement and quality of emotional relationships have positive associations with memory, executive functioning and diagnosed clinical impairment [529-533].

6.1.2 Studies that considered repeated measures of cognition and balance

Very few studies have investigated if changes in cognitive and balance capabilities occur at the same time or if changes in one capability precede and possibly contribute to the other. Two studies examined bidirectional patterns of association in both cognition and balance [522,534], with a third study examining the direction of association between cognition and a physical performance measure based mainly on gait and balance [434]. These three studies are described below.

The first study considered 610 healthy, community-dwelling adults aged ≥65 in Western Japan at baseline and after a two-year follow-up [534]. Separate multiple regression analyses examined if baseline balance (eyes open, one-legged stand test) was associated with subsequent cognitive function (measured with the Montreal Cognitive Assessment) and if baseline cognitive function was associated with subsequent balance. The authors concluded that baseline balance “predicted” cognitive function and that there was no evidence that baseline cognition “predicted” balance ability. There are several limitations to this study including misuse of causal language, short follow-up, ceiling effect of the eyes open test and most crucially, analytical limitations. The authors based their conclusions about a bidirectional association on two distinct unidirectional models. Rather than using visual inspection to compare the strength of these associations as the authors did, it would be more appropriate to utilise analyses that model both directions simultaneously.

The second study examined 813 community-dwelling adults aged ≥50 at baseline from the Swedish Adoption/Twin Study of Aging [522]. The authors assessed temporality of a composite measure of balance and four different factors of cognition (verbal ability, spatial ability, memory and processing speed) using bivariate dual change score models in a 19-year follow-up (6 waves of data). This analytical strategy captures the extent to which change in balance or cognition is a function of the other [535,536]. There was no evidence of a longitudinal association in either direction between balance ability and any of verbal ability, spatial ability or memory. However, there was evidence of a unidirectional association between balance and subsequent processing speed. Changes in balance were reported to occur first, which led to subsequent changes in processing speed.

The third and final study assessed the association of a composite cognitive score with an aggregate physical score (mainly based on gait and balance) in 764 community-dwelling American adults aged ≥50 [434]. The authors investigated how baseline status (categorised as cognitive impairment, gait/balance impairment, both or neither) was associated with subsequent decline in cognition and balance-gait over an 8-year follow-up. The authors concluded that the direction of the association was from cognitive impairment to decline in balance-gait performance, with a minor impact of balance-gait impairment on cognitive decline. Similar to the first study [534], the authors did not utilise an analytical strategy that appropriately modelled a bidirectional association. By categorising individuals into four groups at baseline, information on trajectories of decline was lost. The balance and gait tasks were grouped together, thus the specific role of balance cannot be disassociated from the gait component. Although the authors concluded that there was stronger evidence of a unidirectional association, the results provide inconclusive evidence on a possible bidirectional association.

The findings of these three studies provide conflicting evidence on the temporal order of the association between cognition and balance [434,522,534]. All three studies had moderate sample sizes (n=500 to 1000) with varying periods of follow-up (2 to 19 years). Although the age demographic across studies was similar, each study sample came from a different country (U.S.A, Japan, Sweden). Only one study appropriately tested the bivariate association [522]; another tested unidirectional associations in separate models [534] while the other examined how baseline cognitive and balance impairment was associated with subsequent cognitive and balance/gait functioning [434]. Further evidence on both the temporality and relative contribution of cognition and balance in the ageing process must consider an analytical approach that allows the directionality to be formally assessed. This chapter addresses this issue by applying two structural equation modelling (SEM) techniques (see section 6.2.2) that allow the direction of association to be formally assessed.

6.1.3 Studies that considered repeated measures of cognition and gait

As the evidence of bidirectional associations between balance and cognition is sparse (i.e. only three studies), it is also valuable to consider research that investigates bidirectional associations between cognition and other measures of physical capability. These studies have primarily examined bidirectional associations of cognition with gait speed [537-544], with minimal evidence on chair stands [541], grip strength [541] or aggregate measures of physical capability [76]. As gait speed encompasses many components of balance, this evidence could provide informative insight into bidirectional cognition-balance associations [545,546].

Yet, studies of cognition and gait speed have also demonstrated inconsistent bidirectional associations. For example, four studies reported positive bidirectional associations between cognition and gait speed [537,539,543,544] while another four studies found no evidence of bidirectional associations. Of the four latter studies, two reported that baseline cognition was associated with subsequent physical capability [541,542], while the other two reported that baseline physical capability was associated subsequent cognitive decline [538,540]. The heterogeneity of results may be due to varying durations of follow-up, differences in analytical techniques or measures of gait and cognition and heterogeneous characteristics of participants (i.e. sex, country, age).

Of the studies that suggested there were bidirectional associations, several considered how different domains of cognition showed different patterns of association with gait speed. For example, Krall et al. [539] found that the bidirectional associations were strongest for memory compared with measures of executive function or even global cognition, while Gale et al. [537] demonstrated that the bidirectional associations were strongest for tests of executive function and verbal memory compared with tests of search speed and verbal fluency. Both the verbal memory and search speed tasks are nearly identical to those used in NSHD and thus comparisons can be made.

6.1.4 Limitations of current evidence base

The literature described above has several gaps and limitations. First, the bidirectional association between cognition and balance has been scarcely investigated. Only three studies have considered dual directions and there were contrasting findings. Second, two of these studies (and many of the cognition-grip strength studies) did not consider bidirectional associations within the same analytical model. Decline in cognitive and balance abilities with age is common; as such, one would expect to find an association between these two constructs. This is especially true in age heterogeneous samples. Using an analytical model that encompasses both directions can help determine if the association is an artefact of correlation or if one direction of association is stronger than the other. Third, evidence from other studies of cognition and physical capability (e.g. gait speed) suggest that the temporal relationship may differ across cognitive domain as well as across types of physical capability. There may be specific associations within certain cognitive domains; this is supported by the evidence in Chapter 5 which identified different patterns of associations between various cognitive domains and balance. Fourth, these studies did not take account of the possibility that the direction of association may change with age. Evidence from Chapters 3, 4 and 5 have demonstrated that risk factors for balance ability as well as its association with cognition change with age. Thus, a bidirectional association between balance ability and cognition may have a dynamic component across time.

There is a strong theoretical framework to support hypotheses of associations between cognition and subsequent balance. Evidence of bidirectional associations is sparse and may be limited by the data available. Balance ability tends to be measured in later life only (as discussed in section 1.3.2), whereas cognitive ability is commonly measured across the life course. Consequently, longitudinal studies have frequently modelled balance ability as a function of cognitive ability. Furthermore, it is unclear if there has been a lack of investigation or if there is a publication bias due to failure to find an association. It is noteworthy that the studies summarised above do not comment on potential mechanisms explaining associations between balance and subsequent cognition association. There is a need not just to report evidence of associations but also to consider the underlying mechanisms and implications of these associations.

Utilising NSHD data and employing an analytical strategy that appropriately assesses a bidirectional association can mitigate most of these limitations. Balance and cognitive data were collected at multiple ages from midlife in NSHD. Furthermore, verbal memory and search speed were collected at four different waves which allows one to investigate if each domain exhibits a similar association with balance. All of the studies above have been largely confounded by age. Adjusting for age may not be sufficient to avoid age confounding as some age-related differences in cognitive functioning may be primarily due to cohort differences [502]. Using a birth cohort such as NSHD can also help eliminate age confounding and allow differences in association at different ages to be assessed.

6.1.5 Objectives and hypotheses

To build on the findings from Chapter 5 and to address the gaps in research identified above, the primary objectives of this chapter are:

i) to investigate the direction of the associations between balance ability and cognitive ability (verbal memory and search speed) between ages 53 and 69;
ii) to determine if cognitive ability or balance subsequently contributes to changes in the other.

Verbal memory and search speed are the two cognitive domains that will be explored in this chapter. Both domains exhibited strong patterns of association with balance in Chapter 5 and are the two measures of cognition in NSHD that were collected at four different time points (ages 43, 53, 60-64 and 69), thus allowing associations over time to be investigated.

As both physical and cognitive decline commonly co-occur in mid to later life, balance ability and cognitive ability are hypothesised to have bidirectional associations. However, it is expected that cognitive ability may have a greater impact on subsequent balance ability (objective i). This is due to the direct role of cognition in the balance process compared with a potential indirect pathway between balance and subsequent cognition via social engagement and physical activity. Building on the findings of objective i, decline in cognitive ability is expected to be associated with decline in balance ability and vice versa (objective ii).

Verbal memory and search speed are expected to have different associations with balance, specifically across time. Chapter 5 demonstrated that the association between verbal memory and balance was stronger than that of search speed and balance; however, the latter association remained constant across ages while the former became smaller. Trajectories of verbal memory and search speed in NSHD also suggest different patterns of decline [322]. Decline in search speed was strongest between ages 43 and 53, whereas decline in verbal memory increased after age 60 [322]. Taken together, the association between verbal memory and balance is hypothesised to be stronger than that of search speed and balance, although both associations are expected to be smaller at older ages.

6.2 Methods

6.2.1 Study sample and overview of cognitive tests

As in previous chapters, up to 3111 participants were included in the analyses if they had at least one valid balance measurement and at least one score on either the verbal memory or search speed tests. Measures of balance (section 2.2.1, Chapter 2), cognitive ability (section 5.2.2, Chapter 5) and covariates (section 2.2.3, Chapter 2) were previously described.

6.2.2 Statistical analyses

6.2.2.1. Autoregressive cross-lagged model (objective i)

6.2.2.1.1 Overview of the model

An autoregressive cross-lagged model is a type of SEM that can describe directional associations between variables over time. The major advantage of using this model instead of a series of regression models is that multiple regression pathways and correlations can be simultaneously included [547]. There are three main parts in an auto-regressive cross-lagged model: autoregressive estimates, cross-lagged estimates and covariance estimates. These are shown in Figure 6.2 and explained below.

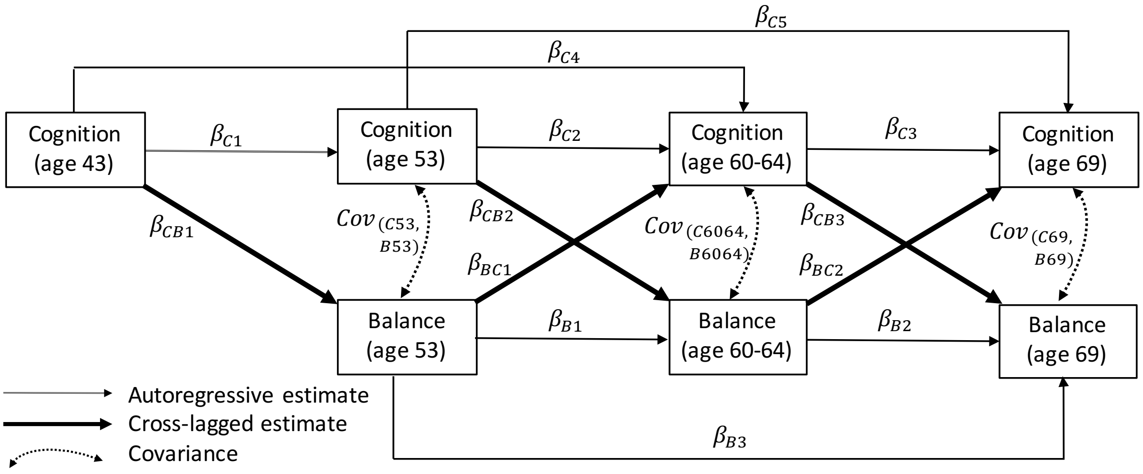


Figure 6.2 Analytical model of the autoregressive cross-lagged model used for objective i

There are two auto-regressive components of the model, one for cognition (β_{C1}, β_{C2}, β_{C3}) and one for balance (β_{B1}, β_{B2}). For each component, scores at one age are a function of the value of the same variable at the previous time point [548]. For example, β_{C1} is a linear regression coefficient that describes cognition at age 53 as a function of cognition at age 43 (see Figure 6.2 and 6.3). These autoregressive effects describe the stability of each construct over time. A large coefficient would suggest that an individual’s cognition has remained constant over time, whereas a smaller coefficient would suggest that cognition at age 53 is not associated with cognition at age 43. In a first order autoregressive model, each score at time *‘t’* depends on the score at time *‘t-1’* (see Figure 6.3A), where t=1, 2, 3, 4 correspond to ages 43, 53, 60-64 and 69. In a second order autoregressive model, each score at time *'t'* depends on the score at time *'t-1'* and the score at time *'t-2'* (see Figure 6.3B).

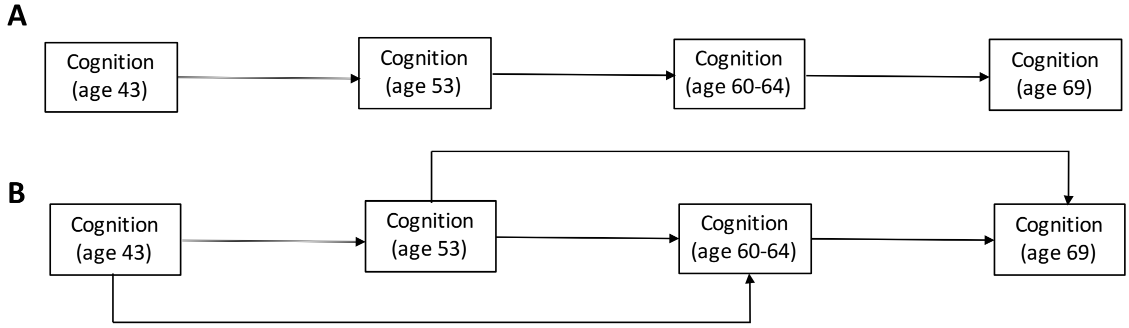


Figure 6.3 A. First and B. Second order autoregressive model examples for cognition

The cross-lagged components of the model describe the reciprocal associations over time. In Figure 6.2, the regression coefficients β_{CB1}, β_{CB2} and β_{CB3} represent the effect of cognition at time *'t'* on balance at time *'t+1'* (e.g. β_{CB1} is the effect of cognition at age 43 on balance at age 53). Equivalently, β_{BC1} and β_{BC2} represent the effect of balance at time *'t'* on cognition at time *'t+1'*. The inclusion of both autoregressive and cross-lagged estimates ensures that previous levels of the variables are controlled for when cross-lagged effects are estimated. As a result, the cross-lagged effects are not due to correlations between the two constructs at a previous time point.

The third and final component of the autoregressive cross-lagged model are the covariance estimates. These estimates allow for the expected correlation of variance between cognition and balance at each age. For example, $Cov_{(C53,53)}$ in Figure 6.2 is an estimate of the joint variability of cognition at age 53 and balance at age 53.

6.2.2.1.2 Building the model

Separate autoregressive cross-lagged models were created for each cognitive domain (i.e. verbal memory and search speed). Standardised coefficients for all variables are presented. All models were estimated using Mplus v6.1. An initial autoregressive cross-lagged model was created based on the theoretical model (see Figure 6.2). This included all autoregressive components, cross-lagged components and covariance estimates at each age. Both first and second order autoregressive pathways for balance and cognitive score were considered. In order to evaluate the model fit and determine the best model, χ^2 tests and goodness of fit indices were considered and modification indices suggestions were utilised. Using an iterative approach, non-significant pathways were removed from the model in order to improve model fit.

The ‘MLR’ estimator in MPlus was used. This estimator provides maximum likelihood parameter estimates and standard errors that are robust to the non-normality and non-independence of the balance data [549], thus mitigating the need for log transformations as previously used in the thesis. Full information maximum likelihood (FIML) was used to estimate the models. FIML deals with missing data by utilising all available variables to estimate the model regardless of an individual’s missing data [550]. Due to sex differences identified in Chapter 5, the model was estimated as a multiple group model for search speed, which provides separate estimates for men and women within the same model.

The following indices were used to assess model fit: Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA) and Standardised Root Mean Square Residual (SRMR) [551]. A CFI or a TLI of ≥ 0.90 indicates adequate model fit, while scores ≥ 0.95 are considered an excellent fit [552,553]. RMSEA and SMR values of ≤ 0.08 indicates adequate fit and scores ≤ 0.06 indicate an excellent fit. The chi-square test is also reported, but was not used when assessing model fit. The chi-square test is very sensitive to large sample sizes or models with many degrees of freedom and thus, tends to over-reject the majority of models [552].

6.2.2.1.3 Comparing pathways within the model

Once the main model was built and satisfied goodness of fit criteria, specific pathways within the model and between groups were examined. Satorra-Bentler Scaled chi-square difference tests allows pathways within the same model to be formally compared and for differences between groups (i.e. sex differences) to be assessed [554]. First, the strength of the pathways of interest were constrained to be equal to one another and the fit of the newly constrained model was assessed. For example, balance at age 60-64 regressed on cognition at age 53 and cognition at age 60-64 regressed on balance at age 53 were constrained to be equal in order to compare effect sizes. The scaling correction factor tool is then used to calculate the difference in chi square between models [555]. If the model fit of the newly constrained model was significantly worse than the main model, this provides evidence that the paths are different in strength. For search speed, pathways were also compared between men and women.

6.2.2.2 Bivariate dual change score model (objective ii)

6.2.2.2.1 Overview and building of the model

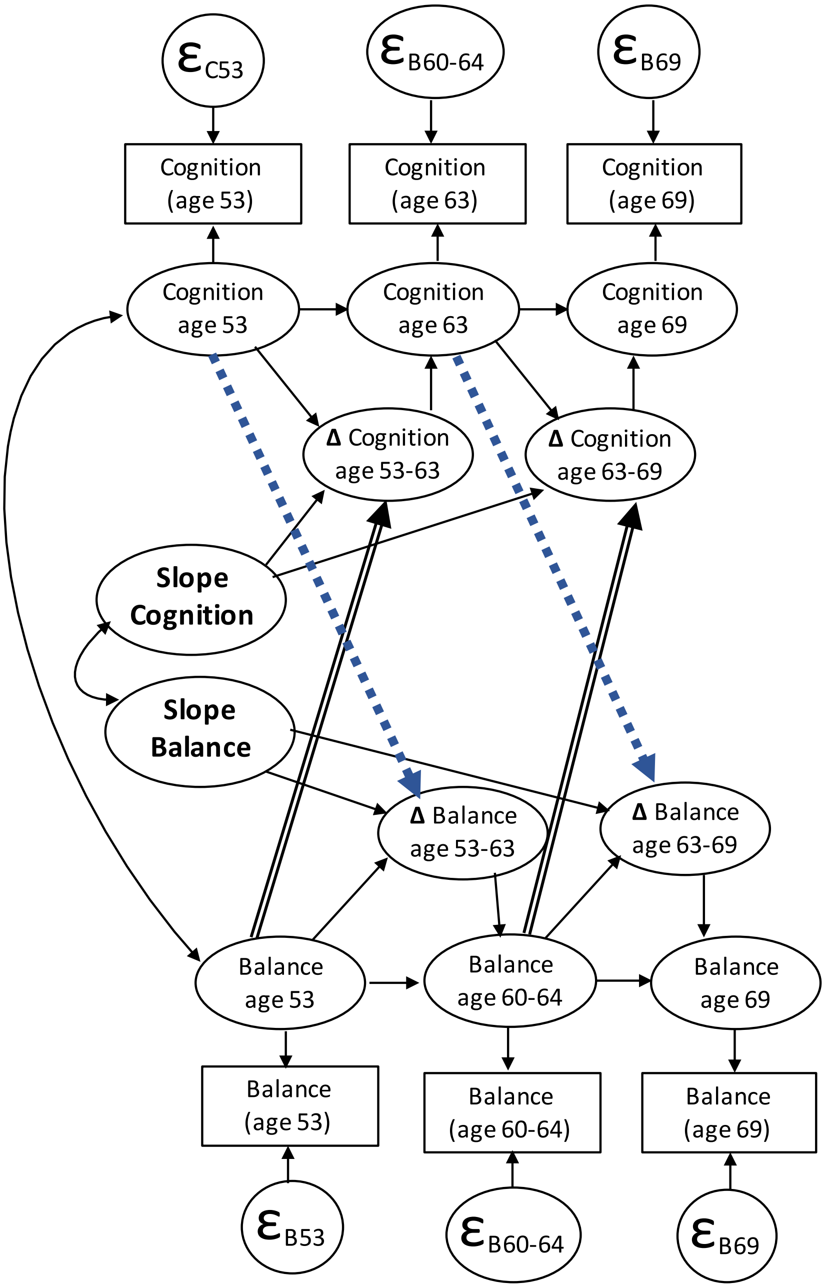
Bivariate dual change score models (DCSMs) were employed to evaluate the extent to which one construct (i.e. cognitive ability or balance ability) predicts the other across time. By combining aspects of growth modelling and autoregressive cross-lagged models, DCSMs allow specific hypotheses about the direction of the association to be tested [549]. Figure 6.4 outlines the model, which has several components. First, observed scores at each age (e.g. balance at age 53) are expressed as a latent true score and a residual score (i.e. error term) for each observation. Next, latent change scores at specific time points (e.g. change in balance from age 53 to age 60-64) are expressed as a combination of the latent true score at that age (e.g. age 60-64), previous scores (e.g. age 53) and the remaining residual score. Next, a growth curve for each construct (e.g. slope of balance) can be modelled using the latent change scores. The latent true score at the initial time point (i.e. age 53) is the intercept of each construct.

Once univariate DCSMs have been created for each measure of cognitive ability and balance, they can be combined in a bivariate DCSM. The addition of coupling parameters enables the association between balance ability and the cognitive domain to be assessed. The coupling mechanism allows change in one construct to depend on previous scores in the other (e.g. change in balance from age 53 to 60-64 to depend on cognition at age 53). Four coupling pathways are shown in Figure 6.4; two indicate a pathway from cognition to change in balance and two indicate a pathway from balance to change in cognition. By constraining or restricting the coupling parameters, it is then possible to test hypotheses about the direction of association.

6.2.2.2.2 Testing hypotheses within the model

For each of verbal memory and search speed, four models were examined to determine the direction of association between these two constructs. For all models, indicators of model fit are recorded including the CFI, TLI, RMSEA, SRMR, Akaike Information Criterion (AIC) and Bayesian Information Criterion

(BIC). First, a full model that includes all coupling parameters was freely estimated (as shown in Figure 6.4). A second model set the coupling parameters to zero, which is indicative of no association between cognition and balance. The third and fourth models were constrained such that only a unidirectional association can be tested. For example, the third model constrains the coupling parameters of balance to changes in cognition to zero, whilst allowing the coupling parameters of cognition to changes in balance to be freely estimated. The fourth model constrains the opposite coupling parameters to estimate the unidirectional association of balance to changes in cognition. The fit of each models was compared with the first model, which is the only model to freely estimate a bidirectional association.



▭ *represents error term (or residual variance) for each measure of cognition or balance*
represents observed scores.
⬭ *represents latent scores (either latent scores or latent change scores)*
▪▪▪▶ *represents coupling mechanism of cognition to subsequent change in balance*
⇒ *represents coupling mechanism of balance to subsequent change in cognition*

Figure 6.4 Analytical model of the bivariate dual change model used for objective ii

6.3 Results

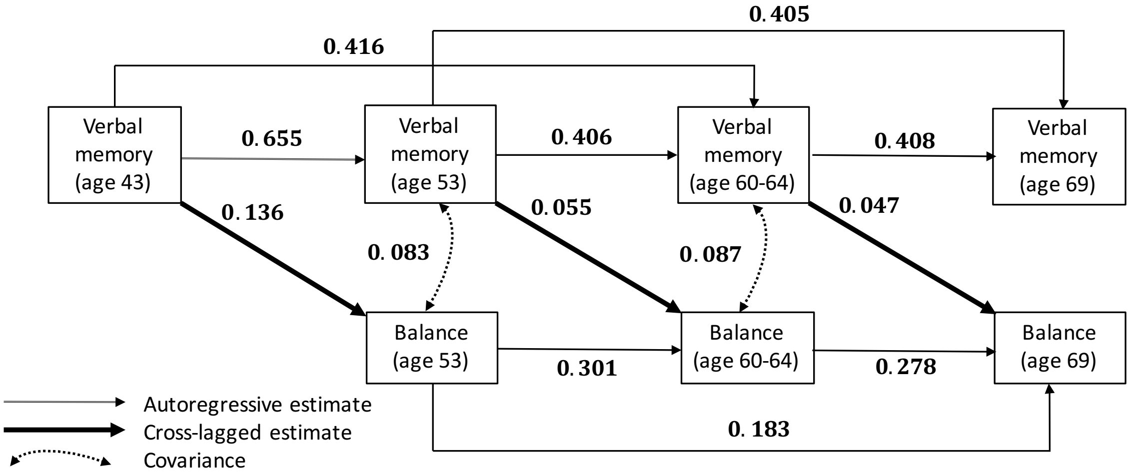
6.3.1 Autoregressive cross lagged model

As there was no evidence of sex differences in associations between balance and verbal memory in Chapter 5, one set of estimates were considered for the full sample (i.e. men and women). For search speed, the grouping indicator provided separate estimates for men and women within the same model. Estimates of men and women for verbal memory are provided in the Appendix for comparison purposes.

6.3.1.1 Verbal memory and balance ability

Table 6.1 and Figure 6.5 demonstrate the results of the autoregressive cross-lagged model for verbal memory. Both balance and verbal memory had the best fit as second order autoregressive models, which indicates that scores at one time point were a function of scores at the previous two-time points. There were not sufficient degrees of freedom to test a third order model. The stationary autoregressive effects of balance from age 53 to 69 and verbal memory from age 43 to 69 suggest that there is low to moderate stability of one-legged balance times with age and moderate to high stability of verbal memory scores with age. Next, the covariance between balance and verbal memory suggests correlations at ages 53 and 60-64 (both $p<0.001$), however this correlation weakens and is no longer present at age 69 ($p=0.69$).

Finally, the cross-lagged estimates are examined. The lagged effect of verbal memory on balance at the next wave is statistically significant at all ages ($p<0.05$ at all ages), however there is no evidence of an effect of balance ability on verbal memory at any age ($p=0.49$ at age 60-64, $p=0.77$ at age 69). Satorra-Bentler scaled chi square difference tests revealed that the effect size was bigger at age 53 than at age 60-64 (x^2 difference= 21.23, df=3, $p<0.001$) or 69 (x^2 difference= 28.84, df=3, $p<0.001$), with no difference in effect size between ages 60-64 and 69 (x^2 difference= 2.84, df=3, $p>0.25$). Results were consistent when the model was grouped by men and women (see Appendix 6.1), with no sex differences in any pathway ($p>0.25$). Model fit indicators are provided in Figure 6.5 and demonstrate that the model is an excellent fit.



Model fit: CFI=0.984, TLI=0.935, RMSEA =0.068, SRMR =0.018, chi-square test value =68.074 (df=5), p<0.0001). Only significant pathways (p<0.05) are shown here, while all pathways including estimates, p-values and 95% CI are presented in Table 6.1

Figure 6.5 Autoregressive cross-lagged model of the association between verbal memory and balance

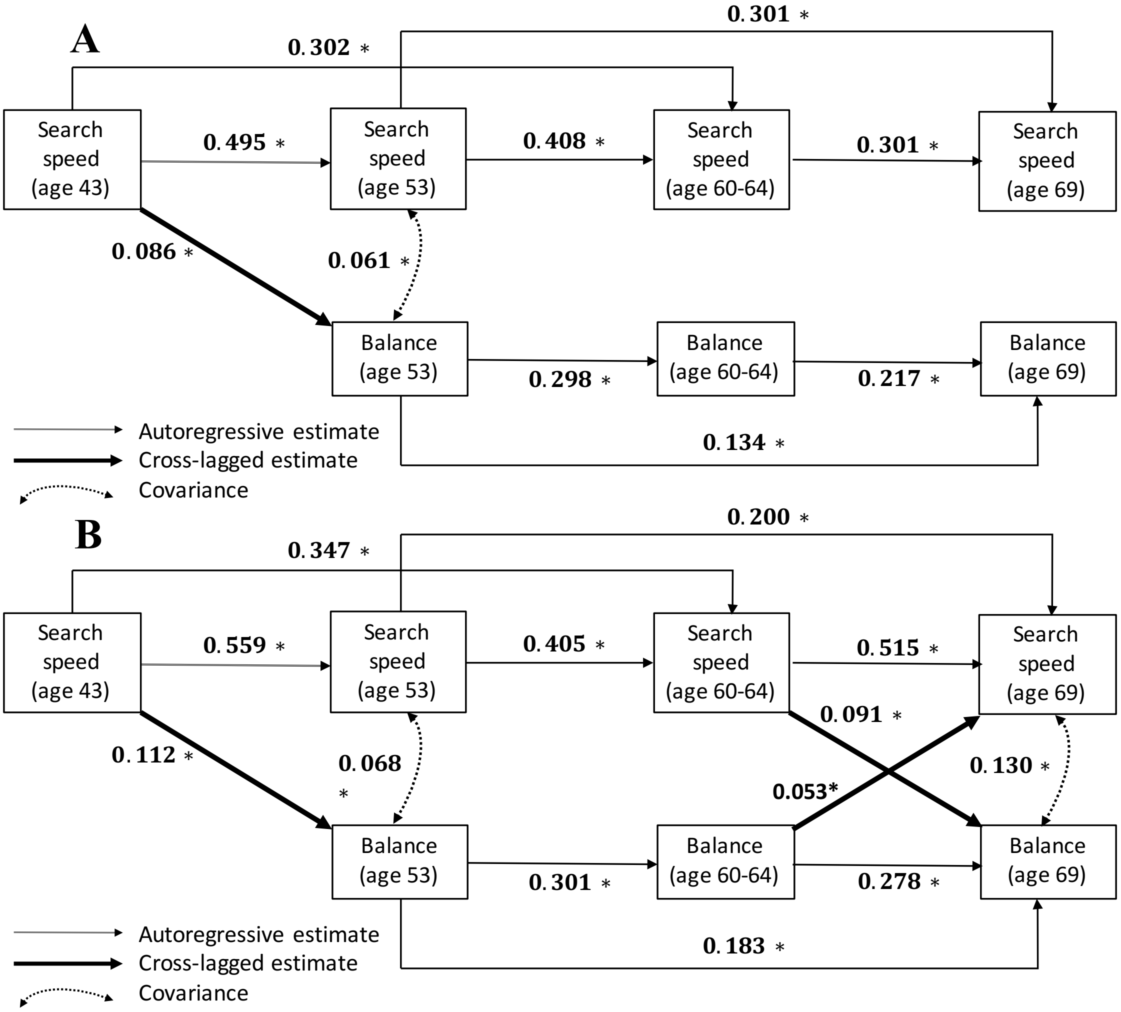
Table 6.1 Standardised results from the autoregressive cross-lagged model of balance and verbal memory

		Change in balance time per SD change in cognition (95% CI)	**p-value**
AUTOREGRESSIVE ESTIMATES			
Balance at age 60-64	*ON Balance age 53*	0.301 (0.243, 0.358)	<0.001
Balance at age 69	*ON Balance age 60-64*	0.278 (0.200, 0.355)	<0.001
	ON Balance age 53	0.183 (0.126, 0.240)	<0.001
Verbal memory at age 53	*ON Verbal memory age 43*	0.655 (0.631, 0.678)	<0.001
Verbal memory at age 60-64	*ON Verbal memory age 53*	0.406 (0.365, 0.447)	<0.001
	ON Verbal memory age 43	0.416 (0.376, 0.456)	<0.001
Verbal memory at age 69	*ON Verbal memory age 60-64*	0.408 (0.367, 0.450)	<0.001
	ON Verbal memory age 53	0.405 (0.364, 0.446)	<0.001
CROSS-LAGGED ESTIMATES			
Balance at age 53	*ON Verbal memory age 43*	0.136 (0.097, 0.174)	<0.001
Balance at age 60-64	*ON Verbal memory age 53*	0.055 (0.012, 0.098)	0.01
Balance at age 69	*ON Verbal memory age 60-64*	0.047 (0.007, 0.087)	0.02
Verbal memory at age 60-64	*ON Balance age 53*	0.011 (-0.020, 0.041)	0.49
Verbal memory at age 69	*ON Balance age 60-64*	0.005 (-0.027, 0.036)	0.77
COVARIANCE ESTIMATES			
Verbal memory age 53	*WITH Balance age 53*	0.083 (0.042, 0.125)	<0.001
Verbal memory age 60-64	*WITH Balance age 60-64*	0.087 (0.040, 0.134)	<0.001
Verbal memory age 69	*WITH Balance age 69*	0.009 (-0.036, 0.054)	0.69

n=2735; corresponding estimates in Figure 6.6

6.3.1.2 Search speed and balance ability

Figure 6.6 and Table 6.2 demonstrate the results of the autoregressive cross-lagged model for search speed. Due to strong sex differences in the association between balance and search speed in Chapter 5, the grouping option in MPlus estimates separate parameters for men and women within the same model. As with verbal memory and balance, search speed had the best fit as second order autoregressive models. For both men and women, the stationary autoregressive effects of search speed from age 43 to 69 showed moderate stability over time, while balance ability from age 53 to 69 had low to moderate stability. There was weak correlation between balance and search speed at age 53 for men and women (p<0.05), no correlation at age 60-64 (p=0.21 in men; p=0.30 in women) and a moderate correlation at age 69 in men only (p<0.001 in men; p=0.22 in women).



Model fit: CFI=0.985, TLI=0.938, RMSEA =0.054, SRMR =0.018, chi-square test value =50.195 (df=10), p<0.0001) Only significant pathways (p<0.05) are shown here, while all pathways including estimates, p-values and 95% CI are presented in Table 6.2

Figure 6.6 Autoregressive cross-lagged model of the association between search speed and balance in A) women and B) men.

Table 6.2 Standardised results from the autoregressive cross-lagged model of balance and search speed

		MEN (n=1375)		**WOMEN (n=1416)**	
		Change in balance time per SD change in cognition (95% CI)	**p-value**	**Change in balance time per SD change in cognition (95% CI)**	**p-value**
AUTOREGRESSIVE ESTIMATES					
Balance at age 60-64	*ON* Balance age 53	0.301 (0.225, 0.378)	<0.001	0.298 (0.217, 0.380)	<0.001
Balance at age 69	*ON* Balance age 60-64	0.285 (0.175, 0.395)	<0.001	0.217 (0.137, 0.298)	<0.001
	ON Balance age 53	0.196 (0.118, 0.274)	<0.001	0.134 (0.071, 0.198)	<0.001
Search speed at age 53	*ON* Search speed age 43	0.559 (0.518, 0.601)	<0.001	0.495 (0.449, 0.542)	<0.001
Search speed at age 60-64	*ON* Search speed age 53	0.405 (0.032, 0.153)	<0.001	0.408 (0.346, 0.469)	<0.001
	ON Search speed age 43	0.347 (0.288, 0.406)	<0.001	0.302 (0.242, 0.361)	<0.001
Search speed at age 69	*ON* Search speed age 60-64	0.515 (0.454, 0.577)	<0.001	0.408 (0.343, 0.474)	<0.001
	ON Search speed age 53	0.200 (0.126, 0.273)	<0.001	0.301 (0.235, 0.367)	<0.001
CROSS-LAGGED ESTIMATES					
Balance at age 53	*ON* Search speed age 43	0.112 (0.060, 0.163)	<0.001	0.086 (0.034, 0.139)	<0.001
Balance at age 60-64	*ON* Search speed age 53	0.067 (-0.005, 0.139)	0.07	-0.045 (-0.105, 0.015)	0.14
Balance at age 69	*ON* Search speed age 60-64	0.091 (0.023, 0.159)	<0.01	0.049 (-0.012, 0.111)	0.12
Search speed at age 60-64	*ON* Balance age 53	0.028 (-0.022, 0.077)	0.27	0.030 (-0.017, 0.077)	0.21
Search speed at age 69	*ON* Balance age 60-64	0.053 (0.004, 0.102)	0.03	0.044 (-0.008, 0.096)	0.10
COVARIANCE ESTIMATES					
Search speed age 53 *WITH* Balance age 53		0.068 (0.014, 0.122)	0.01	0.061 (0.007, 0.116)	0.03
Search speed age 60-64 *WITH* Balance age 60-64		0.045 (-0.026, 0.117)	0.21	0.029 (-0.026, 0.084)	0.30
Search speed age 69 *WITH* Balance age 69		0.130 (0.069, 0.191)	<0.001	0.038 (-0.022, 0.099)	0.22

In men and women, search speed at age 43 was associated with subsequent balance at age 53 (p<0.001 for both). No other cross-lagged paths were significant in women (see Figure 6.6A). In men, there was evidence of a bidirectional association between ages 60-64 and 69 (Figure 6.6B). As with verbal memory, model fit indicators demonstrate that the model was an excellent fit.

Satorra-Bentler scaled chi square difference tests compared several pathways. First in men from age 60-64 to 69, the pathway from search speed to balance was significantly stronger than the pathway from balance to search speed (p<0.001). The strength of association between search speed at age 43 and balance at age 53 was similar in men and women (p>0.20). Despite evidence of a bidirectional association in men only between ages 60-64 and 69, there was no evidence that these pathways significantly differed between men and women (p>0.20). Further investigation of estimates suggests that this is likely due to a lack of power as estimates were similar in men and women- particular for balance at age 60-64 to search speed at age 69 (β=0.053 (0.004, 0.102), p=0.03 in men; β=0.044 (-0.008, 0.096), p=0.10 in women; see Table 6.2).

6.3.2 Dual change score models

6.3.2.1 Non-convergence difficulties

The estimation strategies used for structural equation models are iterative; MPlus derives an initial model then improves the model via iterations. This process continues until it reaches convergence, whereby further iterations do not improve the model. Difficulties with convergence for dual change score models were encountered and the steps to find a solution to this merits discussion. Extensive search for a solution was undertaken [549,556] and advice from experts in the field was sought [557-560]. A summary of potential reasons for non-convergence and the attempted solutions is provided in Table 6.3. These reasons include: insufficient iterations, an under-identified model, skewed data, inappropriate covariance, inaccurate starting values, uneven measures of cognition and balance, software limitations and missing data.

No attempt was successful until analyses were restricted to those with complete data on cognition and balance. This restriction allowed the DCSM of verbal memory and balance ability to run, however the search speed model still failed to converge. The results of the verbal memory model in this restricted sample are presented below and must be carefully interpreted due to the bias introduced from using complete data only. This is discussed further in section 6.4.4.

Table 6.3 Potential reasons for non-convergence of DCSM and solutions attempted

Potential reason for non-convergence	Attempted solution
1. Insufficient iterations	Increased limit from default of 1000 iterations to 10 000 and 100 000
2. Under-identified model	Unable to simplify model due to complexity of observed, latent and change variables required in the DCSM
3. Skewed balance data	Log-transformed balance ability
4. Scale of covariance matrix	Transformed and standardised variables to minimise variance of cognitive and balance data
5. Inaccurate starting values	Used suggested starting values from a previous model as well as suggested values from SEM manual
6. Uneven number of balance and cognitive measures	Utilised cognition at ages 53, 60-64 and 69 only
7. Inability of software to handle complex model	Attempted to re-estimate models in Stata, despite the knowledge that MPlus is able to handle more complex models
8. Insufficient n	n at each and for each measure was determined to be more than sufficient
9. Missing data	Restrict analyses to complete cases only (i.e. cognitive and balance measure at each age)

6.3.2.2 Verbal memory and balance ability

Analysis of this model was restricted to individuals with complete data only (n=1641). Model fit parameters of the following four models are provided in Table 6.4:

1. Freely estimated bidirectional model
2. No coupling
3. Verbal memory → balance only
4. Balance → verbal memory only

Parameters such as the CFI, TLI, RMSEA, SRMR can be used to assess model fit as in the autoregressive cross-lagged models, however AIC and BIC are additionally used. A higher AIC of 10 or more can be considered a significantly worse model fit [561].

Table 6.4 Model fit parameters for dual change score model between balance ability and verbal memory from age 53 to 69

Model fit parameter	**Model 1: Freely estimated**	**Model 2: No coupling**	**Model 3: VM—> Bal only**	**Model 4: Bal→ VM only**
CFI	0.989	0.957	0.988	0.958
TLI	0.968	0.929	0.974	0.911
RMSEA	0.046	0.069	0.041	0.077
SRMR	0.032	0.084	0.032	0.084
AIC	-3727.874	-3679.759	-3727.978	-3679.559
BIC	-3609.007	-3585.504	-3619.917	-3571.498

complete cases only (n=1641)

Based all on model fit parameters, the freely estimated model (Model 1) and unidirectional verbal memory to balance model (Model 3) demonstrated very similar fits. These two models also had the best model fit as demonstrated by the highest CFI and TLI and the lowest RMSEA, SRMR, AIC and BIC parameters. That there was no difference in fit when the model was restricted (Model 3) suggests a unidirectional association between verbal memory and subsequent balance ability persists even when freely estimated (Model 1),

This was further confirmed by the results of Model 2 and 4. Here, the no coupling model (Model 2) and unidirectional balance to verbal memory model (Model 4) had similar model fits. Notably, AIC scores of the freely estimated and unidirectional (VM→ balance) model (Model 1: -3727.874, Model 3: -3727.978) were nearly 50 lower than Model 2 (-3679.759) and 4 (-3679.559) [561]. As these models were a significantly worse fit than Models 1 and 3, this suggests that there is little evidence of an association between a unidirectional model of balance to verbal memory.

6.4 Discussion

6.4.1 Main findings

In the autoregressive cross-lagged models, there was evidence of a unidirectional association between verbal memory and subsequent balance but no evidence of the reverse association. This unidirectional association was present at all ages, but the effect size weakened over time. Search speed at age 43 was associated with subsequent balance at age 53 in men and women. There were no associations at older ages in women, while there was weak evidence of a bidirectional association between search speed and balance ability between ages 60-64 and 69 in men.

Due to convergence challenges, only a restricted complete cases DCSM for verbal memory and balance ability could be estimated. The unidirectional model of verbal memory to subsequent balance and the freely estimated model demonstrated the best model fit. This is consistent with the findings of the autoregressive cross-lagged model, suggesting that there is primarily a unidirectional association between verbal memory and subsequent balance ability.

6.4.2 Comparisons to other studies

Due to the limited existing evidence on bidirectional associations, few comparisons can be made. As Finkel et al. [522] also used dual change score models to examine bidirectional associations between several domains of cognition and balance, comparisons are possible. Finkel reported that there was no longitudinal coupling between balance and memory [522]; thus, the results presented above are the first to suggest that there is a unidirectional association between memory and subsequent balance ability. Finkel also reported that balance was unidirectionally associated with subsequent processing speed [522]. This finding also contradicts the chapter results, which primarily showed a unidirectional association between search speed and subsequent balance at ages 43 and 53 and at ages 60-64 and 69. There was also weak evidence that this association may be bidirectional between ages 60-64 and 69 with an, albeit weaker, reverse association between balance ability and subsequent search speed.

Age, country or measurement differences may partially explain the conflicting findings. Using NSHD data, this chapter examined repeated bidirectional balance-cognitive associations between ages 43 and 69, whereas the other three studies examined an older sample: age 65 [434,522] or 75 at baseline [534]. Within NSHD, the association changed from age 43 to 69, with a smaller effect size at older ages for verbal memory and the emergence of a dynamic pattern of association for search speed. The association appears to be very age-dependent and further evidence is required to investigate if these associations change across different periods of life. Differences may also be a result of country (U.S.A, Sweden, Japan) or cohort effects, where longevity and patterns of cognitive and physical capability in ageing may differ [562,563]. Only one study assessed balance ability using the one-legged stand [534]; Finkel created a balance factor from ten motor tasks [522], while Tolea et al. [434] used an aggregate measure of gait and balance. These methods likely failed to capture an isolated measure of balance due to the contribution of several gait and mobility components.

6.4.3 Explanation of findings

Evidence for a unidirectional association from cognitive ability to subsequent balance ability has been explored in detail in previous chapters. To recap, cognitive integration of sensory input and motor output is crucial in order to main postural equilibrium and to maintain stability when standing on one leg [509]. Individuals with higher cognitive ability are thought to have increased neural activity, particularly in the prefrontal cortex and brain stem [512,513].

6.4.3.1 Verbal memory

The evidence on verbal memory shown in this chapter is consistent with a proposed role of cognition in maintaining balance. Working memory is associated with greater white matter volume [564,565], increased hippocampal activity [566] and sustained activation in the prefrontal cortex [567]. In turn, neural activity in these areas is thought to be directly related in balance ability. Previous evidence examining memory and balance does not directly differentiate between the role of working memory in balance ability and their shared dependence on the functionality of common neural structures. Working memory operates when information has to be retained and manipulated over a short period of time [568]. Whilst dynamic balance ability, such as known environmental hazards or unintentional postural disturbances, may rely on working memory, it is unclear if passive ability, as measured in the one-legged stand test, relies on a more automated process to maintain stability. That balance ability was not associated with subsequent verbal memory suggests that there is not simply a correlation between neural structure or function, but that components of memory may directly contribute to balance ability.

6.4.3.2 Search speed

Following the proposed cognitive processing mechanism involved in balance, it follows that search speed would have a similar pattern of association with balance. While there is a unidirectional association between search speed and subsequent balance, this is only present between ages 43 and 53. Identifying the neural structures associated with search speed is considerably more complex. Search speed tasks are thought to measure speed of processing, which is considered as an underlying domain of cognition that has an impact on the efficiency of all other cognitive operations [471].

Between ages 60-64 and 69, there was a bidirectional association between search speed and balance ability in men only. These results must be interpreted cautiously as the effect sizes were very similar between men and women ($p>0.25$; see Table 6.2) although reached statistical significance in men ($p<0.01$, $p=0.03$) and not women ($p=0.12$, $p=0.10$). While this suggests that pathways may be similar in men and women, there are a few reasons why the association between processing speed and balance may be slightly stronger in men. For example, the emergence of the search speed to subsequent balance pathway in men between ages 60-64 and 69 could indicate that their balance ability relies to a small extent on their processing speed. As visual and musculoskeletal systems begin to deteriorate with increased age, it is possible that men may experience increased reliance on their speed of processing. Earlier in this chapter (section 6.1.1), it was proposed that social engagement and support may play an intermediate role in the association between balance ability and cognitive functioning. Evidence from the English Longitudinal Study of Ageing suggests that older men are more socially isolated than older woman [569] and have significantly less contact with their family and friends. Low balance ability in men may increase their activity restriction, further exacerbating their low levels of engagement, which in turn is known to impact cognitive processing [529].

6.4.4 Strengths and limitations

There are several strengths of this chapter. It is one of few studies to directly examine and compare the directions of the associations between cognition and balance. This chapter utilises 25 years of follow-up of several different cognitive domains and 15 years of follow-up of balance data. Studies that have previously examined the association are limited in their analytical methodology and have tended to utilise either latent (based on several observed variables) or aggregate measures of balance or cognition. This is the first study to examine the directionality in associations between cognitive and balance abilities in an age homogenous sample in midlife, thus identifying changes with age without any age confounding.

Analyses are limited by the number of waves of data collection. The balance ability trajectory could only be modelled linearly due to having only three time points. All models assumed that there was one single trajectory across 25 years; utilising data that has more waves of follow-up could allow models to be estimated that consider piecewise trajectories that could reflect changes in balance mechanisms with age. One limitation of this chapter is that there were only three measures of balance, whereas there were four for each cognitive measure. A sensitivity analysis of the autoregressive cross-lagged model utilised only three measures of cognition (ages 53, 60-64, 69) and revealed similar patterns of association. The estimate from cognition at age 43 to balance at age 53 is slightly larger than that of any other cross-lagged pathway; this is because the variance in balance at age 53 explained by balance ability at age 43 could not be included in the model.

6.5 Conclusions and further research

This chapter provided evidence of a unidirectional association between verbal memory and subsequent balance and showed no evidence of association in the opposite direction. The association between search speed and balance was unidirectional between ages 43 and 53, with evidence of a bidirectional association at later ages. Due to the shortage of evidence on this topic, further investigation of these relationships and replication of findings is required before any clinical implications can be considered. Future research could examine trajectories in an extended follow-up (e.g. in older ages) over a longer across a wider range of cognitive domains. Although associations generally appear to decrease with age, a bidirectional association emerged for search speed at older ages. Taken with the higher levels of activity restriction and social isolation at older ages [233,527-529] as well as evidence from Finkel et al. [522] of an association between balance and subsequent processing speed in an older sample (up to age 80), it is worth investigating if balance plays a role in future cognitive ability. Cross-country analysis could examine if there are differences in patterns of associations as suggested by the heterogeneity of findings across country. Many current observational cohort studies in Sweden, the United States of America (USA) and several European countries have collected data on balance ability and several cognitive domains across numerous waves; secondary analysis of this data could be valuable in contributing to the current evidence on the topic.

The association between verbal memory and subsequent balance ability may have implications for ongoing interventions aimed to improve balance ability and decrease falls risk. These interventions tend to be limited to physical training programmes such as flexibility, balance or resistance training [570,571]. Few interventions have included a cognitive component, although there is some evidence to suggest that dual or multi-task training (that combines cognitive and physical training) can improve balance ability and reduce falls risk [572,573]. It is important to assess if the cognitive component has an additive benefit, beyond physical training, in improving the neural pathways involved in balance – thus improving overall balance ability.

CHAPTER 7: BALANCE ABILITY AS A RISK FACTOR FOR FALLS

Previous chapters of this thesis have investigated how factors across life are associated with balance ability. This final analytical chapter examines how balance ability is associated with falls in mid and later life. Balance ability plays an important role in falls due to postural instability and the inability to maintain one's centre of gravity after unexpected movement [574,575]. As this introduction section explores, associations between balance and falls have been examined almost exclusively in individuals aged ≥65. By utilising NSHD data from ages 43 to 69, this chapter investigates if the association between balance and falls emerges earlier in life and if balance testing can accurately screen for falls risk in younger adults. In this introduction section, the rising concern of falls in the ageing population (section 7.1.1) and key risk factors (section 7.1.2 and 7.1.3) are described, evidence on balance ability as a risk factor for falls is examined (section 7.1.4) and the limitations of this literature are highlighted (section 7.1.5). Finally, the specific chapter objectives and hypotheses are outlined (section 7.1.6).

7.1 Introduction

7.1.1 Falls in older adults: an increasing problem

Used to guide the most recent falls data collection in NSHD, the Prevention of Falls Network Europe (ProFaNE) guidelines define falls as “an unexpected event in which the participants come to rest on the ground, floor, or lower level” [576,577]. The WHO estimates that, globally, a third of individuals aged ≥65 and half of individuals aged ≥80 fall every year [577,578]. This high prevalence of falls is a severe burden at both the individual (e.g. individuals, families) and population level (e.g. healthcare system). Estimates of the proportion of falls that require medical attention are not established, ranging from 5% to 20% [579,580], with the WHO estimating that, globally, 37.3 million falls necessitate medical care. A WHO report estimated that falls contribute to more than 40% of admissions to nursing homes across Europe [578]. Likewise, UK data suggests that more than 10% of ambulance calls to adults aged ≥ 65 are for falls and more than half of these individuals are subsequently conveyed to the hospital [581]. Falls are estimated to cost the National Health System (NHS) more than two billion pounds and four million bed days every year, with numbers continuing to rise [582,583]. Fall-related injuries often restrict mobility, decrease independence and can increase risk of premature death [579,584]. Global data from the WHO suggest that falls are the leading cause of injury-related death in adults aged ≥65 [577,585-590].

Fall prevalence in both clinical and research settings is underestimated. For example, clinical records may underestimate injurious fall incidence rates as they include falls that have been reported to a medical professional. Both USA and UK community-based interviews of individuals aged ≥65 suggest that 75-80% of falls go unreported to an individual’s primary care provider [591,592]. Similarly, cohort data that relies on self-report can underestimate injurious falls recall due to subjective differences in what constitutes an injury or even a fall.

Analysis of secular trends show that prevalence of fall-related injuries [590,593], hospitalisation [593-596] and mortality [597-599] has gradually increased over time. These increases in fall-related injuries and hospitalisation persist in age-adjusted analyses, suggesting that fall prevalence is increasing at a faster rate than can be attributed to population ageing [578,590,593-596]. Reasons for this increase over time may differ amongst age groups. For example, current older adults are more likely to engage in activities that may be higher risk for falls [593]. In contrast, adults aged ≥80 may be at higher risk of falling compared with previous cohorts due to increased polypharmacy, decreased mobility and increased comorbidities [253,593].

7.1.2 Risk factors for falls

Identifying individuals at highest risk of falling is important in order to determine appropriateness and maximise effectiveness of interventions. Falls have many distinct risk factors that often co-occur in individuals [600]. Risk factors for falls can broadly be classified into intrinsic and extrinsic risk factors, although falls commonly result from a combination of the two. Extrinsic factors account for approximately a quarter of all falls [601,602]. These include inappropriately fitting footwear or clothing, unsuitable walking aids or environmental hazards such as pets, objects and slippery or uneven surfaces [578]. Interventions targeting extrinsic risk factors occur at both the individual and population level. For example, the NHS offers a Falls Risk Assessment Tool, which includes a home visit, to identify avoidable hazards (e.g. loose rugs, need for railings) for individuals at high risk of falling [603]. On a larger scale, the WHO has developed the concept of 'age-friendly environments' to refer to environments that "enable and encourage people to age well according to their needs, desires and capacities" [604]. Age-friendly changes can minimise common environmental hazards that contribute to falls risk; examples include smooth, non-slip pavements with dropped curbs, shallower steps with railings or clearer signage identifying hazards [604,605].

Intrinsic factors are considered to contribute to 70-80% of falls [601,602]. History of previous falls is the strongest and most reliable predictor of falls in adults aged ≥ 65, followed by impaired gait or balance ability [600]. When identifying those at risk of falling for the first time, gait or balance abnormalities appear to be most reliable as a screening criterion [600]. As previously noted, gait and balance ability are highly related and deficits in one area often co-occur with deficits in the other [329,606]. For example, it is common for older adults to reduce their gait speed as a compensatory mechanism to maintain their balance [607]; similarly, older adults who walk too quickly sometimes do so at the expense of their balance. Other well-established intrinsic factors include age, sex, muscular strength, cognitive impairment, sedentary behaviour and depression [578,600,608,609]. Age-related morbidities and physiological changes can contribute to increased risk of falling as decreased sensory input and weakened motor output can increase falls risk via decreased balance ability [610].

Given the number and complexities of falls risk factors, a multidisciplinary assessment is likely to best predict those at risk for falls [578,611]. Due to limitations in time and cost, a parsimonious screening process would have advantages [611]. For example, a jointly developed guideline between the American Geriatrics Society and the British Geriatrics Society suggests that the initial screening stage should only include a question about falls history along with an objective assessment (e.g. time up and go test or visible gait or balance abnormalities) [260]. This recommendation is supported by a review of the accuracy of screening tools for predicting falls risk in community dwelling older adults [612], which reported that history of falls along with gait or balance abnormalities are consistently the best predictors for future falls and that there is no additional value in a complex multidisciplinary screening [612]. Studies that have tested the accuracy of the guideline's algorithms reported high specificity and low sensitivity [613,614]. Low sensitivity may be because individuals with no history of falling are automatically considered to not be at risk of falling. Thus, using history of falls to screen for future falls can be problematic when trying to identify those at risk of first-time falls; a performance-based measure such as balance ability may be useful to help identify fall risk in those with no fall history. Section 7.1.4 explores the existing evidence on the associations between balance ability and falls in substantial detail.

7.1.3 Using predictive or explanatory modelling for risk factors

The WHO defines a risk factor as “any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury” [615]. This term can be applied to two distinct concepts: 1) predictive modelling and 2) explanatory modelling. Predictive modelling, often referred to as risk prediction or screening, utilises prognostic models to identify individuals at risk of a poor health outcome [616-618]. Explanatory models aim to understand the underlying aetiology of poor health outcomes, and specifically identify factors on the causal pathway [616-618].

Predictive and explanatory modelling often have substantially different interpretations and implications. The aim of prediction models is to ‘predict’ the outcome [617] and results often inform screening practices. In contrast, the aim of exploratory modelling is to identify appropriate targets for intervention by understanding the causal pathway [616,617]. In many cases, a risk factor acts as both a predictor and a causal explanatory factor. High blood pressure, for example, is both a predictor and a cause of cardiovascular disease [616]. Poor balance ability could be considered in the same way as it is known to be a direct cause of falls but has also been used as a tool to identify those at increased risk of falling. That balance ability is relevant in both risk prediction (as an approach to screening) and aetiological research (by identifying a plausible intervention point) indicates multiple ways in which its consideration may have an impact on falls management.

These two concepts often utilise similar methods – such as logistic regression analysis [617] –, however predictive modelling can further evaluate the discriminatory ability of the screening tool by calculating the sensitivity (number of 'true positives'), specificity (number of 'true negatives') and resulting receiver operating characteristic (ROC) curves [619]. ROC curves plot the true positive rate (sensitivity) against the false positive rate (1- specificity) at multiple cut-off points of the risk factor. The area under the curve (AUC) provides a number from 0 to 1 and indicates the ability of a tool or model to distinguish between two groups [620]. An AUC of 1 means that the screening tool (e.g. balance test) is 100% accurate in differentiating between those with and without the outcome (e.g. fall), while an AUC of 0.5 suggests that the tool has a 50% chance of correct discrimination. An AUC greater than 0.9 is considered excellent, greater than 0.8 to 0.9 very good, 0.7 to 0.8 good, 0.6 to 0.7 average, <0.6 poor and ~0.5 indicating no discriminatory ability [621]. The coefficient of determination, the R^2 value yielded from regression output, is also commonly used in predictive modelling and indicates what percent of variation in the outcome variable (e.g. falls) is explained by the independent variable (e.g. balance) [622].

7.1.4 Evidence of association between balance and falls

In this section, evidence of both explanatory and predictive associations between balance ability and falls is described. Although the section does not examine evidence from intervention studies, there is strong evidence from meta-analyses that balance and functional training interventions can minimise falls risk in community-dwelling older adults [278,279,281]. The implications of this are discussed further in section 7.4 and in Chapter 8.

7.1.4.1 Reviews of various balance measures and falls risk

Associations between balance performance and falls risk have been widely investigated. Despite the general consensus that balance ability is a strong predictor of falls, many systematic reviews have advised caution when utilising specific balance scales [623-626]. Synthesis and meta-analysis of evidence on balance and falls can be difficult due to different assessment of balance measures (as outlined in Chapter 1, section 1.2). However, four systematic reviews separately summarised the ability of specific balance/mobility scales – the Berg Balance Scale [623], Functional Reach Test [624], Timed Up and Go (TUG) [625] and Four-Square Step Test [626] – to predict subsequent falls in older adults. All four reviews [623-626] concluded that there was insufficient evidence to support any tool as a reliable predictor of falls. These reviews had broad inclusion criteria as three reviews included older adults from any setting [623,624,626], while the fourth did not have any age restrictions [625]. Further details of the reviews are provided in Table 7.1

Three additional systematic reviews compared the utility of various balance ability measures in predicting prospective falls in community dwelling samples. Similar to the four reviews of specific tests, studies used heterogeneous analytical methods or samples and did not identify any single tool that could accurately predict falls [612]. Two of the reviews identified performance-based measures such as the TUG, five times sit-to-stand, walking speed and standing balance, that may have clinical utility if considered together [627,628]. With no clear consensus, the results of these reviews confirm that there is currently no agreed gold standard tool to predict falls risk.

Table 7.1 summarises the findings of these seven reviews. Notably, alongside diverse conclusions, there was substantial heterogeneity of analytical strategies. Examples of analyses in the reviews included regression models, t-tests for comparison of means, correlations, pre-test/post-test probabilities, calculations of sensitivity and specificity and ROC curves [623,624,626]. Some of the latter methods are appropriate for assessing prognostic accuracy, while others simply describe associations between balance and falls. Only two reviews selected studies based

Table 7.1 Summary of systematic reviews on balance instruments and their ability to predict falls

Author	Measure	Sample inclusion criteria	Number of studies	Analyses	Conclusion
Lima et al. 2018 [623]	Berg Balance Scale	Any setting (≥60 years)	8	- Logistic regression - Comparison of means - Correlations - Tests of sensitivity and specificity	*"Evidence to support the use of BBS to predict falls is insufficient, and should not be used alone to determine the risk of falling in older adults."*
Rosa et al. 2019 [624]	Functional Reach	Any setting (≥60 years)	21	- Meta-analysis (n=5) of comparison of means	*"Functional Reach Test should not be used to predict risk of falls on older adults."*
Barry et al. 2014 [625]	Timed Up and Go	Community dwelling older adults (no age)	25	- Meta-analysis (n=10) of sensitivity and specificity using 13.5s cut-off - Meta-analysis (n=10) of logistic regression	*"TUG has limited ability to predict falls in community dwelling elderly and should not be used in isolation to identify individuals at high risk of falls in this setting."*
Moore & Barker, 2017 [626]	Four Square Step Test	Adult populations (≥18)	15	- Tests of sensitivity and specificity using different cut-points in each study (range 9.68 to 15 seconds)	*"Clinicians using the FSST to identify falls risk should do so in conjunction with other multi-factorial fall risk screens."*
Gates et al. 2008 [612]	29 different screening tools	Community dwelling or independent older adults (no age)	25	- Tests of sensitivity and specificity - Positive/negative predictive values	*"Most tools discriminated poorly between fallers and non-fallers… Insufficient evidence exists that any screening instrument is adequate for predicting falls"*
Lusardi et al. 2017 [627]	46 different screening tools	Community-dwelling older adults (≥65 years)	59	- Meta-analysis (n=21) using post-test, pre-test probabilities	*"No single test/measure demonstrated strong PoTP [post-test probability] values … 5 performance-based measures may have clinical usefulness in assessing risk of falling on the basis of cumulative PoTP."*
Power et al. 2014 [628]	25 different screening tools	Community-dwelling older adults (≥60 years)	37	- Logistic regression - Comparison of means - Tests of sensitivity and specificity	*"Strong evidence in favour of using the Timed Up-and-Go test, Five Times Sit-to-Stand test and assessments of gait speed to predict falls … was found, along with weaker evidence for tests of standing balance and reaching task performance."*

Only two reviews selected studies based on both an age cut-off and a community-dwelling sample [627,628]; the remaining reviews either had no age specification or no setting restrictions. Heterogeneity in population sampling and analytic strategies could partially explain inconsistencies in findings.

7.4.1.2 Standing balance and falls risk

No systematic review has examined associations between the one-legged balance test and falls risk, thus individual studies are summarised in this section. A small scoping review was performed by searching several databases using the following search strategy: (“standing balance” OR “one*legged balance” OR “one*legged stand” OR “flamingo stand” OR “OLS”) AND (“fall*”). Reference lists of relevant papers were also searched. Sixteen studies were found; full characteristics, measurement of balance and falls, analytic methodology and study findings are summarised in Table 7.2.

Seven studies reported an association between lower balance time and higher risk of falling [253,485,629-633], while four studies did not find evidence of an association [129,274,634]. The remaining five studies found that there were no associations between absolute balance time and falls risk but reported associations with some aspects of one-legged balance [32,273,635-637]. For example, raising arms during the balance test [32] or higher postural sway measured with a force plate [635] indicated higher falls risk. Two further studies found that balance ability was associated with injurious falls but not any fall [636,637], while Mulasso et al. reported an association between balance and falls at baseline that was no longer present at a 12-month follow-up [273].

Studies were primarily based in the USA (n=5) and Europe (France=2, Italy=1, Denmark=1) with three studies in Asia (Taiwan=1, China=1, Japan=1), two in Brazil and one in each of Canada and Australia. The mean age ranged from 66 to 83, with all studies except for one [631] examining a sample aged ≥60. Ten studies examined prospective fall outcomes; seven studies had a twelve-month follow-up, two studies had a three-year follow-up and one study reported associations at both baseline and 12-month follow-up. The remaining six studies employed a cross-sectional design and examined associations between one-legged balance and fall history in the previous twelve months.

Notably, every study utilised the eyes open one-legged stance, with only two studies examining both eyes open and eyes closed conditions [129]. The maximum duration of the one-legged stance differed amongst studies and included 5, 10, 30, 45 and 60 seconds, with four studies not reporting the time [253,274,633,638]. Studies utilised either continuous balance time (n=11) or categorised balance ability into those able to maintain the position for ≥5 seconds vs those who could not (n=4). One study created a points system based on the ability to maintain both eyes open and eyes closed position for more than 10 seconds [485]. Although a five second cut-off has commonly been utilised to identify those with balance impairment, one study excluded individuals who could not maintain the position for at least five seconds [635], which biases the sample by excluding those with the worst balance performance and further limits comparability.

As with the systematic reviews above, the statistical analyses (as chosen by the authors) differed significantly. Most studies used analytical techniques to examine the association between balance and falls, rather than predictive modelling tools to assess the prognostic accuracy of the balance test. For example, regression analyses (logistic or Cox regression) were utilised in ten studies, as were t-tests or chi square tests to compare means. Only two studies examined the sensitivity/specificity of distinct cut-points (5 seconds, 30 seconds) [32,631], two studies utilised ROC curves [274,632] and one study examined the percent of variance explained [273].

Table 7.2 Characteristics of studies examining association between one-legged stand test and falls

	Author	Sample characteristics	Details of one-legged stand test	Follow-up	Analyses	Findings
ASSOCIATION FOUND						
1	Cho et al. [629]	- Adults recruited for a fall-reduction program - n= 167, USA - mean age: 78 ± 7	- Eyes open, max 30 sec - Continuous score	- Cross-sectional - Reported fall in previous 12 months	- Logistic regression	↓ balance time = ↑ risk of falling
2	Delbaere et al. [630]	- Community dwelling - n= 1037, Australia - mean age: 77.9	- Eyes open, max 10 sec - Continuous score	- 12-month follow-up - Monthly fall diaries	- Classification and regression tree analysis	↓ balance time = ↑ risk of falling
3	Hurvitz et al. [631]	- Patients from electro-neuromyography lab - n=53, USA - mean age: 65.7±8.5	- Eyes open, max 45 sec - Categorised <30sec vs ≥30 sec	- Cross-sectional - Reported fall in previous 12 months	- Logistic regression - Tests of sensitivity and specificity (30 sec cut-off)	↓ balance time = ↑ risk of falling
4	Laesso et al. [485]	- Community dwelling - n= 101, Denmark - mean age: 73.7 ± 2.9	- Eyes open and closed, max 10 sec - Point system 0-6 • EC >10sec= 6pts • EC <10sec =5.5 pts • EO >10sec only=5 pts • EO<10sec only=4pts	- 12-month follow-up - Received phone call every six months	- Comparison of mean points	fallers = ↓ balance time
5	Moreira et al. [632]	- Community dwelling - n= 773, Brazil - mean age: 71.9 ±5.9	- Eyes open, max 60 sec - Continuous mean score across 3 trials	- Cross-sectional - Reported fall in previous 12 months	- Comparison of means - Logistic regression - AUC	- ↓ balance time = ↑ risk of falling - AUC: 0.55 (0.49-0.60), 0.62 (0.55-0.68)
6	Tinetti et al. [253]	- Community dwelling - n=336, USA - mean age: 78.3 ±5.1	- Eyes open, time not given - Categorised <5 vs ≥5sec	- 12-month follow-up - Received phone call every two months	- Logistic regression	↓ balance time = ↑ risk of falling
7	Yamada et al. [633]	- Community dwelling - n= 780, Japan - mean age: 76.0 ± 7.4	- Eyes open, time not given - Continuous score	- Cross-sectional - Reported fall in previous 12 months	- Comparison of means	fallers = ↓ balance time

	Author	Sample characteristics	Details of one-legged stand test	Follow-up	Analyses	Findings
ASSOCIATION FOUND FOR SOME ASPECTS						
8	Beauchet et al.[32]	- Community dwelling - n= 1759, France - mean age: 70.7 ±4.6	- Eyes open, max 5 sec - Categorised <5sec, ≥5 sec - Categorised raised arms vs no movement	- 12-month follow-up - Received phone call every month	- Kaplan-Meier log-rank test - Cox regression model - Tests of sensitivity / specificity (5 sec cut-off)	- No association between balance and risk of falling - Raised arms = ↑ risk of falling
9	Maki et al.[228]	- Independent old age residence - n= 100, Canada - mean age: 83 ± 6	- Eyes open, max 30 sec - Best score across 3 trials	- 12-month follow-up - Filled out postcard every week	- Comparison of means	- No association between balance and risk of falling - ↑ postural sway =↑ risk of injurious fall
10	Mulasso et al.[273]	- Community dwelling - n= 192, Italy - mean age: 73.0 ±6.2	- Eyes open, max 60 sec - Continuous score	- 12-month follow-up - Associations assessed at baseline and follow-up	- Comparison of means - Logistic regression - Percent of variance explained	- No association between balance and risk of falling - ↓ balance time = ↑ risk of falling at baseline
11	Oliveira et al.[635]	- Community dwelling - n= 170 - Brazil - mean age: 67	- Eyes open, max 30 sec - Continuous mean score across 3 trials - Excluded if time <5 sec - Postural sway: force plate	- Cross-sectional - Reported fall in previous 12 months	- Comparison of means	- No association between balance and risk of falling - Fallers = ↑ postural sway
12	Vellas et al.[637]	- Community dwelling - n=316, USA - mean age: 72.7±6.1	- Eyes open, max 5 sec - Categorised <5sec vs ≥5 sec	- Three-year follow-up - Subjects called coordinator every fall and were sent reminder every 2 months	- Logistic regression	- No association between balance and risk of falling - ↓ balance time = ↑ risk of injurious fall

	Author	Sample characteristics	Details of one-legged stand test	Follow-up	Analyses	Findings
NO ASSOCIATION FOUND						
13	Briggs et al. [129]	- Community dwelling - n= 71, USA - mean age: 72.3 ± 7.0	- Eyes open and eyes closed trials, max 30 sec - Continuous best score across 3 trials	- Cross-sectional - Reported fall in previous 12 months	- Comparison of means	No association between balance and risk of falling
14	Buatois et al. [634]	- Community dwelling - n= 1618, France - mean age: 70.3 ±4.5	- Eyes open, 5 sec - Categorised <5sec vs ≥5 sec	- 18-36-month follow-up	- Comparison of means - Logistic regression	Difference in mean balance No association between balance and risk of falling
15	Lin et al. [274]	- Community dwelling - n=1200, Taiwan - mean age: 73.4	- Eyes open, time not specified	- 12-month follow-up - Subjects called coordinator every fall and were sent a reminder every 3 months	- Comparison of means - Logistic regression - AUC	Difference in mean balance No association between balance and risk of falling AUC: 0.64 (no 95% CI)
16	Yamada & Ichihashi [638]	- Community dwelling - n=171, China - mean age: 80.5±5.6	- Eyes open, time not specified - Continuous score	- 12-month follow-up - Received phone call every month	- Comparison of means - Logistic regression	Difference in mean balance No association between balance and risk of falling

7.1.5 Limitations of previous studies

There are several limitations of the studies above. First, there are large differences amongst test protocols which may partially explain inconsistent findings. It is important to be cautious when comparing evidence that has different limits on balance times (e.g. 10 second maximum vs 60 second maximum). Second, six studies examined ‘cross-sectional’ associations between balance ability and history of falls within the last 12 months. By considering falls that occurred prior to balance assessment, these study results contribute neither to risk prediction nor to potential understanding of a causal association. Analyses must ensure that temporality of balance and falls data are consistent with the question being investigated.

Third, although most studies claimed to examine the utility of balance as a screening tool for falls, the majority of these studies utilised mean comparison or regression modelling rather than appropriate predictive modelling. As discussion in section 7.1.3, these techniques address explanatory associations, and do not assess the predictive accuracy of balance. There is a common narrative that balance ability is a validated tool to assess falls risk, however the studies above provide limited evidence of an association between balance ability and falls, with weak evidence overall to support it as a screening tool. With 10 of the 16 studies having a sample size <500, it is possible that the weak associations are due to a lack of power.

Fourth, twelve of the thirteen studies examined samples aged ≥60, with only one study examining a sample aged ≥50 (mean=65.7) [631]. This confirms that there is no evidence examining whether balance screening in a middle-aged sample can predict falls risk, despite recent calls for earlier fall prevention [639]. Fifth, while some studies adjusted for sex in their analyses, no studies examined how these associations may differ amongst men and women. There is consistent evidence that men have better mean balance ability than women (as shown in Chapters 2 and 3) and that women are more likely to fall [138,139]. Analyses should reflect this and investigate if there is a sex interaction in this association. Finally, only one study examined the association between eyes closed balance and falls risk [129]. As previously indicated, a major limitation of the eyes open is a ceiling effect, particularly in a middle-aged sample. As the studies summarised above targeted older samples, it is possible that the eyes open test was preferred for safety reasons as well as to avoid a possible floor effect of the eyes closed at older ages. When examining a younger sample, the eyes closed test may be most appropriate.

In summary, although balance ability is considered to be an important component of falls risk, systematic reviews have not provided evidence of an appropriate balance tool than can capture falls risk. This is also true for the one-legged stand test, where the existing literature has focused primarily on adults aged ≥ 65, with dissimilar assessment of falls and application of balance test protocols. Studies seldomly used appropriate analytical models to assess the accuracy of the one-legged stand as a reliable prognostic test for falls risk. Data from NSHD allows both explanatory (e.g. regression modelling) and predictive (e.g. AUC from ROC curves) models to be appropriately investigated in midlife. By using continuous balance times and considering those unable to complete the task due to health reasons, balance performance information can be maximised. Both cross-sectional and longitudinal associations throughout midlife can be assessed to better understand how this association changes with age.

7.1.6 Objectives and hypotheses

This chapter aims to address the limitations of previous research outlined above and the lack of evidence on balance and falls in middle aged adults to:

i) describe the prevalence and characteristics of falls (fall within last 12 months, number of falls, injurious vs non-injurious falls) from age 43 to 68;
ii) examine associations of eyes-closed standing balance at age 53 and 60-64 with fall outcomes at ages 53, 60-64 and 68;
iii) utilise ROC curves to examine prognostic accuracy of the eyes-closed standing balance test in predicting falls.

Fall prevalence is expected to increase with age. It is hypothesised that balance ability will be associated with falls at all ages, with stronger patterns of association for recurrent falls. Finally, it is expected that balance ability will have mixed accuracy in predicting falls; this is due to the inconsistent associations found in previous literature as well as to the inability of the one-legged stand to pick up sensitive changes in midlife. These hypotheses are discussed further in section 7.4.

7.2 Methods

7.2.1 Study sample

Individuals with a valid response on any of the falls measures (as described below) were included in the initial fall descriptive characteristics (n=3 563 participants). As only 1777 had valid falls data at all four ages (43, 53, 60-64 and 68), maximal and complete cases (with all covariate data) samples were used in each analysis and thus, the sample size differs and is reported throughout. Assessment of balance data was previously described in section 2.2.1 (Chapter 2).

7.2.2 Overview of fall data

All fall questions were self-reported by the study member during nurse visits at ages 43, 53 and 60-64 and in a postal questionnaire at age 68. Although questions varied slightly, at all ages individuals were asked if they had fallen in the last twelve months and how many times. Table 7.3 provides a summary of fall data collected across the four ages.

Table 7.3 Summary of falls questions collected at ages 43, 53, 60-64 and 68

	Age 43	Age 53	Age 60-64	Age 68
Falls (yes/no)	✔	✔	✔	✔
Number of falls	Categorical (0, 1-2, ≥3)	Categorical (0, 1-2, ≥3)	Continuous	Continuous
Injurious falls (yes/no)	✘	✘	✔	✔

At age 43, in a disability checklist based on the Office of Population Censuses and Surveys of Disability in Great Britain [640], study members were asked if they “have the following difficulties due to long-term health problems or disabilities: …. falling or difficulty keeping balance?” At age 53 and 60-64, study members were asked two questions: if they “easily fall or have difficulty keeping [their] balance because of long term health problems?” and subsequently if they had “fallen at all in the past 12 months?” Only the latter question was used to estimate fall prevalence. Based on specific guidance from falls experts and the ProFaNE guidelines [576], at age 68, individuals were asked “in the past 12 months [if they] had any fall including a slip or trip in which [they] lost [their] balance and landed on the floor or ground or lower level?” These questions were combined with the frequency questions below to provide a binary indicator of falls (yes, no) within the last year.

At all four ages, participants who responded yes were asked to select “how many times [they had] fallen in the past year”. There were four possible response categories at ages 43 and 53: 0, 1-2, 3-11, ≥12. Due to small sample size of those with ≥12 falls, they were grouped with those who reported 3-11 falls. At age 43, individuals were only asked this question if they reported difficulties with falling or keeping balance as described above. At ages 60-64 and 68, individuals were asked to report the exact number of falls. To enable comparison of prevalence across time and due to the skew of the data (range: 1- 121; median=0), number of falls at ages 60-64 and 68 were categorised as at ages 43 and 53. However, for all longitudinal analyses, falls at ages 60-64 and 68 were categorised as 0, 1 and ≥2 to examine associations between balance and both single and recurrent falls. At ages 60-64 and 68, individuals were asked “on how many of these occasions [they had] injured [them]self badly enough” to “see a doctor” (age 60-64) or “seek medical attention” (age 68)”?

There were some discrepancies between responses to the initial question about falling and the number of falls reported. At age 43, individuals who reported difficulty with falling or keeping balance but reported zero falls in the last year were coded as no falls (n=22). Individuals who reported difficulty with falling or balance but did not respond to the number of falls were coded as missing (n=6). Six and eight individuals, at age 60-64 and 68 respectively, reported having fallen but did not provide the number of falls; thus, there are slight differences in sample size in the descriptive characteristics. In summary (see Table 7.3), fall history within the last 12 months (yes/no) is available at ages 43, 53, 60-64 and 68. The number of falls within this time period was reported categorically at age 43 and 53 (0, 1-2, ≥3), while it was available continuously at age 60-64 and 68. Finally, prevalence of injurious and non-injurious falls is available at age 60-64 and 68 only. An individual was considered to have a history of falls if they had a fall at previous data collection waves (e.g. history of falls at age 68 if they reported a fall at age 43, 53 or 60-64).

7.2.3 Statistical analyses

Analyses are conducted in three parts: (1) falls descriptive characteristics; (2) regression models between balance ability and falls data; and (3) assessment of the prognostic accuracy of a one-legged balance test to predict falls using ROC curves. In part one, chi square tests and Bonferroni post hoc tests are utilised to assess differences in all fall outcomes between men and women and across time. Characteristics of fallers and non-fallers by each covariate are described and differences are assessed using t-tests, chi square tests and either Bonferroni or Dunn's post hoc tests.

In the second part, multinomial logistic regression models modelled associations between balance ability and fall outcomes. Evidence has shown that single fallers are more similar to non-fallers than they are to recurrent fallers [630,641,642]. To avoid misclassification by using a binary fall question (yes/no), only number of falls (0, 1-2, $\geq$3 at age 53; 0, 1, $\geq$2 at ages 60-64 and 68) as well as the type of fall (no fall, injurious fall, non-injurious fall) are examined. In multinomial regression models, independent (i.e. explanatory) variables are not assumed to be normally distributed and as such, the skew of balance as an explanatory variables is more widely accepted than the skew of an outcome [643,644]. As the balance ability residuals were not abnormally distributed, balance ability could used as a continuous untransformed variable to aid interpretability in this chapter.

The limitations of examining cross-sectional associations due to temporal order was discussed in section 7.1.5. Thus, longitudinal regression will be the primary analyses of interest. However, to enable comparison with the studies outlined in the introduction, cross-sectional associations at ages 53 and 60-64 are first tested in sex and fully-adjusted models and results are provided in the appendices. As balance data were collected at age 69 and falls data at age 69, cross-sectional associations at this age were not considered.

Subsequently, sex and fully-adjusted longitudinal associations of balance at age 53 with fall data at each of ages 60-64 and 68 and of balance at age 60-64 with fall data at age 68 are assessed. Sex and balance interactions are tested in all models and reported; where these are statistically significant ($p<0.05$), analyses are stratified by sex. Consistent with previous chapters in this thesis, full adjustment included the following covariates: death, attrition, height, weight, smoking history, physical activity, diabetes, knee pain, CVD events, respiratory symptoms, paternal social class, maternal education, own social class, own education and verbal memory. Associations between these covariates and balance were previously explored in Chapter 3.

In the third part, ROC curves are calculated to determine how well one-legged balance ability could predict number and type of falls. As there are three categories for each fall outcome, two separate ROC curves were calculated for binary variables (no falls vs one fall and no falls vs ≥2 falls; no falls vs non-injurious falls and no falls vs injurious falls). Equality of ROC curves are compared amongst several models [645]. First, a sex and balance model is compared to one with sex only. Second, the same sex and balance model is compared to a sex and fall history model as well as to a combined sex, balance and fall history model. These comparisons aim to determine whether balance or fall history is the best predictor of falls and if a combination of the two is an adequate screening tool as recommended by the American Geriatrics Society and British Geriatrics Society [260]. No covariates are considered in these models.

As in earlier chapters, individuals who were unable to attempt the balance test due to health reasons are imputed with a score of 0 seconds throughout the thesis, as they reasonably would have been expected to have low balance if they had tried to complete the test (see Chapter 2). Additional sensitivity analyses explored if inability due to health reasons is associated with fall prevalence and falls risk. Using a binary indicator (1=unable to complete the balance test due to health reasons; 0= participated in balance test), the three analyses components above are repeated.

7.3 Results

7.3.1 Fall prevalence

7.3.1.1 Descriptive data on falls

Between ages 43 and 68, the prevalence of any self-reported fall in men increased from 1.1% (at age 43) to 12.8% (at age 53), to 13.6% (at age 60-64), and to 17.8% (at age 69). In women, the prevalence increased from 1.4% to 21.9% to 22.7% to 25.7% (trend p<0.001 for both sexes; see Table 7.4). Bonferroni post-hoc tests revealed that there were significant increases in fall prevalence from age 43 to 53 and from age 60-64 to 68 (all $p<0.001$), with no difference between ages 53 and 60-64. Falls were more common in women than men at ages 53, 60-64 and 69 (all $p<0.001$), with an equally low prevalence at age 43 ($p=0.41$).

Individuals who had fallen were more likely to report falling 1-2 times in the last year than ≥3 times at ages 53, 60-64 and 68. Although women reported falling more often than men, there were no sex differences in prevalence of recurrent falls at ages 43, 60-64 or 68. However, men were more likely than women to experience multiple falls at age 53 ($p<0.005$; see Table 7.4). The exact number of falls experienced in the last year ranged from 1 to 121 at age 60-64 and from 1 to 42 at age 68, with three individuals reporting “more than [they] could remember”. High number of falls (such as 42 and 121) were extremely rare with 99% of individuals reporting ≤5 falls at these ages.

Only categorical number of falls was used in analyses due to the skew of these data. Prevalence of falls at age 60-64 and 68 categorised as 0, 1 and ≥2 (as utilised in longitudinal associations) are presented in Appendix 7.1 and are similar to Table 7.4. In men and women at ages 60-64 and 68, approximately a quarter of fallers experienced one or more fall that was severe enough to warrant medical attention. These frequencies were similar across time and between sexes (see Table 7.4).

Table 7.4 Prevalence of falls in last 12 months (yes/no), number of falls in last 12 months (1-2, ≥3) and injurious falls in last 12 months (yes/no) amongst men and women at ages 43, 53, 60-64 and 68

	Total n	Men	Women	Tests of sex difference (p-value)
Fall in last 12 months				
Age 43	3220	17/1615 (1.1%)	22/1583 (1.4%)	0.41
Age 53	2987	187/1280 (12.8%)	333/1520 (21.9%)	<0.001
Age 60-64	2226	144/1063 (13.6%)	264/1163 (22.7%)	<0.001
Age 68	2428	207/1163 (17.8%)	325/1265 (25.7%)	<0.001
Number of recurrent falls (amongst fallers)				
Age 43				
1-2 falls	39	8/17 (47.1%)	11/22 (50.0%)	0.86
≥3 falls		9/17 (52.9%)	11/22 (50.0%)	
Age 53				
1-2 falls	520	132/187 (70.6%)	271/333 (81.4%)	<0.005
≥3 falls		55/187 (29.4%)	62/333 (18.6%)	
Age 60-64 [a]				
1-2 falls	402	114/141 (80.9%)	207/261 (79.3%)	0.70
≥3 falls		27/141 (19.1%)	54/261 (20.7%)	
Age 68 [b]				
1-2 falls	524	153/203 (75.4%)	255/321 (79.4%)	0.45
≥3 falls		50/203 (24.6%)	66/321 (20.6%)	
Injurious fall in last 12 months (amongst fallers)				
Age 60-64				
Non-injurious falls	408	110/144 (76.4%)	190/264 (72.0%)	0.33
Injurious falls		34/144 (23.6%)	74/264 (28.0%)	
Age 68				
Non-injurious falls	532	163/207 (78.7%)	243/325 (74.8%)	0.29
Injurious falls		44/207 (21.3%)	82/325 (25.2%)	

[a] n=6 individuals could not recall # of falls at age 60-64; [b] n=8 individuals could not recall # of falls at age 69

7.3.1.2 Sensitivity analysis: fall prevalence by inability to complete balance test due to health reasons

Fall prevalence of those who completed the balance test was compared to those who could not due to health reasons. Individuals who could not complete the test had a substantially higher prevalence of falls at all ages than those with a valid balance time ($p<0.001$; Table 7.5), with nearly half of individuals reporting a fall. Amongst fallers, individuals who could not complete the test were also more likely to experience multiple falls at all ages (all $p<0.001$). There was no difference in the type of fall (injurious or non-injurious) (Table 7.5).

Table 7.5 Prevalence of falls in last 12 months (yes/no), number of falls in last 12 months (1-2, ≥3) and injurious falls in last 12 months (yes/no) by inability to complete balance test at ages 53, 60-64 and 68

	Total n	**Completed balance test**	**Inability to complete balance test**	**Tests of difference (p-value)**
Fall in last 12 months, n (%)				
Age 53	2896	457/2792 (16.4%)	44/104 (42.3%)	<0.001
Age 60-64	2188	352/2099 (13.6%)	46/89 (51.7%)	<0.001
Age 68	1933	384/1825 (21.0%)	45/108 (41.7%)	<0.001
Number of recurrent falls (amongst fallers), n (%)				
Age 53				
1-2 falls	501	375/457 (82.1%)	19/44 (43.2%)	<0.001
≥3 falls		82/457 (17.9%)	25/44 (56.8%)	
Age 60-64[a]				
1 fall	392	216/348 (62.1%)	9/44 (20.5%)	<0.001
≥2 falls		132/348 (37.9%)	35/44 (79.5%)	
Age 68[b]				
1 fall	424	221/381 (58.0%)	10/43 (23.3%)	<0.001
≥2 falls		160/381 (42.0%)	33/43 (76.7%)	
Injurious fall in last 12 months (amongst fallers), n (%)				
Age 60-64				
Non-injurious falls	398	264/352 (75.0%)	29/46 (63.0%)	0.08
Injurious falls		29/352 (25.0%)	17/46 (37.0%)	
Age 68				
Non-injurious falls	429	298/384 (77.6%)	34/45 (75.6%)	0.76
Injurious falls		86/384 (22.4%)	11/45 (24.4%)	

[a] *n=6 individuals could not recall number of falls at age 60-64*

[b] *n=5 individuals could not recall number of falls at age 69*

7.3.2 Associations between balance ability and falls

In the second stage of analysis, associations between balance ability and falls were investigated including: 1) descriptive characteristics of falls, 2) sex-adjusted and fully-adjusted cross-sectional and 3) longitudinal models and 4) a sensitivity analysis examining inability to complete the balance test and subsequent risk of falling.

7.3.2.1 Descriptive characteristics of individuals by fall status

In order to understand how adjustment for covariates may influence the association between balance ability and falls, descriptive characteristics of each covariate by fall category were first examined. Table 7.6 provides mean (SD) scores or frequencies (%) for non-fallers, individuals who fell once or twice and individuals who fell ≥3 times at age 53. Individuals who experienced either 1-2 falls or ≥3 falls at age 53 were shorter, had a higher BMI, did not participate in physical activity, were more likely to have poor physical and mental health and had lower verbal memory than those who reported no falls. There were no differences in childhood or adulthood SEP between fallers and non-fallers. Bonferroni post hoc tests suggested that there were minimal differences between non-fallers and those with 1-2 falls, with larger differences between those with 1-2 falls and those with ≥3 falls. Characteristics for non-fallers, single fallers and recurrent fallers at age 60-64 and 68 are comparable and are provided in Appendix 7.2 and 7.3. There was some evidence at ages 60-64 and 68 that fallers had lower educational attainment, while the association between falls and verbal memory weakened at later ages.

Table 7.6 Descriptive characteristics of analytical sample with balance and falls data at age 53

	Non-fallers (n=2395)	**1-2 falls** (n=394)	**≥3 falls** (n=107)	**p-value between groups**
BALANCE ABILITY, median (Q1, Q3)	5 (3, 8)	4 (3, 7)	3 (1, 5)	<0.001
ANTHROPOMETRY, mean (SD)				
Height (m)	1.68 (0.09)	1.66 (0.09)	1.67 (0.10)	<0.001
BMI (kg/m^2)	27.3 (4.6)	27.9 (5.3)	28.6 (6.5)	<0.005
SOCIOECONOMIC INDICATORS, n (%)				
Paternal occupational class				
I Professional/II Intermediate	608 (26.8)	94 (25.3)	27 (26.5)	0.65
III Skilled (non-manual or manual)	1067 (47.0)	190 (51.1)	51 (50.0)	
IV Partly skilled/V Unskilled	594 (26.2)	88 (23.6)	24 (23.5)	
Maternal education				
Secondary and further education	233 (11.0)	58 (16.2)	12 (12.4)	0.08
Secondary only	244 (11.5)	44 (12.3)	12 (12.4)	
Primary and further education	315 (14.9)	45 (12.5)	19 (19.6)	
Primary only	1327 (62.6)	212 (59.1)	54 (55.7)	
Highest household occupational class				
I Professional/II Intermediate	1050 (44.1)	162 (41.7)	41 (39.4)	0.46
III Skilled (non-manual or manual)	955 (40.1)	157 (40.4)	41 (39.4)	
IV Partly skilled/V Unskilled	374 (15.7)	70 (18.0)	22 (21.2)	
Educational attainment at age 26				
Degree or higher	229 (10.1)	35 (9.3)	7 (6.9)	0.50
GCE A level or Burnham B	587 (26.0)	91 (24.3)	26 (25.5)	
GCE O level or Burnham C	452 (20.0)	83 (22.1)	21 (20.6)	
Sub GCE	160 (7.1)	38 (10.1)	7 (6.9)	
None attempted	832 (36.8)	128 (34.1)	41 (40.2)	
BEHAVIOURAL RISK FACTORS, n (%)				
Leisure time physical activity				
None	1166 (48.7)	188 (47.7)	67 (62.2)	0.03
1-4 times/month	434 (18.1)	61 (15.5)	12 (11.2)	
≥5 times/month	794 (33.2)	145 (36.8)	28 (26.2)	
Smoking status				
Current	554 (23.1)	81 (20.6)	30 (28.0)	0.53
Previous smoker	1131 (47.2)	197 (50.0)	48 (44.9)	
Never smoker	710 (30.0)	116 (29.4)	29 (27.1)	
HEALTH STATUS				
History of diabetes, n (%)	57 (2.4)	20 (5.1)	6 (5.6)	<0.005
History of CVD events, n (%)	100 (4.2)	11 (2.9)	12 (11.8)	<0.001
Respiratory symptoms, n (%)	428 (17.9)	86 (21.9)	32 (29.9)	<0.005
Knee pain, n (%)	367 (15.5)	104 (26.6)	48 (46.2)	<0.001
Symptoms of anxiety/ depression, mean (SD)	16.6 (8.7)	20.0 (12.2)	24.5 (14.7)	<0.001
VERBAL MEMORY, mean (SD)	24.0 (6.2)	24.1 (6.5)	21.7 (6.9)	<0.005

Equivalent tables at ages 60-64 and 69 can be found in Appendices 7.2 and 7.3
Q1= quartile 1 (25th percentile); Q3= quartile 3 (75th percentile)

7.3.2.2 Cross-sectional associations between balance ability and falls

Estimates for all cross-sectional models between balance ability and falls are provided in Appendix 7.4 and are briefly described hereafter. Recall that cross-sectional associations should be interpreted with caution given the temporality of the balance and falls assessments, but are presented in appendices for reference with previous literature. The reference category for all models was no falls and estimates give the relative risk ratio (RRR) for every second of balance; a RRR <1 indicates that higher balance ability was associated with lower odds of falling.

At age 53, balance ability was associated with multiple falls (i.e. ≥3) in a sex-adjusted model but was fully attenuated after adjustment for covariates (see Model 1, Appendix 7.4). At age 60-64, balance ability was associated with risk of both a single fall and recurrent falls (i.e. ≥2) in a sex-adjusted model, but only the association with recurrent falls remained after adjustment (Model 2, Appendix 7.4). Finally, at age 60-64, balance ability was associated with both non-injurious and injurious falls in men and only non-injurious falls in women; estimates remained largely unchanged after adjustment (Model 3, Appendix 7.4). In all cases, attenuation was mainly explained by adjustment for physical indicators of health status (i.e. knee pain, diabetes, CVD history or respiratory symptoms).

7.3.2.3 Longitudinal associations between balance ability and falls

Longitudinal associations between balance ability and falls were assessed over three different time periods: 1) balance at age 53 and falls at age 60-64; 2) balance at age 53 and falls at age 68; and 3) balance at age 60-64 and falls at age 68. Sex-adjusted and fully-adjusted estimates are provided in Table 7.7. At all ages, there was no association between balance and single occurrence of falls, however higher balance ability was associated with lower risk of recurrent (≥2) falls (Models 4,6,8). Sex-adjusted estimates were largest for balance ability at age 60-64 and recurrent falls at 68 [RRR=0.92 (95% CI: 0.88, 0.97), Model 7].

Associations of balance ability with injurious and non-injurious falls were inconsistent. Better balance ability at age 53 was associated with lower risk of injurious falls at age 60-64 [0.95 (0.92, 0.99), Model 5] but this association was not present at other ages (Models 7, 9). Conversely, there was an association between better balance ability and lower risk of non-injurious falls between ages 60-64 and 68 (Model 9), but this was present solely in men. For both the recurrent and injurious falls models, all associations were attenuated in the fully adjusted models.

Table 7.7 Longitudinal associations between balance ability and falls (number of falls, injurious falls) at age 53 and 60-64 (per 1 sec increase in balance ability)

	Sex-adjusted (max)		**Sex adjusted (ccs)**		**Fully-adjusted**	
	RRR (95% CI)	**p-value**	**RRR (95% CI)**	**p-value**	**RRR (95% CI)**	**p-value**
BALANCE (age 53) AND FALLS (age 60-64)						
Model 4: Outcome: 0 falls (ref) [a]	n=2052		n=1657		n=1657	
1 fall	0.99 (0.97, 1.01)	0.31	0.99 (0.96, 1.01)	0.36	0.98 (0.95, 1.01)	0.15
≥2 falls	0.97 (0.94, 1.00)	0.07	0.97 (0.93, 1.00)	0.05	0.98 (0.94, 1.02)	0.29
Model 5: Outcome: 0 falls (ref) [b]	n=2057		n=1661		n=1661	
Non-injurious falls	0.99 (0.97, 1.01)	0.38	0.99 (0.96, 1.01)	0.27	0.99 (0.96, 1.01)	0.34
Injurious falls	0.95 (0.92, 0.99)	0.03	0.96 (0.91, 1.00)	0.05	0.96 (0.91, 1.01)	0.08
BALANCE (age 53) AND FALLS (age 68)						
Model 6: Outcome: 0 falls (ref) [c]	n=2111		n=1707		n=1707	
1 fall	1.01 (0.99, 1.03)	0.35	1.02 (1.00, 1.04)	0.12	1.01 (0.99, 1.03)	0.39
≥2 falls	0.97 (0.94, 0.99)	0.01	0.97 (0.94, 1.00)	0.03	0.98 (0.95, 1.01)	0.11
Model 7: Outcome: 0 falls (ref) [b]	n=2117		n=1713		n=1713	
Non-injurious falls	0.99 (0.97, 1.01)	0.35	1.00 (0.98, 1.02)	0.90	1.00 (0.98, 1.02)	0.89
Injurious falls	0.99 (0.96, 1.02)	0.52	0.99 (0.96, 1.02)	0.54	0.99 (0.96, 1.03)	0.60
BALANCE (age 60-64) AND FALLS (age 68)						
Model 8: Outcome: 0 falls (ref) [d]	n=1920		n=1312		n=1312	
1 fall	0.99 (0.96, 1.02)	0.42	0.99 (0.96, 1.03)	0.71	0.99 (0.95, 1.03)	0.69
≥2 falls	0.92 (0.88, 0.97)	<0.001	0.93 (0.88, 0.99)	0.02	0.95 (0.89, 1.00)	0.07
Model 9: Outcome: 0 falls (ref) [e]	n=905; n=1020		n=616; n=700		n=616; n=700	
Men: Non-injurious falls	0.90 (0.85, 0.96)	<0.005	0.93 (0.86, 0.99)	0.03	0.94 (0.88, 1.01)	0.09
Injurious falls	1.00 (0.93, 1.06)	0.89	1.01 (0.94, 1.08)	0.89	1.03 (0.96, 1.11)	0.42
Women: Non-injurious falls	0.99 (0.95, 1.03)	0.58	0.99 (0.94, 1.04)	0.71	0.99 (0.94, 1.04)	0.65
Injurious falls	0.95 (0.88, 1.03)	0.21	0.93 (0.84, 1.03)	0.21	0.92 (0.82, 1.03)	0.16

max = maximal available sample; ccs = complete cases sample; RRR = relative risk ratio of fall outcome relative to reference category

[a] No sex interaction (p=0.16); [b] No sex interaction (p=0.17); [c] No sex interaction(p=0.91); [d] No sex interaction(p=0.24); [e] Sex interaction (p<0.05); [f] All models adjusted for death, attrition, height, BMI, depression, diabetes, CVD history, respiratory events, knee pain, smoking status, leisure time physical activity, maternal education, paternal occupational class, own occupation, education

7.3.2.4 Sensitivity analysis: inability to complete balance test due to health reasons and falls risk

Building on the sensitivity analysis of fall prevalence, inability to complete the balance test was associated with a higher risk of falling. First, in cross-sectional models, there was strong evidence that individuals who could not complete the test had higher risk of recurrent, injurious and non-injurious falls (see Appendix 7.5). For example, individuals who could not complete the test at age 53 had an 11.81 (95% CI: 7.04, 19.80) times higher risk of recurrent falls in sex-adjusted models (Model 10, Appendix 7.5). Associations remained strong in all fully-adjusted-models. There were some sex differences at age 60-64, where associations between balance ability and falls risk were larger in men than women. Due to low numbers of individuals who could not complete the balance test due to health reasons (age 53: n=113, 60-64: n=89, 69: n=133) and who reported a fall (see Table 7.5), confidence intervals are wide and therefore, estimates should be interpreted with caution.

Associations were similar in longitudinal models. In sex-adjusted models, individuals who could not complete the test at age 53 had 5.00 (1.53, 3.11) and 2.07 (0.93, 4.61) times higher risk of recurrent falls at age 60-64 and 68 respectively, while those who could not complete the test at age 60-64 had a 4.38 (2.42, 7.93) times higher risk of falling at age 68 (see Models 13, 15, 17; Table 7.8). As before, there was no association with single falls. Inability to complete the test was also associated with higher risk of both injurious and non-injurious falls, however this was only present for those associations with shorter follow-up such as from age 53 to 60-64 and 60-64 to 69 (Models 14 and 18; Table 7.8). Overall, patterns of association remained in fully-adjusted models, whereby associations were strongest between age 60-64 and 68, with weaker associations between age 53 and age 68.

Table 7.8 Longitudinal associations between inability to complete balance test and falls (number of falls, injurious falls) at age 53 and 60-64

		Sex-adjusted (max)		**Sex-adjusted (ccs)**		**Fully-adjusted**	
		RRR (95% CI)	**p-value**	**RRR (95% CI)**	**p-value**	**RRR (95% CI)**	**p-value**
BALANCE (age 53) AND FALLS (age 60-64)							
Model 13:	Outcome: 0 falls (ref)	n=2052		n=1657		n=1657	
	1 falls	0.82 (1.32, 2.38)	0.75	1.30 (0.37, 4.53)	0.68	1.31 (0.37, 4.62)	0.68
	≥2 falls	5.00 (1.53, 3.11)	<0.001	4.57 (1.82, 11.44)	<0.005	3.70 (1.37, 9.98)	0.01
Model 14:	Outcome: 0 falls (ref)	n=2057		n=1661		n=1661	
	Non-injurious falls	1.94 (0.89, 4.20)	0.09	1.40 (0.46, 4.25)	0.55	1.30 (0.42, 4.00)	0.65
	Injurious falls	4.10 (1.72, 9.77)	<0.005	4.10 (2.18, 15.39)	<0.001	5.25 (1.88, 14.67)	<0.005
BALANCE (age 53) AND FALLS (age 68)							
Model 15:	Outcome: 0 falls (ref)	n=2110		n=1707		n=1707	
	1 falls	1.26 (0.51, 3.07)	0.61	1.20 (0.40, 3.57)	0.68	1.26 (0.42, 3.79)	0.68
	≥2 falls	2.07 (0.93, 4.61)	0.07	1.83 (0.68, 4.96)	0.46	1.50 (0.51, 4.45)	0.46
Model 16:	Outcome: 0 falls (ref)	n=2117		n=1713		n=1713	
	Non-injurious falls	1.50 (0.72, 3,11)	0.28	1.29 (0.51, 3,27)	0.58	1.24 (0.48, 3.20)	0.66
	Injurious falls	1.96 (0.66, 5.61)	0.23	1.98 (0.58, 6.83)	0.28	1.78 (0.50, 6.37)	0.38
BALANCE (age 60-64) AND FALLS (age 68)							
Model 17:	Outcome: 0 falls (ref)	n=1920		n=1312		n=1312	
	1 falls	1.76 (0.70, 3.38)	0.28	1.97 (0.71, 5.44)	0.19	1.73 (1.01, 2.95)	0.05
	≥2 falls	4.38 (2.42, 7.93)	<0.001	4.54 (1.29, 10.43)	<0.001	3.24 (1.29, 8.13)	0.01
Model 18:	Outcome: 0 falls (ref)	n=1925		n=1316		n=1316	
	Non-injurious falls	2.39 (1.32, 4.35)	<0.005	2.64 (1.16, 6.01)	0.02	2.24 (0.93, 5.38)	0.07
	Injurious falls	4.99 (2.44, 10.20)	<0.001	6.25 (2.50, 15.63)	<0.001	4.18 (1.52, 11.53)	<0.001

max = maximal available sample; ccs = complete cases sample; RRR= relative risk ratio of fall outcome relative to reference category

7.3.3 Balance screening as a prognostic tool

In order to compare prognostic accuracy of the one-legged balance test for falls risk, the AUC of several different longitudinal models were assessed. As in section 7.3.2, three time periods were assessed: 1) balance ability at age 53 and falls at age 60-64, 2) balance ability at age 53 and falls at age 68, and, finally, 3) balance ability at age 60-64 and falls at age 68. As both fall outcomes had three categories, two separate binary models were used for each fall variable. For number of falls, this compared no fall to one fall and to recurrent falls, while for type of fall, no fall was compared with both injurious and non-injurious falls.

7.3.3.1 Comparing prognostic accuracy of balance ability with a sex only model

First, the prognostic accuracy of the one-legged balance test to predict subsequent falls was compared directly to a model which included sex only. Table 7.9 displays the AUC, 95% CI and the p-value for the AUC test of comparison [645]. Prognostic accuracy of most of these models was poor, with the majority having an AUC of less than 0.6; as stated in section 7.1.3, an AUC less than 0.6 is considered poor while an AUC of ~0.5 indicates no discriminatory ability [621]. The addition of balance ability to the baseline sex-only model did not improve prediction of a single fall at any age (Models 19,21,23; Table 7.9). In models that sought to identify those at risk of recurrent falls, AUCs improved with the addition of balance ($p<0.05$ at all ages), however discriminatory ability remained low (Models 20,22,24; Table 9.9). For example, the addition of balance ability at age 53 in predicting recurrent falls at age 60-64 improved the AUC slightly from 0.597 (95% CI: 0.559, 0.635) to 0.623 (0.579, 0.667; p=0.05; Model 20). Similar patterns were shown for both non-injurious and injurious falls, where the addition of balance at age 53 had little impact on the model fit (Models 25-30), although the addition of balance at age 60-64 demonstrated improvements (Model 29,30). Overall, balance ability remained a poor discriminator of those at highest risk of falling with only three models reaching an AUC of >0.6; these were models 19 (balance age 53 + recurrent falls at age 60-64), 26 (balance age 53 + injurious falls age 60-64) and 30 (balance age 60-64 + injurious falls at age 68).

Table 7.9 Prognostic accuracy of a sex only model compared to a balance and sex model using area under ROC curves (AUC)

	Sample size	**AUC (95% CI)**		**Test of comparison** [a]
		Model: sex only	**Model:** sex and balance	
1. Outcome: RECCURENT FALLS (ref: no falls)				
Model 19: Bal 53 → One fall, age 60-64	1894	0.569 (0.535, 0.604)	0.576 (0.538, 0.614)	0.49
Model 20: Bal 53 → ≥2 fall, age 60-64	1838	0.597 (0.559, 0.635)	0.623 (0.579, 0.667)	0.05
Model 21: Bal 53 → One fall, age 68	1900	0.571 (0.539, 0.603)	0.579 (0.541, 0.616)	0.46
Model 22: Bal 53 → ≥2 fall, age 68	1860	0.554 (0.519, 0.589)	0.588 (0.547, 0.628)	0.01
Model 23: Bal 60-64→ One fall, age 68	1727	0.569 (0.535, 0.602)	0.582 (0.544, 0.619)	0.22
Model 24: Bal 60-64→ ≥2 fall, age 68	1695	0.531 (0.494, 0.568)	0.580 (0.538, 0.622)	<0.001
2. Outcome: INJURIOUS FALLS (ref: no falls)				
Model 25: Bal 53 → Non-inj fall, age 60-64	1956	0.572 (0.541, 0.602)	0.581 (0.547, 0.616)	0.30
Model 26: Bal 53 → Inj fall, age 60-64	1781	0.606 (0.560, 0.651)	0.634 (0.581, 0.687)	0.06
Model 27: Bal 53 → Non-inj fall, age 68	2008	0.557 (0.529, 0.585)	0.566 (0.534, 0.598)	0.31
Model 28: Bal 53 → Inj fall, age 68	1759	0.582 (0.536, 0.628)	0.592 (0.536, 0.649)	0.47
Model 29: Bal 60-64→ Nom-inj fall, age 68	1821	0.546 (0.516, 0.575)	0.570 (0.537, 0.575)	0.04
Model 30: Bal 60-64→ Inj fall, age 68	1606	0.569 (0.521, 0.616)	0.609 (0.551, 0.667)	0.01

AUC = area under the curve

[a] *tests the equality of each ROC area (sex vs sex and balance) within the same sample*

7.3.3.2 Comparing prognostic accuracy of balance ability, history of falls and a combined model

Several guidelines have recommended using an initial screening tool of an objectively measured balance test along with self-reported fall history [260]. To determine which aspect of this screening tool could better predict falls in this cohort, AUC estimates of a balance and sex model with a past fall history and sex model were compared (see Table 7.10). For all models, AUCs were higher for past history of falls compared balance ability. However, the improvement in model fit and prognostic accuracy was only significant for recurrent and non-injurious falls. Model prediction remained poor to average (all AUCs <0.700), demonstrating the same trends as above, where prognostic accuracy was highest for those at highest risk (i.e. recurrent falls) and at older ages (i.e. balance age 60-64 and falls age 68).

A final model that combined balance ability and history of falls was compared to the initial balance ability and sex model. This combined model was significantly better than using only one of balance ability or history of falls (see Table 7.10), with all AUCs between 0.600 and 0.700. Due to low power and low sensitivity of the binary variable of whether or not an individual was unable to complete the balance test due to health reasons, a sensitivity analysis to examine the prognostic ability of this question was not conducted.

Table 7.10 Prognostic accuracy, comparison of a balance and sex-adjusted model to 1) a sex and past falls model and 2) a sex, balance and past falls model using area under ROC curves (AUC)

		AUC (95% CI)							
	Sample size	**Model: sex and balance**		**Model: sex and past falls**		**Test of comp [ac]**	**Model: balance, sex and past falls**		**Test of comp [bc]**
1. Outcome: RECCURENT FALLS (ref: no falls)									
Model 31: Bal 53 → One fall, age 60-64	1894	0.576	0.538, 0.614	0.586	0.548, 0.624	0.45	0.596	0.557, 0.635	<0.05
Model 32: Bal 53 →≥2 fall, age 60-64	1838	0.623	0.579, 0.667	0.684	0.643, 0.725	<0.01	0.697	0.655, 0.739	<0.001
Model 33: Bal 53 → One fall, age 68	1900	0.579	0.541, 0.616	0.602	0.567, 0.637	0.16	0.609	0.572, 0.646	0.03
Model 34: Bal 53 → ≥2 fall, age 68	1860	0.588	0.547, 0.628	0.612	0.574, 0.650	0.19	0.627	0.586, 0.668	<0.01
Model 35: Bal 60-64→ One fall, age 68	1715	0.578	0.542, 0.628	0.610	0.572, 0.648	0.09	0.615	0.577, 0.654	0.03
Model 36: Bal 60-64→ ≥2 fall, age 68	1684	0.594	0.551, 0.637	0.641	0.600, 0.681	0.05	0.669	0.626, 0.713	<0.015
2. Outcome: INJURIOUS FALLS (ref: no falls)									
Model 37: Bal 53 →Non-inj fall, age 60-64	1956	0.581	0.547, 0.616	0.625	0.591, 0.658	<0.01	0.632	0.597, 0.667	<0.001
Model 38: Bal 53 →Inj fall, age 60-64	1781	0.634	0.581, 0.687	0.632	0.579, 0.684	0.91	0.657	0.604, 0.710	<0.005
Model 39: Bal 53 →Non-inj fall, age 68	2008	0.566	0.534, 0.598	0.605	0.574, 0.635	<0.01	0.606	0.574, 0.639	<0.005
Model 40: Bal 53 →Inj fall, age 68	1759	0.592	0.536, 0.649	0.603	0.554, 0.652	0.51	0.604	0.549, 0.660	0.55
Model 41: Bal 60-64→Non-inj fall, age 68	1810	0.570	0.537, 0.575	0.624	0.592, 0.657	<0.005	0.633	0.600, 0.670	<0.001
Model 42: Bal 60-64→ Inj fall, age 68	1594	0.605	0.547, 0.664	0.626	0.572, 0.680	0.40	0.636	0.577, 0.695	0.13

AUC = area under the curve

[a] *tests the equality of the ROC area of the sex and balance model with the ROC area of sex and past falls model within the same sample.*

[b] *tests the equality of the ROC area of the sex and balance model with the ROC area of sex, balance and past falls model within the same sample.*

[c] *p<0.05 signifies that the model with the higher AUC is a significantly better prognostic model.*

7.4 Discussion

7.4.1 Main findings

Chapter 7 had three main aims: describing the prevalence of falls in midlife, testing associations between balance ability and falls and assessing the prognostic utility of the one-legged balance test to predict falls. Prevalence of falls increased with age from age 43 to 68 although prevalence at ages 53 and 60-64 were similar. Higher balance ability was associated with decreased risk of falling. These associations were strongest under several conditions: 1) for recurrent falls, 2) in sex-adjusted models, 3) cross-sectionally or 4) at later ages (i.e. between age 60-64 and 68). Individuals who were unable to complete the balance test due to health reasons demonstrated a much higher risk of falling compared to those who completed the test. This suggests that inability to complete the balance test due to health reasons can be informative in both research and clinical practice.

Despite associations between balance ability and falls, predictive ability of the one-legged balance test was poor. Combining history of falls with balance ability improved prognostic fit from poor to average [621]; this supports the idea that falls are complex and a single parsimonious assessment, such as the one-legged eyes closed balance test, may not be a sufficient screening tool in non-clinical samples. In summary, this chapter provided evidence of associations between balance and falls in midlife, but these associations did not translate into the use of the one-legged balance test as an effective screening tool in middle aged adults.

7.4.2 Comparison with other studies and explanation of findings

7.4.2.1 Fall prevalence

The prevalence of falls reported in this chapter is comparable to what has been reported elsewhere [609,639]. Peeters et al. [639] examined fall prevalence in midlife using four cohorts from the UK (NSHD, as explored in this thesis), Ireland (The Irish Longitudinal Study of Ageing (TILDA)), the Netherlands (Longitudinal Aging Study Amsterdam) and Australia (Australian Longitudinal Study on Women's Health). TILDA was the only included cohort to report fall prevalence between ages 40 and 44 (8.7% in women; did not examine men), which was higher than the 1.37% reported in this chapter. Falls at age 43 in NSHD were not included in these co-ordinated analyses due to concerns about the gating question and how this would affect comparability with other fall prevalence measures. Thus, underestimation of fall prevalence at age 43 in NSHD is likely due to this gating question, as individuals were only asked about whether or not they had fallen if they reported having difficulties with falling or balance in a disability checklist. Peeters et al. [639] also reported a similar, sharp increase in falls during midlife, beginning with those aged 50-54. The pooled prevalence of falls at age 50-54 was 20.9% and 13.4% in women and men, respectively [639], which is notably similar to the prevalence at age 53 reported in this chapter (21.91% and 12.75%). This may be partially because NSHD data contributed to the pooled estimates although there is some variation in estimates from the other cohorts. At age 60-64, the pooled prevalence was 29.9% in women and 15.7% in men, which is slightly higher than the prevalence reported here (22.7% in women, 13.55% in men).

Prevalence from these four cohorts [639], as well as from the English Longitudinal Study of Ageing [609], provides consistent evidence that fall occurrences rise during midlife. While most falls research has focused on individuals aged ≥65, falls risk in midlife is relatively common suggesting the need to address falls risk at earlier ages in both research and policy [639,646]. As prevalence of more severe falls including recurrent or injurious falls appears to be similar in mid and later life, intervening earlier could reduce resources used to address the consequences of these falls. In NSHD, approximately 25% of all falls at ages 60-64 and 68 required the individual to seek medical attention; this is comparable to prevalence of injurious falls reported in other samples aged ≥65 (22.1% [647], 27.1% [648]). Similarly, the proportion of women who reported ≥3 falls did not change from age 53 to 68 (18.6%, 20.5%, 20.3%). The high prevalence of falls in midlife group suggest that is not too early to intervene. Interventions that target those at greatest risk of falls (i.e. recurrent or injurious falls) could minimise negative consequences that arise from falls (e.g. fractures, hospitalisation, fear of falling) [593,610,647,649].

7.4.2.2 Associations between balance ability and falls

The associations between poor standing balance ability and increased risk of falling are consistent with the majority of evidence in the literature [32,253,273,629-632,635,637], though direct comparison with other studies are limited for several reasons. As outlined in section 7.1.4, previous evidence has focused primarily on samples aged ≥65, using a one-legged stand test with eyes open. Length of balance test, length of follow-up, collection of falls data and analytical methodology also differ considerably between studies, further limiting comparability (see Table 7.2 for details of other studies). Several studies used cut-points (ranging from 5 to 30 seconds) to identify associations between impaired balance and falls risk and thus comparison of odds ratios are not always possible. Finally, most studies examined risk of no fall vs any fall, with only a few investigating multiple or injurious falls [630,637]. Analyses of this dichotomous fall outcome were removed from the thesis as there were unmistakeable differences in using balance ability to identify risk of single vs multiple falls. By dichotomising fall risk, the tempered estimates failed to provide important information about the nature of the association.

7.4.2.2.1 Temporality of associations: cross-sectional vs longitudinal

Studies have also reported that cross-sectional associations were stronger than longitudinal associations. Of eight studies that reported a clear association between one-legged standing balance time and falls (summarised in section 7.1.4), five examined cross-sectional associations [273,629,631-633]. Conversely, only two of nine studies that reported no association were cross-sectional [129,635]. The one study that examined both cross-sectional and longitudinal associations reported a significant cross-sectional association but no association after a 12 month follow-up [273]. The lag time between balance and falls is crucial in understanding these associations for two reasons.

First, the cross-sectional associations may be partially due to reverse causality. In section 7.1.4, the limitations of the temporality of cross-sectional associations were identified as they rely upon retrospective fall history (falls within the previous twelve months). Although this was a major limitation of the literature, cross-sectional associations were repeated in this chapter in order to compare to previous studies. Assessment of balance ability occurred after the fall reporting period, thus one must be cautious in making any inferences about this as the temporal order is incorrect. Individuals with a history of falling are expected to have worse balance ability and suffer from mobility impairments as a result of their fall [650]. Thus, if an individual experienced one or more falls in the twelve months before their test, it could directly impact their subsequent balance performance. The timing of the fall could impact this as an individual who recently experienced a fall may not have returned to their baseline balance ability at the time of the assessment. Similarly, a fall within this twelve month period could have precipitated an increased fear or falling and a subsequent decrease in activity; these factors could both have a detrimental impact on balance ability. This is further explored in the limitations in section 7.4.3.

Second, the complexity of falls risk is well established and falls can be attributed to multiple interacting factors rather than one identifiable cause [651]. As such, there is more opportunity for residual confounding if the follow-up time is longer. This was shown in the chapter results as the shortest follow-up (between ages 60-64 and 68) had the strongest associations and the longest follow-up (53 and 68) had the weakest associations. However, one must be cautious in this interpretation as the difference in strength and size of the associations is likely to be due to both follow-up length and the ages of both the balance test and reporting of falls. It is not possible to disassociate follow-up length with age and understand how much each contributes using the data currently available. Future research should consider this in study design, by considering multiple appropriate follow-up points.

7.4.2.2.2 Effect sizes: odds ratios for falls

Many studies have examined associations between dichotomised impaired balance and falls [32,253,631,634,637], which limits comparability to odds ratios (ORs) in this chapter. However, the studies which reported the ORs of one second change in balance reported similar sex-adjusted ORs: 0.97 (0.95-0.99) [632], 0.99 (0.97-1.01) [273] and 0.99 (0.98–1.01) [274] for a fall after a 12-month follow-up. Cho et al. [629] reported a substantially larger OR (0.38 (0.17-0.84)); this is likely due to the sample which was a subset of individuals with balance difficulties who had been recruited for a fall reduction program. All of these associations used any fall vs no fall as the outcome. As shown in Tables 7.7 and 7.8, balance may be more strongly associated with high risk falls such as recurrent or injurious falls and as such, separate analyses of these falls may be more informative. This is because individuals who fall one time may be more similar to non-fallers than they are to recurrent or injurious fallers, as shown in Table 7.6, Appendices 7B & 7C and previous literature [630,641,642]. There are few risk factors associated with single falls and many factors associated with multiple falls [579,641]. Intrinsic factors, such as balance, are thought to play a dominant role in recurrent falls [641,650], whereas single occurrence falls are more commonly a result of extrinsic factors (e.g. environmental hazards) in chance circumstances. This provides support for why balance exhibited stronger associations with recurrent falls than single falls in this chapter.

Intrinsic factors (as described in section 7.1.2) may also explain injurious falls more than non-injurious falls [652]. A series of strategies that occur in quick succession has been proposed to explain how individuals try to avoid a fall and why some falls have injurious consequences [653]. In the first stage, the ‘ankle strategy’ aims to correct small perturbations, while the ‘hip strategy’ corrects larger disturbances. If neither strategy is successful, the individual engages the ‘stepping strategy’ by taking a step to increase the base of support. If these strategies fail to stop a fall, a series of ‘rescue strategies’ are drawn upon; this includes grabbing something for support or extending one’s arm to limit the severity of a possible injury. It is hypothesised that an individual with few intrinsic risk factors (e.g. muscle weakness, cognitive impairment, sedentary behaviour, depression) would find success with these strategies, thereby avoiding a fall or minimising an injurious consequence.

Several studies have investigated the strength of association between one-legged balance and type of fall. Delbaere et al. [630] reported an OR per second increase in balance time of 0.80 (0.67-0.97) for those with either recurrent falls or a single injurious fall (mean age: 77.9; see Table 7.2 for study characteristics). This is a similar strength of association to ORs for recurrent or injurious falls reported in this chapter (see Tables 7.7 and 7.8). Vellas et al. [637] found that impaired balance (inability to maintain one-legged stand for ≥5 seconds) was associated with injurious falls (RR: 2.13 (1.04, 4.34)), but was not associated with any reporting of a fall (RR: 0.99 (0.46, 2.13)) after a three-year follow-up (mean age: 72.7, see Table 7.2). Patterns of associations between balance ability and high-risk falls (either injurious or recurrent) were similarly stronger in this chapter. Individuals with poor one-legged standing balance ability appear to be more susceptible to recurrent or injurious falls and as such, these individuals are more likely to benefit from a balance intervention. As the prevalence of falls in middle and older aged adults continue to increase, prevention efforts could partially improve efficiency by targeting high risk falls [654].

7.4.2.3 Prognostic screening using balance ability to predict falls

The presence of observational associations do not imply that the risk factor can be used as a reliable predictive tool [655,656]; the predictive ability of risk factors must be formally established. The majority of evidence on the topic has not examined the prognostic utility of the one-legged balance test. Of the sixteen studies identified in Table 7.2, only two studies examined AUCs [274,632] (mean ages: 71.9 and 73.4). AUCs were similarly low to the sex and balance AUCs reported in Table 7.9: 0.55 (0.49-0.60) [632] to 0.64 (no 95% CI given) [274].

Two further studies from Table 7.2 reported that postural sway parameters could better predict falls and examined the predictive accuracy of these tests [228,635]. First, Oliveira et al. [635] – who notably showed no differences in one-legged stand time between fallers and non-fallers – reported that the diagnostic accuracy of postural sway on several centre of pressure (CoP) parameters was high. These parameters were total area CoP (total postural sway), anteroposterior CoP velocity (speed of sway in the forward-backward plane) and mediolateral CoP velocity (speed of sway from left to right). The AUCs of these three parameters – 0.65 (0.57-0.72), 0.68 (0.60-0.76) and 0.72 (0.66-0.68), respectively – were higher than nearly all of the AUCs reported in this chapter and in the studies reported above [274,632]. Second, Maki et al. [228] – who also found no association between one-legged balance time and falls after a 12-month follow-up – reported that anteroposterior and mediolateral sway could predict specific types of falls including: single falls, recurrent falls, and first-time falls as well as falls preceded by base of support disturbances (e.g. trip or slip) or by centre of mass disturbances (e.g. during bending, reaching or a collision). Mediolateral sway was most strongly able to predict recurrent falls (AUC: 0.87 (SE: 0.05) and 0.82 (0.06)) and falls preceded by a disturbance in the base of support (AUC: 0.83 (0.05) and 0.76 (0.06)). The lowest AUCs were 0.67 (0.06) for mediolateral sway predicting single fallers. Although the high AUCS are promising, this study was in an older sample than NSHD (mean age: 83) with a shorter follow-up, and thus, comparisons should be made with caution.

Taking the evidence of one-legged stand tests and sway parameters to predict falls risk together, several conclusions can be made. Prognostic accuracy of a timed one-legged balance test to predict falls is poor (majority of AUCs: 0.50-0.65), while postural sway, particularly in the mediolateral plane, appears to be a better predictor (AUCs: 0.65-0.90). Both postural sway and one-legged standing time were better able to predict recurrent or injurious falls than single falls. This is consistent with stronger associations between intrinsic factors (such as balance) and dangerous falls (such as recurrent or injurious). Furthermore, postural sway may be a more sensitive predictor of falls than balance time as it may identify specific aspects of balance ability that precipitate falls. For example, fallers are more likely to fall to the left or right as opposed to forwards or backwards [657,658]. Falls to the left or right are also more likely to result in injury than falls in the anterior-posterior plane [657,658]. This may explain why mediolateral sway, a key feature of balance, predicted falls better than one-legged balance time [228,635,659]. The time yielded from the one-legged stand test may not be sensitive enough to detect early impairments, especially in a middle-aged population as the timed test does not capture the degree of difficulty an individual experiences during the test or the mediolateral sway utilised to maintain the static position. This hypothesis is supported by evidence showing a weak correlation between postural sway and one-legged stand parameters [660,661].

Finding a single tool to identify those at increased risk of falling is difficult for many reasons. First, as noted above, falls risk is complex and evidence has shown that models with multiple risk factors have higher predictive accuracy [662-664]. For example, one study suggested that fall screening tools with fewer than five predictors were suboptimal and reported that the ideal number of variables to maximise predictive accuracy was 20-30 [664]. While parsimony is often the aim, a multifactorial assessment tool for balance – similar to the Framingham Risk Score for cardiovascular risk [665] or the Fracture Risk Assessment Tool [666]– may provide the most accurate risk prediction. This is consistent with the highest AUCs in the model that combined balance ability and fall history. Further research is necessary to identify a tool that provides the optimal combination of parsimony and accuracy. When aiming to identify this, it is important to consider that it may require multiple tools targeted at different ages and for different types of falls outcomes.

Although NSHD provides a unique opportunity to identify risk factors independent of age, risk prediction in an age-homogenous sample is expected to be lower than a heterogeneously aged sample. This is because age explains a lot of the heterogeneity of age-related conditions [667]. In a systematic review of health indicators and all-cause mortality in adults aged ≥50, the authors found that age contributed the most to mortality prediction (AUCs: 0.65 – 0.78) and that additional predictors such as genetics, function, disease, frailty, lifestyle factors, psychological factors, etc. added very little to the predictive model (AUCs: 0.01-0.10) [667]. Due to the age-homogeneity in NSHD, age was not able to contribute to fall prediction; this may partially explain why the ROCs of a fully-adjusted model remained smaller than expected.

7.4.2.4 Sensitivity analyses: inability to complete balance test due to health reasons

In section 2.4, missing balance data were explored in detail. The pattern of missing data could be partially explained by the reason for being unable to complete the test (e.g. health reasons). It is unsurprisingly that at all ages nearly half of individuals who could not participate in the balance assessment due to health reasons reported a fall. The reason for not being able to complete the test is likely directly associated with falls risk. For example, those who were unable to or had difficulty walking and standing (n=36 at age 69) are more susceptible to instability that could result in a fall. Similarly, neurological problems such as dizziness or vertigo (n=9) or specific musculoskeletal or connective tissue diseases (n=15, e.g. osteoarthritis) are also specific risk factors for fall.

This chapter found strong evidence that these individuals were at a higher risk of falling. Both clinical and research settings should utilise reasons for not completing the balance test as it may help understand health outcomes. These individuals may be an appropriate high-risk target group for intervention. AUCs were not used to assess whether inability to complete the test could predict falls risk. This is because the power and sensitivity of the test are expected to be low as there are a small subset of individuals to which this applies (~100), particularly at younger ages (e.g. ages 53 and 60-64).

7.4.3 Strengths and weaknesses

The analyses presented in this chapter are limited by the design and data collection of the study. Recall bias is expected as individuals could have difficulty remembering if they had fallen within the last year. Accuracy of fall reporting could be improved by asking individuals to keep daily fall diaries over a twelve-month period. While this is considered the gold standard for falls assessment [576] and was considered during NSHD data collection planning, it was not possible due to financial and logistical restraints. Measurement of injurious and non-injurious falls may also be inconsistent as only falls where the individual sought medical attention were considered to be injurious. It is likely that some falls resulted in injury but the individual did not go to a doctor or hospital.

A major assumption is that balance performance on the test day is reflective of an individual's true performance. The variability of blood pressure has been well established [668], and it is reasonable to assume that balance performance may exhibit a similar phenomenon. Furthermore, an individual's balance performance could be impacted by acute health conditions, psychological factors, or other extenuating circumstances on the day. This is especially important when considering how reverse causality may explain the strength of the cross-sectional associations. Individuals who recently experienced a fall (within the last week or month) may not have recovered back to their baseline balance ability. This could partially explain why individuals who could not complete a balance test due to health reasons had such high prevalence of falls.

A major strength of this chapter - and the thesis as a whole - is the wide range of covariates that were considered when examining associations between balance ability and falls. Polypharmacy, the use of multiple medications, was not included in analyses and warrants discussion given its probabe contributory role in both poor balance and higher risk of falls. Adequate data on polypharmacy was not available at all three waves (e.g. ages 53, 60-64 and 69), which is why it could not be included as a time-varying covariate throughout the thesis. However, evidence from both NSHD (at age 69) and other studies have shown that polypharmacy is associated with poorer balance ability, even after potential explanatory factors (e.g. age, physical and cognitive multi-morbidities, depressive symptoms, hospitalisations) are controlled for [669,670]. Similar dose-response associations between polypharmacy and increased risk of falls have been reported [671-673]. Type of medication may contribute more to fall risk and postural instability than polypharmacy alone [672]; this may include ototoxic drugs, benzodiazepines, anti-hypertensives or analgesics [674-676]. It is hypothesised that these medications may have side effects that decrease postural stability and inhibit the ability to make postural adjustments needed to maintain balance and avoid a fall. Further research must investigate this hypothesis to inform if polypharmacy is a risk factor for falls due to its impact on balance ability or via a separate pathway.

It is possible that ORs and AUCs are lower than expected due to death as a competing risk. Balance is the strongest predictor of mortality compared with other physical capability measures in NSHD [247]. Individuals with poor balance ability, who would have been at the highest risk of falls, were more likely to die before follow-up of falls data at age 60-64 or 68. A final limitation is that the one-legged balance test was the only test of balance assessed in NSHD. As review of other studies have shown, other measures of balance (e.g. mediolateral postural sway) may be more accurate in predicting fall outcomes. While the one-legged test has advantages due to its simplicity, replicability and cost-effective properties, the prognostic accuracy of a balance test must remain the most important quality in a predictive model.

Despite these limitations, this chapter was one of the first studies to assess both explanatory and predictive associations between balance ability and falls. The evidence provided challenges two commonly held beliefs: 1) that fall prevention should focus on individuals aged ≥65 and 2) that primary care should implement a low-cost, feasible, replicable balance test such as the one-legged balance test to identify those at higher risk of falling. Other strengths include the assessment of balance ability and falls data in midlife as all other studies of one-legged balance and falls have focused on samples aged ≥65.

7.4.4 Implications and next steps

This chapter provided evidence of an association between balance ability and falls in midlife, but suggests that the one-legged stand test may not reliably predict falls. The findings of this chapter are limited to the one-legged balance stand test, which is an isolated test of static balance. Maintaining a one-legged stand with eyes closed is different to everyday situations, where an inability to correct one’s posture to a balance disturbance often precipitates a fall. Examples of this include stepping off a curb, tripping on a carpet or an accidental narrowing of the base of support.

Before evidence of associations can be appropriately translated, more research is needed to investigate if there are better balance tools. For example, further research must first investigate if mediolateral sway is the particular aspect of balance that is causing a fall and subsequently examine if it can accurately predict falls risk. Although assessing an individual's postural sway appears be a promising, accurate and effective screening tool, research must confirm the predictive ability of the test in a range of populations as well as calculate the cost-effectiveness of such a tool. With the emergence of low-cost force plates [677] and the development of balance assessment tools within common technology such as mobile phones or gaming devices [678,679], there is potential for mediolateral sway to be included in regular medical check-ups. Nevertheless, falls in middle and older aged adults are complex and there may not be one single tool that can identify those at risk. Understanding the complexities of risk prediction models is crucial.

Research of balance and falls should always differentiate between predictive and explanatory modelling. The presence of an association using regression techniques does not equate to a predictive association. The challenge is to find a way to translate these observed associations into valuable contributions in the health and ageing sector, including but not limited to a prediction tool. It is also important to distinguish between frequency and type of fall. As previously discussed, balance ability may be a better predictor of recurrent or injurious falls than single falls, due to intrinsic factors that directly cause a fall. Allocating resources that target individuals at risk of most severe consequences should be a priority. There may be value in examining longitudinal assessments of balance; limited evidence has suggested that those who have consistently low balance over time, followed by those who decline, are at highest risk of falling. Understanding whether or not rate of decline in balance ability influence falls risk could also help identify individuals who need interventions.

7.5 Conclusions

Falls are common in midlife, even before the age of 65, and as such, fall intervention and screening could be beneficial at earlier ages. While there is an observational association between balance ability (here demonstrated with the one-legged stand test with eyes closed) and falls, the one-legged stand test has poor prognostic ability to predict falls. Further research is needed to examine how empirical associations can be translated into effective screening tools to address problems encountered by the ageing population.

CHAPTER 8: FINAL DISCUSSIONS

This PhD project aimed to use a life course perspective to examine associations of factors across life with one-legged balance in mid and later life and to investigate translational utility of the one-legged balance test in predicting falls. Using data from the MRC National Survey of Health and Development, this thesis provided the first comprehensive investigation of socioeconomic, cognitive, behavioural and health pathways during childhood, adolescence and adulthood that contribute to balance ability in mid and later life. Better understanding of these factors and pathways can provide an opportunity to intervene earlier in life to minimise, prevent or delay balance impairment or decline. One aim of a life course approach is to identify when and what type of intervention may be most effective [680] as different stages may require different interventions. This thesis successfully identified multiple factors across the life course that are associated with balance ability and demonstrated some evidence of an association between low balance ability and falls in mid and later life. This final chapter will summarise the main findings of this thesis (section 8.1), discuss key implications in further detail (section 8.2), examine methodological considerations (section 8.3) and suggest areas of future research (section 8.4). Concluding remarks are provided in section 8.5.

8.1 Summary of findings

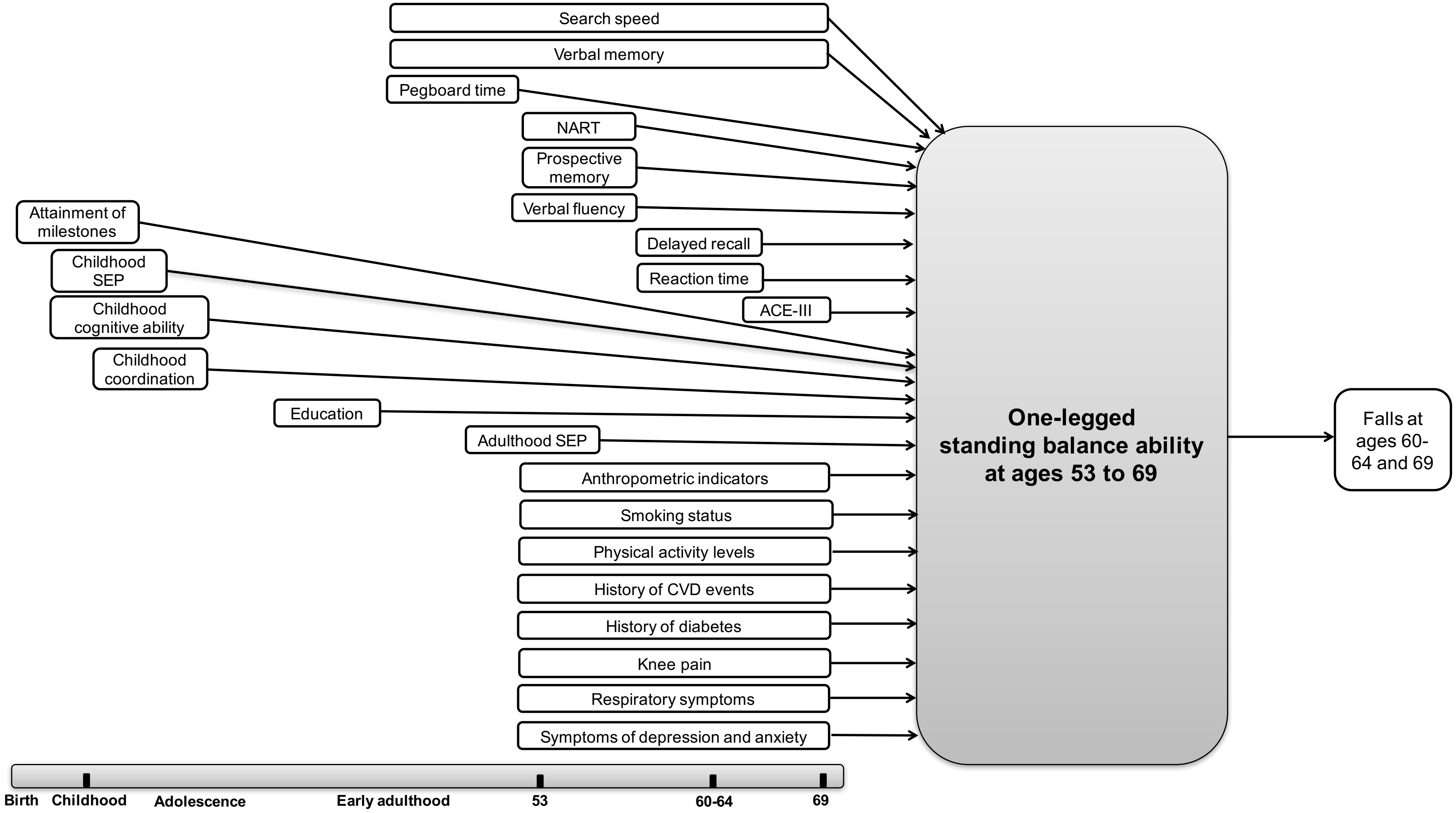
Following a thorough introduction and literature review (Chapter 1) and a detailed methodological chapter (Chapter 2), Chapter 3 investigated associations between traditional risk factors across life and balance and is the first study to provide evidence on how these associations changed with age and sex. Individuals with better balance ability were more likely to be male, taller, participate in healthier activities (high physical activity levels, no smoking), have higher SEP across life, have higher education and cognitive ability and were physically and mentally healthier (lower BMI, no history of diabetes or CVD events, no respiratory symptoms, no knee pain, no symptoms of depression and anxiety). The association of balance with anthropometric indicators, smoking and most physical health indicators was constant with age. Several associations became smaller at older ages (sex differences, socioeconomic indicators, physical activity, cognition), while two grew larger with age (knee pain, depression/anxiety). Unlike substantial sex differences in associations of similar factors in NSHD and grip strength [681], no sex differences were present. Figure 8.1 provides a summary of all associations examined throughout this thesis.

Chapter 4 demonstrated that neurodevelopmental factors, including higher levels of childhood cognitive ability and motor coordination as well as average age of first sitting and walking, were associated with better balance performance in mid and later-life. In order to extend the life course perspective of cognition and balance, the subsequent two chapters sought to investigate adult cognition in relation to balance in more detail. Chapter 5 identified that higher cognitive performance across all domains of cognition studied (verbal memory, delayed recall verbal memory, picture memory, prospective memory, search speed, reading, verbal fluency, reaction time and ACE-III) were associated with better balance ability. These associations were strongest in early midlife at ages 43 and 53, with weaker associations at ages 60-64 and 69. Associations of verbal memory, search speed, verbal fluency, reading score and simple reaction time with balance ability were robust across all analyses including adjustment for potential covariates.

Building on Chapter 5 and the lack of clear evidence on bidirectional associations between balance ability and cognitive ability, Chapter 6 aimed to identify the directionality of this association. Auto-regressive cross-lagged models and dual change score models suggested that there was primarily a unidirectional association between verbal memory and subsequent balance ability between ages 43 and 69. This association was less clear for search speed, with evidence of the same unidirectional association in early midlife (men and women) and a bidirectional association between ages 60-64 and 69 (men only).

Finally, Chapter 7 aimed to link the importance of balance ability (as identified in Chapters 3 to 6) with falls. As expected, balance ability was associated with falls– particularly, high-risk falls such as recurrent or injurious – however, prognostic accuracy of the one-legged stand test was limited. This revealed a translational gap between observational associations and subsequent application of balance screening tools; this gap must be addressed in order to tackle the rising prevalence of falls.

Figure 8.1 Associations between factors across life and balance ability at ages 53, 60-64 and 69



8.2 Interpretation and implications of findings

Interpretation and implications specific to balance are discussed in further detail below, however it is important to recognise that intervening in these domains could also have positive benefits for non-balance related health outcomes. Thus, the implications of this life course approach to balance ability can be extended to countless other health outcomes. Life course research has continually showed similarities in risk factors for health outcomes across a broad range of systems such as cognitive impairment, cardiovascular disease, musculoskeletal disorders, disability, frailty, mental health, amongst others [71,74].

Findings from Chapters 3 through 7 suggest that childhood development, socioeconomic inequalities, cognitive ability, and health behaviours amongst others may be appropriate intervention targets to improve balance ability. Explanations of findings were explored earlier in individual chapters, while the main implications fall broadly under three categories: 1) balance ability as a function of factors across the life course, 2) the contribution of cognitive ability to balance performance and 3) associations between balance and falls and subsequent screening implications.

8.2.1. Factors across life contribute to balance ability

This thesis demonstrated that diverse factors across life play an important role in balance ability in adulthood. Most of these factors remained associated with balance ability in fully-adjusted models suggesting that factors that contribute to balance are multifaceted and complex. For example, early life factors such as childhood cognition, SEP and coordination have strong associations with balance ability, even after adjustment for potential mediating, moderating or confounding factors. As discussed in Chapter 1 (section 1.3.1), balance ability improves continually from infancy to adolescence. To ensure appropriate progression of stages of balance development, adequate physical and cognitive development opportunities are crucial.

Positive physical development, such as linear height growth, is associated with positive health outcomes in later life [680]. Physical activity in the first five years of life has benefits for motor coordination and motor skill development [682,683], which has led to governmental recommendations for increased activity in the early years [684-686]. Long term, it has been established that physically active lifestyles develop early in life and show stability into adulthood [442]. Early interventions that increase physical activity levels could have lasting benefits for motor development [683,687] and later life physical capability.

Interventions that target cognitive development in childhood also have a positive impact on both short and long-term outcomes [688-694]. Cognitive developmental disparities have commonly been targeted by ensuring that socioeconomic disadvantaged children have access to appropriate education and developmental programmes. Sure Start programmes, UK area-based interventions for children and their families in deprived areas [688,689], aim to improve the physical, social and intellectual development of disadvantaged children [688]. Evaluation of Sure Start programmes report success across several outcomes including: improved attachment and bonding skills between mothers and babies, improved speech, language and communication in children [695], improved health for children and mothers and more stable homes [696]. Despite the positive outcomes, economic uncertainties and government changes have caused public spending on children to decrease [697] and more than a quarter of Sure Start centres to close [698]. A recent 2018 UN report suggests that government austerity and funding cuts have caused UK poverty to increase, with child poverty rates as high as 40% [699].

Given the findings of the UN report, the importance of adequate developmental opportunities for all children may be more important now than ever. Programmes such as Sure Start aim to reduce socioeconomic and developmental inequalities that impact health across the life course [700]. It is well established that SEP inequalities underlie some cognitive and physical inequalities in early life that have lifelong impacts on health outcomes [159,701-704]. These long-term impacts include increased cardiovascular disease risk [705,706], decreased physical capability [159,707], higher mental health problems [708,709], and increased risk of premature mortality [702,703]. Findings from Chapters 3 and 4, which identify associations between early life factors and balance ability, suggest a further area of benefit, and support the importance of targeting early life factors to improve balance ability across the life course.

This thesis was also novel in its identification of how associations between traditional risk factors across life and balance change with age (Chapter 3). Understanding this is important when designing and delivering interventions that are age-appropriate. While the exact age of peak balance ability is uncertain, evidence suggests it occurs before the age of 40 with a sharper decline from age 50 onward [25,42]. There was a steady decline in mean balance ability from age 53 to 69 in NSHD (Chapter 2, section 2.3). It is evident that different risk factors should be targeted depending on the age of the target population and the desired outcome. For example, socioeconomic indicators across life and contemporaneous physical activity levels demonstrated the strongest associations with balance at younger ages (i.e. at age 53) so could be reasonable targets to improve peak balance performance before age-related decline becomes significant. Equally, interventions aimed at a middle-aged sample (i.e. between ages 53 and 69) could target changes in smoking behaviour, respiratory symptoms or reducing CVD symptoms due to the consistent association at all three ages.

Knee pain and symptoms of depression or anxiety became more strongly associated with balance ability with age and could represent two critical factors for intervention that target older adults. For example, these factors could be targeted as an intervention later in life or be targeted with prevention efforts before individuals develop symptoms in either area. Knee pain is a common symptom of osteoarthritis [710], inflammatory arthropathy [710,711] or impaired mobility [712], which all become common with increasing age. Thus, targeting these conditions early could minimise further decline in balance ability [713-715]. Mood disorders, such as depression or anxiety, have a bimodal distribution with age, peaking in adolescence and rising again in later life (i.e. around age 80) [716], and thus may also be an important modifiable factor. Associations between psychological factors and balance performance are discussed further in section 8.4.4. Co-ordinated analyses of four cohort studies, including NSHD, identified nearly 40 demographic, health and lifestyle factors associated with falls in adults age 50-64 [646]. Several of these factors are similar to those investigated throughout the thesis; future steps should investigate if balance ability mediates the association between these risk factors and falls and how the association of each risk factor with falls differs with age.

8.2.2. Contribution of cognitive ability across life to balance ability

Chapter 1 suggested that the integration of sensory input from visual, vestibular and proprioceptive sources and motor output is required for successful balance. The association between cognitive ability and balance ability was then demonstrated across life and across cognitive domains (Chapters 4-6). Evidence from fully-adjusted models of childhood cognition and balance ability suggests that, while not as fundamental as critical periods for attachment or language development [717,718], higher cognitive function in childhood could provide long-lasting advantages in balance ability. Chapter 5 provided support for this across a number of cognitive domains, with Chapter 6 further suggesting a unidirectional association between verbal memory and subsequent balance ability, with evidence of a dynamic association between search speed and balance ability at different ages.

The complex association between cognitive ability and balance ability suggests that age-related changes in balance and cognitive ability should be considered alongside one another. Cognitive training interventions, beyond direct cognitive improvements [719], may also have positive benefits for balance ability due to the ability of the ageing brain to alter cognitive functions to compensate for decline [720]. Studies of such interventions should consider balance and other physical capability outcomes to further understand this association. Some cognitive interventions have demonstrated neuroplasticity of areas of the brain that control balance ability [721]. Single task training programmes targeting working memory [722], visual discrimination reaction time training [216] or global cognition [217] have resulted in improved postural sway [216,722] and balance [216,217]. Several dual task training paradigms have also shown improvement in overall balance ability [487,723,724]. Given the recognised benefit of single and dual task cognitive training in improving balance, intervention design and policy recommendations for both falls should consider the inclusion of a cognitive component. There is limited evidence of a reverse association, where balance-based interventions had a positive effect across multiple cognitive domains [178,725,726], although evidence from Chapter 6 provides little evidence for a longitudinal association in this direction. Further RCTs in larger samples are needed to assess if there may be shorter term associations and thus whether targeted training in both cognitive and balance domains could yield benefits in both areas. Rather than target a single intervention to improve a single outcome, a multidisciplinary intervention that address multiple health domains may be more appropriate.

Consistent with a comprehensive geriatric approach to ageing [727,728], decline in cognitive and balance abilities tend to co-occur. Understanding and recognising decline in one area could indicate change in the other area. Identifying subjective or mild cognitive impairment can be challenging, due to heterogeneity of symptoms and a lack of understanding of when an assessment is needed [729]. It is possible, as speculated in Chapter 6, that impaired balance could be indicative of more sensitive changes in cognition, particularly in the hippocampus or cerebellum, that have not yet been detected by the individual or their doctor. This hypothesis must be tested in further work to determine if balance performance can identify pre-clinical pathological or cognitive changes.

8.2.3. Informing predictive and explanatory modelling of balance ability and falls risk

Increasing incidence of falls in older adults is a growing public health concern [1]. As demonstrated in Chapter 1 and Chapter 7, numerous studies have identified an association between balance ability and falls in older adults [32,129,228,273,274,485,629-635,637]. Chapter 7 reported important findings regarding fall prevalence, as well as associations between balance and falls and the prognostic accuracy of the one-legged stand. There are several important conclusions to be drawn.

First, poor balance ability in midlife and subsequent falls are not health issues constrained to those aged ≥65 [639,646]. Meaningful variations in balance ability were seen in NSHD from age 53 to 69, and are hypothesised to begin at earlier ages [25,42]. Falls before the age of 65 are not atypical [639]; 21.9% and 22.7% of women experienced one or more falls at age 53 and 60-64, respectively. Using age 65 as a cut point for older adults in both clinical and research practice has its origins possibly as far back as the late 1800s [730,731]. While this definition continues to be commonly used [732], it has also become recognised that ageing is a lifelong process occurs at different rates in individuals [75,732,733]. The importance of extending balance and fall- research and clinical practices to adults under the age of 65 has been consistently shown throughout this thesis. Adapting falls prevention, screening and policies to include younger individuals could have a positive impact at both the individual and population level.

Second, the results of the regression analyses suggest an association between balance ability and falls. Improving an individual's balance ability can improve their reaction to disturbances, allowing them to correct body position to maintain stability and avoid a fall. Individuals who experience minor, singular falls – often accidental falls – are not necessarily indicative of the targeted at-risk fall population, as they demonstrate similar characteristics to non-fallers [641,642]. This is consistent with stronger associations for high-risk fallers (i.e. injurious or recurrent falls), which suggests that clinical significance can be maximised by targeting individuals at greatest risk. This can ensure that fall-related resources, such as in-home risk assessments, balance training programmes, and regular examinations, are appropriately allocated.

Finally, it was demonstrated that an observational association does not necessarily translate to prognostic accuracy. While this thesis examined associations of balance ability in midlife (ages 53 and 60-64) with subsequent falls risk rather than in a traditional sample aged ≥65, evaluation of the existing evidence in older samples suggests similar conclusions [30,253,485,629-633]. Lack of caution when translating evidence in major media articles [734-737] has led to public recommendations that testing one's one-legged balance ability can help them better understand their risk of falls, dementia, cerebral small vessel disease, stroke, and premature mortality. This comes despite caution from authors that this test is not ready to be used as a screening tool to identify at-risk individuals in the general population [737]. Short term, it is important to ensure that observational associations are not translated into screening tools without well-defined evidence. While the one-legged balance test provides an easy, feasible and inexpensive screening tool, accuracy remains the most important criterion for translation to a screening tool. Chapter 7 indicated that sufficient levels of sensitivity and specificity were not met within the NSHD sample. The one-legged balance test may be too rudimentary to distinguish falls risk in a general community-dwelling sample, as it only tests a static aspect of balance ability. More sensitive balance assessments (e.g. postural sway measured by a force plate) or aggregate screening tools (e.g. Framingham Risk score for cardiovascular risk) may be required to predict such a complex outcome. The sensitivity of the one-legged test in comparison to postural sway is discussed further in sections 8.3.2 and 8.4.4.

8.3 Methodological considerations

This section addresses the shared methodological considerations that relate to the whole of the thesis: NSHD data, assessment of balance ability, statistical methodology and generalisability of findings.

8.3.1 NSHD data

The advantages and disadvantages of using NSHD data were previously described in Chapter 2 (section 2.1.3), however this final chapter provides an opportunity to reflect further in the context of the thesis findings. This extensive investigation of a life course approach to balance has relied exclusively upon NSHD data. NSHD provides prospectively ascertained information on SEP, developmental factors, health behaviours, health status, and falls as well as repeated measures of balance ability and several domains of cognitive ability in mid and later life. While some studies have prospectively measured early or midlife factors and others have measured balance performance at multiple ages, arguably, no study has life course data that could appropriately address the key questions examined in the thesis. As such, the life course investigation of balance would only have been possible using the NSHD data.

As with any prospective cohort study, there are limitations due to several potential sources of bias. Key explanatory factors and balance ability are prospectively and objectively measured, although recall bias may have had an impact on the falls data as individuals were asked to report if they had experienced a fall within the last twelve months (as discussed in Chapter 7, section 7.4.3). Alternate methods of fall reporting such as fall diaries, regular phone calls by research nurse or pre-stamped post cards could reduce recall bias over the lengthy twelve-month period. Even with improved tracking of falls, underreporting of falls is common [738-741] and likely contributes to an underestimation of the true association between balance and falls. Underreporting of falls could be due to inability to remember a fall or differing perceptions of a fall between study members and researchers or health care professionals [742-744]. Recurrent and injurious falls, which were shown in Chapter 7 to be a greater cause for concern (section 7.4.2.2) may be more likely to be reliably recalled than a single or an inconsequential fall. Furthermore, study members were not asked about potential causes of a fall or details about the situation preceding a fall and as a result, there could be no differentiation between falls due to accidental hazards, loss of balance/stability, syncope or other causes. Falls caused by syncope, a sudden transient loss of consciousness, would reflect an underlying cardiovascular abnormality rather than a consequence of poor balance ability [745,746], as has been discussed for the majority of this thesis.

NSHD has aimed to minimise individuals lost to follow-up through participant engagement and ongoing communications [302]. The employment of research nurses to collect data has also minimised missing data at each wave. Consequently, NSHD has an extremely high response rate (>80% of target sample at each wave), while individuals who participate in a data collection wave have very little missing data at that wave. However, analyses of NSHD data have previously identified that individuals with missing data or those lost to follow-up have lower SEP across life, participate in unhealthy behaviours and are more likely to be in poor health [302,303]. Investigation of missing balance data in Chapter 2 demonstrated that those with missing balance or those lost to follow-up were more likely to have lower balance ability at other ages. Due to an overrepresentation of those with better balance ability included in analyses, it is hypothesised that this may lead to an underestimation of the associations reported throughout the thesis. Several analytical steps were taken to minimise bias from missing data and loss-to follow up; these are explored further in section 8.3.3.

The main explanatory and outcome variables used in the thesis – balance ability and cognitive ability – were collected by trained research nurses using standardised testing protocols; this aimed to reduce within and between subject reliability. As collection of NSHD data occurred prior to the commencement of this thesis, there was no opportunity to provide input on data collection. More parameters of balance ability could have been attained by performing the one-legged stand on a force plate, however this was neither logistically feasible nor economically possible. Furthermore, the age of participants at collection waves and the time between waves is historically determined. It would have been preferable for measurements of balance and cognition to have been taken at short, regular intervals with age homogeneity of the assessment wave that occurred between ages 60 and 64. More frequent assessment and greater numbers of assessment points could have allowed the identification of potential non-linear changes in balance ability that occurred from age 53 to 69 (discussed further in section 8.4.1). For example, if more than three balance assessments were collected, non-linear model fits could have been tested including quadratic, cubic and other polynomial models as well as piecewise models that would allow different slopes at different time periods, as has previously been examined [522].

8.3.2 Assessment of balance ability

Previously in the thesis, Chapter 1 (section 1.2) explored common balance measurements and identified their limitations including subjective assessments (e.g. Berg balance test), inability to assess balance in isolation (e.g. chair stands, TUG) and cost (e.g. force plate). Limitations of these tests explain why the one-legged balance test is the most common assessment of balance ability in large cohort studies and, specifically, why it was included in the battery of physical capability tests in NSHD.

There are several advantages to using the one-legged balance test. First, there is no cost and requires little to no equipment (e.g. stopwatch), which is important given that many nurses carried out home visits. The test has high inter-rater and test-retest reliability [25,747-751], which reduces concern of bias resulting from using multiple research nurses to collect data. The test can be carried out by different research nurses, following a clear study protocol (see Appendix 2.1). This was beneficial in NSHD due to the large sample size and ensuing necessity to have many research nurses collect data. Furthermore, there is strong content and predictive validity as many studies have consistently demonstrated associations between lower one-legged balance performance and higher risk of poor health outcomes including falls, disability, poor mobility, frailty and premature mortality [77,247,630,635,752,753].

Despite these strengths and its widespread use in both clinical and research settings, the one-legged stand test has several limitations, most notably ceiling and floor effects. Ceiling effects can be common in younger adults who are able to maintain the position for the maximum time. This effect was seen in the distribution of the eyes open test at all ages in Chapter 2 (section 2.3) and is the primary reason why the eyes closed test was used in all analyses throughout the thesis. Conversely, floor effects are also common with the eyes closed test at older ages [25,748]. This is why progressive balance tests of side-by-side, semi-tandem and tandem positions are commonly used to test balance ability in older adults. However, comparison of these scores across time is difficult as variation in scores on this test do not emerge until later ages [13]. NSHD was limited by both floor and ceiling effects at different ages, as no single test condition (e.g. eyes open or eyes closed) could capture the full range of functional ability of the sample from age 53 through to age 69.

The one-legged stand could be considered a less sensitive measure of balance compared with force plates as it does not distinguish subtle differences in body position when maintaining balance. Furthermore, the one-legged test assesses an individual’s static balance, which may have reduced external validity in a real-life setting, where dynamic balance is more commonly relied upon. In order to avoid a ceiling effect in a middle-aged cohort – as found in the eyes open test in Chapter 2 (section 2.3) – scores from the eyes closed test were utilised throughout the thesis. This could further limit the generalisability of one-legged balance ability to a real life setting as visual input often contribute to maintenance of an upright balanced position. The unit of balance ability was also improved between waves at age 53 and at age 60-64 (seconds vs milliseconds), allowing for the same protocol to be followed with improved sensitivity.

Finally, it is important to acknowledge that the assessment of balance ability at three different ages across midlife is a major strength, as collection of standardised, repeat measures of balance performance is rare. Collection of balance ability in childhood and in early adulthood would improve understanding of balance ability across the life course; this is discussed further in section 8.4.1. Tracking balance trajectories across all stages of life could also help identify peak balance performance and the age at which decline begins to occur.

8.3.3 Statistical analysis

The analytical methodology was a major strength of this thesis. Meticulous consideration identified the most appropriate model for each chapter objective. In Chapters 3 to 5, multilevel models were employed to account for within and between individual variation, to maximise sample size of each analysis and to examine how associations between risk factors and balance changed with age. By clustering at the individual level, the models reduced bias by avoiding the assumption of independent observations of balance. As identified in Chapter 6 (section 6.1.2), only one previous study appropriately modelled the bidirectional association between balance and cognition. Chapter 6 addressed this lack of evidence by employing two methods to test for bidirectional associations: dual change score models and autoregressive cross-lagged models. Although there were challenges with fitting the dual change score models, both models formally tested the bidirectional associations, rather than relying on inference based on distinct unidirectional models. Most previous studies that examined one-legged balance and falls risk inferred conclusions about diagnostic and prognostic screening tools from comparison of means or regression analyses rather than appropriate prognostic statistics. In Chapter 7, ROC curves were used to appropriately assess the predictive ability of balance as a screening tool. This enabled comparison of the predictive ability of a main balance model with several alternative models (e.g. sex only, history of falls).

Several analytical steps were taken in order to minimise potential bias dues to missing data. Binary indicators for mortality and attrition were included as covariates in adjusted models throughout the thesis (described in Chapter 2, section 2.4.4). Multilevel models permit missing outcome data, therefore allowing the inclusion of individuals who participated in one or more clinic visits between ages 53 and 69. To ensure that missing covariate data did not bias the results, both maximal sample and complete cases estimates were provided for sex-adjusted associations. This also enabled comparison of sex and fully adjusted models within the same sample. Finally, individuals who were missing balance data due to inability to complete the balance test for health reasons were assigned a score of 0 seconds. As explored in Chapter 2 (section 2.2.2), this strategy is hypothesised to reduce bias compared with using those with a measured time only. While both the exclusion and inclusion of these individuals can be argued to introduce some bias, excluding these individuals assumes that they are missing at random. However, this is not accurate as these individuals are more likely to have lower balance performance (Chapter 2, section 2.2.2).

As many different covariates were included in analyses, it is important to discuss the role of potential confounders and mediators. A *confounder* is a variable that can influence the association between a dependent variable and the main independent variable, by way of its individual association with both variables [754]. For example, height is associated with both childhood coordination and balance ability and thus, could confound the association between co-ordination and balance. A *mediator* is part of the causal pathway between the independent variable and the dependent variable [754]. For example, in a hypothesised pathway of childhood cognition to adulthood cognition to midlife balance ability, adulthood cognition could be considered a mediator. Distinguishing between confounders and mediators is not possible statistically as the two are mathematically equivalent [754]. Formal mediation analysis relies on strong assumptions about mechanisms of association [755], which are not always appropriate, particularly when considering the complexity of contributing factors across the life course. Rather than apply these mediation techniques, caution was taken in making any assumptions about causal pathways throughout the life course. Hypotheses were suggested in the discussion of each chapter but no assumption about mediating pathways can be assumed.

8.3.4 Generalisability

While the sample is representative of individuals born in England, Scotland and Wales in 1946, it consists exclusively of Caucasians. Racial disparities in balance ability have not been assessed in a UK or European sample, however USA-based evidence suggests that there are racial disparities in falls risk. Black American older adults have lower falls prevalence compared with their white counterparts [756-759]. This is despite American Caucasians having fewer risk factors for falls such as higher physical capability [757] and fewer comorbidities [258]. Further investigation of racial patterns in balance ability and falls risk in UK or European data is necessary as USA findings may not be generalizable to other countries given the substantial correlation between socioeconomic disparities and race in the USA [760-762].

Contextual circumstances that occurred throughout the participants’ lives must also be considered. Born shortly after the end of World War II, study members experienced rationing throughout their early childhood as well as substantial political, economic and technological changes throughout their life [308]. While rationing makes comparability to more recent born cohorts difficult, it also reduces the likelihood of confounding by nutritional factors. Study members also experienced several recessions, culminating in the Great Recession of 2008 that, for many, coincided with retirement [763]. There have been drastic changes in occupations in the last half century, shifting from physically demanding, labour-based jobs to cognitive-based professional, managerial or clerical careers [764]. Cross-cohort analysis of cohort effects in cognition have suggested that cognitive ability is higher in more recent cohorts compared to older ones [765,766]. It has not been investigated if the role of cognition in balance has changed over time, although it is hypothesised that increased cognitive functioning in the general populations could have strengthened these neural pathways.

8.4 Future work

This thesis has extended the evidence on factors across life associated with balance ability and extended understanding of how balance ability is associated with subsequent falls in midlife. Replication of these findings are necessary to strengthen the evidence reported here. Thesis findings have motivated several other areas of future research including 1) further contribution to the life course approach to balance, 2) identifying mediating pathways between factors across life, balance and falls, 3) psychological factors (e.g. fear of falling, symptoms of depression/anxiety) that impact balance ability, and 4) translational research that can implement thesis findings into primary care and public health prevention efforts. These areas are explored in the following sections.

8.4.1 Expanding life course approach to balance

Collection of the 25th wave of NSHD data collection is due to begin in 2020. As further measures of cognitive and physical capability continue to be collected, the analyses presented in this thesis should be extended to examine how findings change with increasing age. Balance performance and its association with the factors examined throughout this thesis (e.g. cognition, health status, SEP, etc.) have changed considerably throughout midlife and one could expect these changes to continue as individuals reach their eighth and ninth decades of life.

Multilevel models consider mean change in the full sample; as such, individual trajectories were not examined. It is apparent that individuals exhibit different patterns of balance ability in mid to later life. SEM approaches could identify latent classes of balance performance including those who did not exhibit decline, those who exhibited varying degrees of decline and even those who improved with age. Subsequently, this could enable investigation of factors across life that may precede specified balance trajectories. With further collection of balance ability, non-linear trajectories at both an individual and sample level (e.g. mean change) could also be modelled. This could help distinguish individuals who demonstrate earlier or steeper declines in balance ability.

Balance ability in childhood was not measured in NSHD and thus it is not possible to expand understanding of the life course balance trajectory by examining associations between childhood and adulthood balance ability. It is hypothesised that development of balance ability in early life could mirror decline in later life; this would reflect a crucial role of early neural development. Associations of better motor coordination in childhood with adulthood balance ability from Chapter 4 support the idea of early neural coupling of cognitive and balance processes. This is considerably difficult to test given the need for a longitudinal cohort (e.g. birth cohort or similar), however it could be feasible in the National Childhood Development Study (NCDS; 1958 British birth cohort), or the 1970 British Cohort Study (BCS70). In NCDS, four balance skill tasks were assessed at age 11: walking backwards along a straight line, standing on the right foot for 15 seconds, standing on the left foot for 15 seconds, and standing heel to toe for 15 seconds. In the BCS, five tasks were utilised: walking backwards along a straight line, along with movement of hand when standing on each leg, and movement of foot when standing on each leg. A recent study used latent class analysis to identify balance profiles in these two studies [767]; analyses could be extended to examine the association with balance in mid and later life. One-legged balance ability was assessed at age 46 in the 1970 cohort and will be assessed at age 62 in the 1958 cohort (anticipated 2020).

Assessment of bidirectional associations in NSHD was limited by the availability of longitudinal cognitive data, as only verbal memory and search speed were measured across multiple waves. These two domains were intentionally selected as they are known to change with age [461,462], whereas crystallised measures of cognition (such as reading ability) remain more stable over time. However, understanding how associations of reaction time, for example, with balance ability change with age could provide further information on both automated and reactive neural processes involved in balance performance.

8.4.2 Combining risk factors, balance ability and falls

There is scope to expand the findings of this thesis by linking two major aims: how factors across life are associated with balance ability and how balance ability is associated with falls risk. Future research could examine if socioeconomic, health behaviour, health status and cognitive factors are associated with falls. It is hypothesised that balance ability could be on the causal pathway between early and midlife risk factors and falls. For example, low levels of physical activity could be related to falls via a balance, muscle mass and mobility pathway. Impaired cognitive ability is also known to be associated with higher risk of falling [510,768-770], and balance could also mediate this association. As noted in section 8.3.3, inference about potential mediating factors must be cautious. Analysis of longitudinal cohort data using more advanced and appropriate causal methods could test these hypotheses [771].

8.4.3 Fear of falling, depressive symptoms and balance

Despite the rising levels of depression and anxiety in older adults in more research years [716] and increased consideration of physical capability in older adults, the role of psychological health in relation to balance ability is not a common area of investigation. Preliminary evidence has suggested that several psychological factors such as fear of falling or presence of symptoms of depression/anxiety are associated with lower balance performance at age 69 [772]. This is consistent with results from Chapter 3 which reported an increase in the association between symptoms of depression and anxiety and balance with age.

The definition of fear of falling has continually evolved, but is generally understood to be an ongoing apprehension of falling that leads to an unhealthy avoidance of activity [773,774]. Others have suggested that fear of falling directly reflects an individual's lack of confidence in their balance abilities [227,253,775]. In some situations, fear of falling may have a protective effect on fall risk as a result of increased caution and careful deliberation about everyday physical activity [776]. More commonly, it can have a debilitating impact on balance ability and fall risk by impacting activity levels and altering body position. Activity restriction is common in individuals with fear of falling, and can increase sedentary behaviour while minimising physical activity at all levels [776]. This may have a negative impact on dynamic balance skills, whilst contributing to sarcopenia and reduced mobility.

Furthermore, individuals who fear falling tend to have slower gait, a stiffer posture and take shorter steps; these subconscious adaptations can decrease balance stability and increase falls risk by reducing the base of support (e.g. feet closer together) [239,241,242]. Fear of falling is also associated with decline in cognitive function [777], suggesting an additional possible contributor to poor balance ability acting via executive dysfunction.

In addition to activity restriction, biological mechanisms may also explain associations between depressive symptoms and balance. An inflammation hypothesis suggests that co-occurrence of depression and inflammatory joint diseases is common [778]. Increased inflammatory markers that are present in arthritis, such as C-reactive protein or nitric oxide [779], are also more common in individuals with depression than those without. This may explain why individuals with arthritis are more likely to develop depression and vice-versa [778,780]. A recent review has highlighted the need for further consideration of a biopsychosocial framework to explain these bidirectional associations [778].

While traditional risk factors for balance ability and other measures physical capability have focused on socioeconomic, behavioural or physical health factors, psychological factors may play an independent role in balance performance. Further evidence from observational data and RCTs is required as interventions targeting these specific psychological factors could have positive benefits on balance ability and falls risk.

8.4.4 Translational falls research

Falls is often the primary outcome of interest when investigating balance ability, which explains why Chapter 7 focused solely on falls. However, balance ability has been linked to several other health outcomes including cognitive decline [290,781], fractures [782-784], frailty [785] and hospitalisation [786]. Within NSHD, it has been reported that standing balance time at age 53 was more strongly associated with mortality than grip strength or chair rise speed [247]. The association between objective measures of physical capability and mortality may be because physical capability scores can indicate both clinical and preclinical ageing processes that eventually manifest as disease, disability, general health or death [247]. Thus, it is important to consider that balance ability may be a key indicator of other health outcomes aside from falls. While the section below focuses on translational falls research, further research should also consider the utility of balance screening tests for non-fall related outcomes.

While there is a strong empirical and theoretical basis for the association between balance ability and falls, evidence presented in this thesis suggests that the one-legged balance test is not an accurate predictor of falls in midlife. There is the need to identify an accurate and reliable measure that can be established and used in primary care to replace the heterogeneity and current inadequacy of screening tools. There is some evidence that postural sway – as measured by a force plate – could accurately indicate falls risk [635]. A force plate can identify small changes in postural sway and identify variability in a heterogeneously aged sample without floor or ceiling effects [787,788]. To date, the cost and feasibility of using force plates have been major limiting factors. However, costs of force plates are decreasing [677] and there is evidence that low-cost portable prototypes have sufficient validity and reliability [678,679]. Before recommendations about implementing standard force plate assessments into primary care can be made, research must investigate its utility as a predictive tool for falls risk. With a partnership with a local GP surgery, prospectively ascertained postural sway (measured via a force plate during appointments) and assessment of subsequent falls could test the hypothesis that postural sway is an accurate indicator of falls risk. Given that postural sway increases from early midlife (i.e. aged ≥40) [787], such a study should examine both middle and older aged adults to determine if this approach can be extended to multiple life stages.

Several interventions aimed at minimising falls risk have directly targeted balance ability; this includes Tai Chi [789], aquatic training [790], balance-enhancing insoles [791] and balance and resistance training [278,281]. Evidence of an observational association between balance and falls (Chapter 7) further support these intervention types. Nevertheless, it has become increasingly clear that there is no ‘one size suits all’ fall prevention intervention [792]. This is unsurprising given the heterogeneity of falls (e.g. single vs recurrent, injurious vs non-injurious, intrinsic vs extrinsic cause, etc.). While some have suggested that multifactorial approaches are the most effective [571], others report that usual care in older adults is equally as effective as multifactorial interventions [793,794]. The success, or failure, of these interventions mainly depends on three crucial factors: content, process and choice of target group [794]. Most importantly, findings from this thesis could inform the *content* of multifactorial interventions by identifying cognition and balance as appropriate domains and *choice of target group* by identifying those at highest risk; this could include identifying the most appropriate age range or the most appropriate risk factor, as identified in this thesis (e.g. health status). Future research should consider an RCT to examine and compare the efficacy of three interventions to improve fall outcomes: 1) balance only; 2) cognition only; 3) balance and cognition. A combined balance and cognition intervention is hypothesised to have greatest efficacy in reducing falls risk; additionally, such an intervention is likely to have a positive impact on other areas of health.

As outlined in section 8.2.3, further research on falls in individuals under the age of 65 is needed. This thesis has conclusively shown that fall prevalence at this age is not negligible and that associations of balance with falls risk clearly emerge before the age of 65. Where possible, future research on falls in both cohort studies and in primary care should extend their scope to examine a wider age range, at minimum beginning to examine those in midlife (i.e. at minimum aged ≥50). Fall prevention guidelines in primary care need to be extended to include recommendation for those under the age of 65. Earlier understanding of falls risk can ensure appropriate interventions for individuals with the highest need.

8.5 Concluding remarks and final thoughts

This PhD thesis has examined a life course approach to balance ability using data from the MRC National Survey of Health and Development with several key conclusions. First, numerous factors across life – including sex, SEP, health behaviours, health status, and cognition – contribute to balance ability and these associations change with age. Second, there is primarily a unidirectional association between cognitive ability and subsequent balance, with distinct cognitive domains exhibiting different strengths of association with balance. Finally, there is a clear observational association between balance and falls, however further research is needed to identify an appropriate balance screening tool to accurately predict falls risk and assess prognostic accuracy at different ages.

Despite stronger evidence of association between balance ability and mortality [247] compared with other domains of physical capability, there has been less research on balance ability than other physical capability measures including grip strength and walking speed. Thus, this thesis has substantially added to multiple areas of the literature. It provides further support for a life course approach to healthy ageing by identifying multiple intervention targets across life for balance ability (as shown in Chapters 3 and 4). This is particularly important in the current UK climate, with socioeconomic inequalities continuing to rise, rising rates of child poverty and "systematic immiseration" [699]. The evidence presented here provides further support for public services such as Sure Start to address some of these challenges [690,691,694]. It also identifies appropriate intervention targets for different ages in mid and later life, thereby maximising potential impact.

Research on ageing has often examined cognitive and physical domains in isolation, despite theories of common biological processes that may explain changes in both cognitive and physical capabilities [211]. The comprehensive analysis of cognitive domains and balance ability suggests that these constructs should be considered together. The complex, inter-related nature of these constructs (as shown in Chapters 4, 5 and 6) suggest that research in one domain is likely to inform understanding of the other. This could have influential and widespread benefits across several areas of research including: understanding of biological mechanisms, identification of impairments in either domain and organisation of targeted interventions.

This thesis identified that the translation of observational balance-falls associations before establishment of prognostic evidence is problematic. In the short term, this highlights the need for caution in using the one-legged stand to predict falls, while suggesting that other promising measures (e.g. postural sway as assessed by technology) may be used for both falls risk and other health outcomes associated with balance ability. The intent is to carry findings from this thesis forward into future epidemiological research in physical capability and ageing. When considering meaningful outcomes in ageing, balance ability should continue to be regarded as a distinct outcome, alongside other measures of physical capability and frailty, and other indicators of both physical and cognitive health.

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APPENDICES

Appendix 2.1 Nurse's Manual of Procedures 2015, balance module

Standing balance

Introduction:
Balance and coordination are necessary to carry out every day physical tasks at reasonable speeds. Poor balance will be a major cause of falls and fractures as the cohort gets older. You will be prompted to ask the study members if they are willing to attempt two standing balance tests. This involves standing on one leg, up to a maximum of 30 seconds, once with eyes open and once with eyes closed.

Equipment:

- Stop-watch (instruction for use on page 14).

START MODULE

PROCEDURE

READ OUT:
"I would now like to assess your balance and coordination. First I will ask you to fold your arms and, after I say *'And Go'*, stand on your preferred leg and raise your other foot off the floor like this…."

DEMONSTRATE THE TEST

READ OUT:
"I will ask you to hold this position for as long as you can or until I tell you to stop. Then I want to repeat the test with your eyes closed. Are you willing to do this test with your eyes open?"

NOTE:
Exclusion criteria:

- *Inability to stand or walk unaided without zimmer frame or crutches*

If the participant is unwilling or unable to do this test please select the appropriate response option AND then record the reason in the text box. Please provide as much information as you can. This is the end of the test for these participants.

If the participant is willing and able to do the test please select 'Yes' and perform the test, with eyes open as follows:

PROTOCOL (EYES OPEN):

1. Make sure there is a firm support nearby.
2. Shoes should be removed unless they have flat heels.
3. Ask the participant to fold their arms
4. Remind them again that after you say 'And go', you want them to stand on their preferred leg and raise the other leg off the ground a few inches keeping their foot parallel to the floor
5. Allow the participant to practice
6. Check that the stop-watch reads 0:00$_{00}$ and that the participant is stood near a firm support with their arms folded
7. Say '**And go**!', and start the stop-watch as the participant raises one leg off the ground

8. Stop the stop-watch either a) when the raised leg touches the floor as the participant loses their balance or b) after 30 seconds, whichever happens first.
9. Record the time on the stop-watch to 1/100th second on CAPI
10. If the participant falls over straight away and you are unable to record a time please select ‘Fell over straight away’

After completing the test with eyes open,

READ OUT:
“Are you willing to do this test again with your eyes closed?”

If the participant is unwilling or unable to do this test with their eyes closed please select the appropriate response option AND then record the reason in the text box. Please provide as much information as you can. This is the end of the test for these participants.

If the participant is willing and able to do the test please select ‘Yes’ and perform the test, with eyes closed, using the same protocol as above, as follows:

PROTOCOL (EYES CLOSED):

1. Remind the participant again that after you say ‘And go’, you want them to stand on their preferred leg, close their eyes and raise the other leg off the ground a few inches keeping their foot parallel to the floor
2. Allow the participant to practice
3. Check that the stop-watch reads 0:00₀₀ and that the participant is stood near a firm support with their arms folded
4. Say ‘And go!’, and start the stop-watch as the participants raises one leg off the ground (and closes their eyes)
5. Stop the stop-watch either a) when the raised leg touches the floor as the participant loses their balance or b) after 30 seconds, whichever happens first.
6. Record the time on the stop-watch to 1/100th second on CAPI
7. If the participant falls over straight away and you are unable to record a time please select ‘Fell over straight away’
8. End of test

<u>Submit Module</u>

Appendix 2.2 Median (Q1, Q3) eyes open balance times (seconds) and proportion with balance >5seconds (%) by missing data groups at ages 53, 60-64 and 69 [comparable to Table 2.2 for eyes closed]

Group (n)	**Description**	**Age 53**		**Age 60-64**		**Age 69**	
		Median (Q1, Q3), % >5sec	**p-value[¥]**	**Median (Q1, Q3), % >5sec**	**p-value[¥]**	**Median (Q1, Q3), % >5sec**	**p-value[¥]**
1 (n=1659)	Valid time at 53, 60-64, 69	30 (30, 30) 96.8%		30 (13.77, 30) 89.2%		29.22 (9.65, 30) 84.5%	
2 (n=654)	Valid time at 53 only	30 (14, 30) 88.7%	<0.001				
3 (n=51)	Valid time at 60-64 only	-	-	15.81 (4.77, 30) 72.6%	<0.005	-	
4 (n=48)	Valid time at 69 only	-	-	-		27.47 (5.41, 30) 77.1%	0.31
5 (n=330)	Valid time at 53, 60-64 only	30 (22, 30) 94.2%	<0.005	23.05 (7.35, 30) 81.2%	<0.001	-	-
6 (n=235)	Valid time at 53, 69 only	30 (25, 30) 92.8%	0.07	-	-	22.00 (6.65, 30) 81.3%	<0.01
7 (n=82)	Valid time at 60-64, 69 only	-		21.54 (9.06, 30) 85.4%	<0.01	19.19 (4.33, 30) 73.2%	0.01

[¥] *Dunn's test for statistical differences from Group 1 (those with a valid balance time at all 3 ages)*

Q1= quartile 1 (25th percentile); Q3= quartile 3 (75th percentile)

Appendix 2.3 Median (Q1, Q3) eyes open balance times (seconds) by missing data groups at ages 53, 60-64 and 69 [comparable to Table 2.3 for eyes closed]

	Age 53		**Age 60-64**		**Age 69**	
	Median (Q1, Q3), n	**p-value**[¥]	**Median (Q1, Q3), n**	**p-value**[¥]	**Median (Q1, Q3), n**	**p-value**[¥]
AGE 53 status						
Valid time at age 53	-		30 (12.69, 30) n=1934		28.86 (9.19, 30) n=1844	
Unable to complete due to health reasons	-		25.17 (3.23, 30) n=32	<0.05	30 (16.56, 30) n=25	0.31
Missing data- unrelated to health reasons	-		23.22 (9.21, 30) n=156	<0.05	21.28 (5.52, 30) n=155	<0.01
AGE 60-64 status						
Valid time at age 60-64	30 (30, 30) n=1981		-	-	28.87 (9.45, 30) n=1740	
Unable to complete due to health reasons	18.5 (7, 30) n=68	<0.001	-	-	8.62 (3.22, 22.59) n=30	<0.001
Missing data- unrelated to health reasons	30 (18, 30) n=829	<0.001	-	-	25.86 (7.12, 30) n=254	0.10
AGE 69 status						
Valid time at age 69	30 (30, 30) n=1858		30 (13.69, 30) n=1711		-	-
Unable to complete due to health reasons	22 (10, 30) n=108	<0.001	8.49 (3.9, 30) n=71	<0.001	-	-
Missing data- unrelated to health reasons	30 (18, 30) n=912	<0.001	25.18 (8.14, 30) n=340	<0.001	-	-

[¥] Dunn's test for statistical differences from Group 1 (those with a valid balance time at all 3 ages)
Q1= quartile 1 (25th percentile); Q3= quartile 3 (75th percentile)

Appendix 3.1 Associations between covariates and balance ability re-centred at ages 60-64 and 69 in sex-adjusted multilevel models.

	Change in balance time at age 60-64 per covariate unit		**Change in balance time at age 69 per covariate unit**	
Covariates [a]	Coefficient (95% CI)	*p-value*	Coefficient (95% CI)	*p-value*
1: Sex (female)	-0.114 (-0.152, -0.076)	<0.001	0.070 (-0.119, -0.021)	<0.005
2: Height (cm)	No change with age, see estimates in Table 3.1.			
3: BMI (kg/m^2)	No change with age, see estimates in Table 3.1.			
4: Paternal occupational class [b] (per 1 level change)	-0.096 (-0.123, -0.069)	<0.001	-0.065 (-0.100, -0.031)	<0.001
5: Maternal education [c] (per 1 level change)	-0.077 (-0.095, -0.059)	<0.001	-0.055 (-0.079, -0.032)	<0.001
6: Education at age 26 [d] (per 1 level change)	-0.081 (-0.094, -0.067)	<0.001	-0.062 (-0.080, 0.045)	<0.001
7: Own occupational class [b] (per 1 level change)	No change with age, see estimates in Table 3.1.			
8: Leisure time physical activity				
Ref: None				
1-4 times/month	0.173 (0.128, 0.219)	<0.001	0.134 (0.066, 0.202)	<0.001
≥5 times/month	0.194 (0.157, 0.232)		0.171 (0.117, 0.224)	
9: Smoking (per 1 level change) [e]	No change with age, see estimates in Table 3.1.			
10: History of diabetes [f]	No change with age, see estimates in Table 3.1.			
11: History of cardiovascular events [f]	No change with age, see estimates in Table 3.1.			
12: Respiratory symptoms [f]	No change with age, see estimates in Table 3.1.			
13: Knee pain [f]	-0.175 (-0.214, -0.137)	<0.001	-0.216 (-0.271, -0.160)	<0.001
14: Symptoms of anxiety/depression (per 1 SD) [g]	-0.079 (-0.095, -0.062)	<0.001	-0.094 (-0.118, -0.071)	<0.001
15: Adult verbal memory (per 1 SD) [g]	0.095 (0.077, 0.112)	<0.001	0.071 (0.047, 0.094)	<0.001

[a] all models adjusted for sex as no evidence of sex interactions (see Table 3.2); [b] ref: I Professional or II Intermediate; [c] ref: Secondary and further education; [d] ref: Degree or higher; [e] ref: Current smoker; [f] red: Individuals with no health condition; [g] SD estimates at each age are provided in Table 2.1

Appendix 3.2 Categorical estimates for associations of SEP indicators and smoking with balance ability in individual regression models [same models as Table 3.1]

		Change in balance time at age 53 per covariate unit (intercept)		**Age (yr)*covariate interaction**	
Covariates	n participants (n observations)	Coefficient (%) (95% CI)	p-value	Coefficient (%) (95% CI)	*p-value*
4: Paternal occupational class					
Ref: I or II	2947 (6838)				
III		-0.124 (-0.187, -0.061)	<0.001	0.003 (-0.002, 0.008)	<0.001
IV or V		-0.296 (-0.368, -0.223)		0.010 (0.005, 0.016)	
5: Maternal education					
Ref: 2▫ and FE or higher					
2▫ only	2768 (6424)	-0.008 (-0.119, 0.102)		-0.004 (-0.013, 0.004)	
1▫ only and FE		-0.165 (-0.270, -0.061)	<0.001	0.003 (-0.005, 0.011)	<0.001
1▫ only		-0.299 (-0.384, -0.214)		0.008 (0.001, 0.015)	
6: Education at age 26					
Ref: Degree or higher					
A level or equiv	2935 (6830)	-0.124 (-0.220, -0.028)	<0.001	-0.0001 (-0.008, 0.008)	<0.001
O level		-0.250 (-0.351, -0.149)		0.002 (-0.006, 0.010)	
Sub GCE		-0.379 (-0.504, -0.253)		0.004 (-0.006, 0.014)	
None		-0.451 (-0.543, -0.358)		0.011 (0.003, 0.018)	
7: Own occupational class					
Ref: I or II	3075 (7167)		<0.001	Not significant	0.14
III		-0.153 (-0.194, -0.113)			
IV or V		-0.304 (-0.360, -0.247)			
9: Smoking					
Ref: Current smoker	3092 (6996)		<0.001	Not significant	0.53
Past smoker		0.080 (0.030, 0.130)			
Never smoked		0.126 (0.069, 0.183)			

Appendix 5.1 Correlation matrices of all continuous cognitive scores **i.** by test over time and **ii-v.** at each age (correlation coefficients, r, are presented)

i. Repeated cognitive tests, ages 43-69

	Age 53	**Age 60-64**	**Age 69**
Search speed (n=1628)			
Age 43	0.53	0.54	0.48
Age 53	-	0.57	0.51
Age 60-64	-	-	0.60
Verbal memory (n=1592)			
Age 43	0.64	0.66	0.60
Age 53	-	0.66	0.67
Age 60-64	-	-	0.66

ii. Cognitive tests at age 43 (n=2930)

	Verbal memory	**Picture memory**	**Pegboard time**
Search speed	0.16	0.08	-0.21
Verbal memory	-	0.28	-0.13
Picture memory	-	-	-0.15

iii. Cognitive tests and balance ability at age 53 (n=2707)

	Verbal memory	**NART**	**Verbal fluency**	**Balance ability, age 53**
Search speed	0.20	0.15	0.17	0.08
Verbal memory	-	0.53	0.36	0.14
NART	-	-	0.34	0.18
Verbal fluency	-	-	-	0.15

iv. Cognitive tests and balance ability at age 60-64 (n=2063)

	Verbal memory	**Delayed recall**	**Simple reaction time**	**Choice reaction time**	**Balance ability, age 60-64**
Search speed	0.20	0.19	-0.13	-0.24	0.06
Verbal memory	-	0.83	-0.20	-0.31	0.12
Delayed recall	-	-	-0.17	-0.26	0.08
Simple reaction time	-	-	-	0.47	-0.06
Choice reaction time	-	-	-	-	-0.10

v. Cognitive tests and balance ability at age 69 (n=1695)

	Verbal memory	**ACE (III) total**	**ACE (III) fluency**	**ACE (III) language**	**ACE (III) attention**	**ACE (III) memory**	**ACE (III) visuospatial**	**Balance ability, age 69**
Search speed	0.16	0.17	0.21	0.07	0.06	0.09	0.10	0.10
Verbal memory	-	0.58	0.41	0.32	0.18	0.54	0.27	0.09
ACE (III) total	-	-	0.68	0.56	0.52	0.77	0.56	0.11
ACE (III) fluency	-	-	-	0.30	0.18	0.32	0.26	0.07
ACE (III) language	-	-	-	-	0.13	0.35	0.25	0.05
ACE (III) attention	-	-	-	-	-	0.15	0.21	0.08
ACE (III) memory	-	-	-	-	-	-	0.29	0.06
ACE (III) visuospatial		-	-	-	-	-	-	0.11

Appendix 5.2 Cross-sectional associations of verbal memory and search speed (per SD change) with log-transformed balance time in multilevel models; adjustments for each covariate in turn (corresponds to models shown in Table 5.4).

	Change in balance time at age 53 per 1SD change in **verbal memory** n=2696 (obs=5533)				Change in balance time at age 53 per 1SD change in **search speed**			
					Men: n=1372 (obs=2756)		**Women**: n=1354 (obs=2846)	
	Coefficient per SD (95% CI), intercept	p-value	Age interaction (per SD/year) (95% CI)	p-value	Coefficient per SD (95% CI)	p-value	Coefficient per SD (95% CI)	p-value
M1: Age [a] and sex [b]	0.12 (0.10, 0.15)	<0.001	-0.005 (-0.007, -0.003)	<0.001	0.07 (0.04, 0.09)	<0.001	0.03 (0.01, 0.05)	<0.01
M2: M1 + death + attrition [c]	0.12 (0.09, 0.14)	<0.001	-0.005 (-0.007, -0.003)	<0.001	0.06 (0.04, 0.09)	<0.001	0.03 (0.01, 0.05)	<0.01
M3: M2 + anthropometric [d]	0.11 (0.09, 0.14)	<0.001	-0.005 (-0.007, -0.002)	<0.001	0.06 (0.04, 0.09)	<0.001	0.02 (-0.001, 0.04)	0.06
M4: M3 + health status [e]	0.11 (0.08, 0.13)	<0.001	-0.005 (-0.007, -0.003)	<0.001	0.06 (0.03, 0.08)	<0.001	0.02 (-0.001, 0.04)	0.06
M5: M3 + health behaviour[f]	0.10 (0.07, 0.12)	<0.001	-0.004 (-0.007, -0.002)	<0.001	0.05 (0.03, 0.08)	<0.001	0.02 (-0.002, 0.04)	0.07
M6: M3 + adult social class[g]	0.10 (0.07, 0.12)	<0.001	-0.005 (-0.007, -0.002)	<0.001	0.05 (0.03, 0.08)	<0.001	0.02 (-0.003, 0.04)	0.09
M7: M3 + education [h]	0.07 (0.04, 0.10)	<0.001	-0.003 (-0.005, -0.0002)	0.04	0.05 (0.03, 0.07)	<0.001	0.02 (-0.01, 0.04)	0.17
M8: fully-adjusted [i]	0.06 (0.03, 0.09)	<0.001	-0.003 (-0.005, -0.0001)	0.04	0.04 (0.02, 0.07)	<0.001	0.01 (-0.01, 0.04)	0.20

[a] Age is centred at age 53 = 0 in all models. [b]Adjusted for age, sex. [c]Adjusted for M1 + death, attrition. [d]Adjusted for M2 + height, height^2, BMI. [e]Adjusted for M3 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression. [f]Adjusted for M3 + smoking history, leisure time physical activity. [g]Adjusted for M3 + adulthood social class. [h]Adjusted for M3 + education. [i] Adjusted for all covariates in M1–7.

Appendix 5.3 Cross-sectional associations of cognitive tests at age 53 with log-transformed balance time at age 53 in individual regression models; adjustments for each covariate in turn (corresponds to models shown in Table 5.5)

	Change in balance time at age 53 per change in cognition							
	Verbal fluency (n=2507)		**Prospective memory** (n=2499)		**NART** (n=2423)			
	Coefficient per SD (95% CI)	p-value	Coefficient per unit (95% CI) [h]	p-value	Coefficient per SD (95% CI), linear term	p-value	Coefficient (95% CI), quadratic term	p-value
M1: Age and sex [a]	0.10 (0.07,0.12)	<0.001	1: -0.10 (-0.18, -0.01) 0: -0.16 (-0.27, -0.05)	<0.001	0.14 (0.11, 0.17)	<0.001	0.03 (0.01, 0.05)	0.01
M2: M1 + anthropometric [b]	0.09 (0.07, 0.12)	<0.001	1: -0.09 (-0.17, -0.01) 0: -0.16 (-0.27, -0.05)	<0.001	0.13 (0.10, 0.16)	<0.001	0.03 (0.004, 0.05)	0.02
M3: M2 + health status [c]	0.09 (0.06, 0.11)	<0.001	1: -0.09 (-0.18, -0.01) 0: -0.15 (-0.26, -0.05)	<0.005	0.13 (0.10, 0.16)	<0.001	0.03 (0.004, 0.05)	0.02
M4: M2 + health behaviours [d]	0.08 (0.05, 0.10)	<0.001	1: -0.08 (-0.16, 0.002) 0: -0.14 (-0.24, -0.03)	<0.005	0.11 (0.08, 0.14)	<0.001	0.02 (0.001, 0.04)	0.04
M5: M2 + adult social class [e]	0.07 (0.04, 0.10)	<0.001	1: -0.07 (-0.15, 0.02) 0: -0.11 (-0.22, -0.01)	0.01	0.09 (0.06, 0.12)	<0.001	0.02 (-0.001, 0.04)	0.06
M6: M2 + education [f]	0.06 (0.03, 0.09)	<0.001	1: -0.07 (-0.15, 0.01) 0: -0.12 (-0.22, -0.01)	<0.01	0.07 (0.03, 0.11)	<0.001	0.01 (-0.01, 0.03)	0.27
M7: Fully-adjusted model [g]	0.05 (0.02,0.08)	<0.001	1: -0.06 (-0.14, 0.02) 0: -0.09 (-0.19, 0.02)	0.04	0.05 (0.02, 0.09)	<0.005	0.01 (-0.01, 0.03)	0.30

[a] *Adjusted for age, sex.* [b] *Adjusted for M1 + height, height^2, BMI.* [c] *Adjusted for M2 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression.* [d] *Adjusted for M3 + smoking history, leisure time physical activity.* [e] *Adjusted for M2 + adulthood social class.* [f] *Adjusted for M2 + education.* [g] *Adjusted for all covariates in M1–6*

[h] *Reference category is those with both actions correct; estimates provided for one action correct, followed by no actions correct*

Appendix 5.4 Cross-sectional associations of cognitive tests at age 60-64 with log-transformed balance time at age 60-64 in individual regression models; adjustments for each covariate in turn (corresponds to models shown in Table 5.5)

	Change in balance time at age 60-64 per change in cognition					
	Delayed recall (n=1567)		**Simple reaction** (n=1576)		**Choice reaction** (n=1569)	
	Coefficient per SD (95% CI)	p-value	Coefficient per SD (95% CI)	p-value	Coefficient per SD (95% CI)	p-value
M1: Age and sex [a]	0.04 (0.02,0.07)	<0.005	-0.05 (-0.08, -0.02)	<0.005	-0.04 (-0.07, -0.01)	<0.005
M2: M1 + anthropometric [b]	0.04 (0.01,0.07)	<0.005	-0.04 (-0.07, -0.02)	<0.005	-0.04 (-0.07, -0.01)	<0.01
M3: M2 + health status [c]	0.04 (0.01,0.07)	<0.01	-0.04 (-0.07, -0.01)	<0.005	-0.04 (-0.07, -0.01)	0.01
M4: M2 + health behaviours [d]	0.03 (0.01,0.06)	0.02	-0.04 (-0.07, -0.01)	<0.01	-0.03 (-0.06, -0.004)	0.03
M5: M2 + adult social class [e]	0.02 (-0.004,0.05)	0.09	-0.04 (-0.06, -0.01)	0.02	-0.03 (-0.06, 0.002)	0.07
M6: M2 + education [f]	0.02 (-0.01,0.05)	0.22	-0.03 (-0.06, -0.004)	0.03	-0.02 (-0.05, 0.01)	0.12
M7: Fully-adjusted model [g]	0.01 (-0.02,0.04)	0.43	-0.03 (-0.06, -0.0005)	0.05	-0.02 (-0.05, 0.01)	0.25

[a] *Adjusted for age, sex.* [b] *Adjusted for M1 + height, height^2, BMI.* [c] *Adjusted for M2 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression.* [d] *Adjusted for M3 + smoking history, leisure time physical activity.* [e] *Adjusted for M2 + adulthood social class.* [f] *Adjusted for M2 + education.* [g] *Adjusted for all covariates in M1–6*

Appendix 5.5A Cross-sectional associations of ACE (III) total and component scores with log-transformed balance time at age 69 in individual regression models; adjustments for each covariate in turn (corresponds to models shown in Table 5.6)

	Change in balance time at age 69 per change in ACE (III) category					
	Total ACE (III) score (n=1260)		**Visuospatial ability** (n=1270)		**Memory** (n=1274)	
Reference category:	≥88 correct		All 16 correct		All 26 correct	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
M1: Age and sex [a]	<88: -0.09 (-0.17, -0.01)	0.03	15: -0.08 (-0.16, 0.01) ≤14: -0.12 (-0.20, -0.04)	<0.001	25: -0.04 (-0.13, 0.05) 23-24: -0.02 (-0.10, 0.06) ≤23: -0.07 (-0.16, 0.01)	0.04
M2: M1 + anthropometric [b]	<88: -0.06 (-0.14, 0.01)	0.11	15: -0.06 (-0.13, 0.01) ≤14: -0.08 (-0.16, -0.001)	0.03	25: -0.04 (-0.13, 0.05) 23-24: -0.02 (-0.10, 0.06) ≤23: -0.07 (-0.16, 0.01)	0.11
M3: M2 + health status [c]	<88: -0.06 (-0.14, 0.02)	0.12	15: -0.06 (-0.13, 0.01) ≤14: -0.08 (-0.16, 0.002)	0.03	25: -0.04 (-0.13, 0.06) 23-24: -0.02 (-0.10, 0.07) ≤23: -0.07 (-0.15, 0.02)	0.18
M4: M2 + health behaviours [d]	<88: -0.06 (-0.14, 0.01)	0.11	15: -0.06 (-0.13, 0.02) ≤14: -0.07 (-0.15, 0.01)	0.05	25: -0.04 (-0.12, 0.05) 23-24: -0.02 (-0.10, 0.07) ≤23: -0.07 (-0.15, 0.02)	0.18
M5: M2 + adult social class [e]	<88: -0.06 (-0.14, 0.02)	0.17	15: -0.05 (-0.13, 0.02) ≤14: -0.07 (-0.15, -0.01)	0.06	25: -0.03 (-0.12, 0.05) 23-24: -0.01 (-0.10, 0.07) ≤23: -0.06 (-0.15, 0.02)	0.23
M6: M2 + education [f]	<88: -0.06 (-0.14, 0.03)	0.19	15: -0.**05** (-0.13, 0.02) ≤14: -0.07(-0.15, 0.01)	0.08	25: -0.03 (-0.12, 0.05) 23-24: -0.01 (-0.09, 0.07) ≤23: -0.06 (-0.14, 0.03)	0.29
M7: Fully-adjusted model [g]	<88: -0.04 (-0.13, 0.04)	0.32	15: -0.06 (0.13, 0.02) ≤14: -0.06 (-0.16, 0.01)	0.08	25: -0.03 (-0.11, 0.06) 23-24: -0.001 (-0.08, 0.08) ≤23: -0.04 (-0.13, 0.05)	0.50

[a] *Adjusted for age, sex.* [b] *Adjusted for M1 + height, height^2, BMI.* [c] *Adjusted for M2 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression.* [d] *Adjusted for M3 + smoking history, leisure time physical activity.* [e] *Adjusted for M2 + adulthood social class.* [f] *Adjusted for M2 + education.* [g] *Adjusted for all covariates in M1–6*

Appendix 5.5B Cross-sectional associations of ACE (III) total and component scores with log-transformed balance time at age 69 in individual regression models; adjustments for each covariate in turn (corresponds to models shown in Table 5.6)

	Change in balance time at age 69 per change in ACE (III) category					
	Language (n=1262)		**Attention** (n=1274)		**Fluency** (n=1510)	
Reference category:	All 26 correct		All 18 correct		13-14 correct	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
M1: Age and sex [a]					12: -0.001 (-0.08, 0.08)	
	25: -0.01 (-0.09, 0.06)	0.36	17: 0.02 (-0.06, 0.10)	0.03	10-11: -0.02 (-0.10, 0.05)	0.03
	≤24: -0.04 (-0.13, 0.05)		≤16: -0.09 (-0.16, 0.02)		≤9: -0.07 (-0.16, 0.01)	
M2: M1 + anthropometric [b]					12: -0.01 (-0.09, 0.07)	
	25: -0.01 (-0.08, 0.06)	0.48	17: 0.03 (-0.05, 0.10)	0.04	10-11: -0.04 (-0.11, 0.04)	0.11
	≤24: -0.03 (-0.12, 0.05)		≤16: -0.08 (-0.16, 0.01)		≤9: -0.10 (-0.18, -0.01)	
M3: M2 + health status [c]					12: 0.004 (-0.08, 0.08)	
	25: -0.004 (-0.08, 0.07)	0.62	17: 0.03 (-0.04, 0.11)	0.05	10-11: -0.02 (-0.09, 0.06)	0.14
	≤24: -0.02 (-0.11, 0.06)		≤16: -0.08 (-0.15, -0.01)		≤9: -0.07 (-0.15, 0.02)	
M4: M2 + health behaviours [d]					12: 0.004 (-0.08, 0.08)	
	25: -0.004 (-0.08, 0.07)	0.64	17: 0.03 (-0.05, 0.11)	0.05	10-11: -0.01 (-0.09, 0.06)	0.22
	≤24: -0.02 (-0.11, 0.06)		≤16: -0.08 (-0.15, -0.01)		≤9: -0.06 (-0.14, 0.02)	
M5: M2 + adult social class [e]					12: 0.004 (-0.08, 0.08)	
	25: -0.01 (-0.08, 0.07)	0.79	17: 0.023 (-0.04, 0.11)	0.07	10-11: -0.01 (-0.09, 0.06)	0.31
	≤24: -0.01 (-0.10, 0.08)		≤16: -0.08 (-0.15, -0.01)		≤9: -0.05 (-0.13, 0.04)	
M6: M2 + education [f]					12: 0.01 (-0.08, 0.09)	
	25: -0.002 (-0.08, 0.07)	0.90	17: 0.04 (-0.04, 0.11)	0.08	10-11: -0.01 (-0.08, 0.07)	0.34
	≤24: -0.04 (-0.10, 0.08)		≤16: -0.07 (-0.15, -0.002)		≤9: -0.05 (-0.14, 0.04)	
M7: Fully-adjusted model [g]					12: 0.01 (-0.07, 0.09)	
	25: 0.01 (-0.07, 0.08)	0.81	17: 0.04 (-0.03, 0.12)	0.11	10-11: 0.0001 (-0.08, 0.08)	0.55
	≤24: 0.01 (0.08, 0.10)		≤16: -0.07 (-0.14, 0.003)		≤9: -0.03 (-0.12, 0.06)	

[a] *Adjusted for age, sex.* [b] *Adjusted for M1 + height, height^2, BMI.* [c]*Adjusted for M2 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression.* [d]*Adjusted for M3 + smoking history, leisure time physical activity.* [e]*Adjusted for M2 + adulthood social class.* [f]*Adjusted for M2 + education.* [g] *Adjusted for all covariates in M1–6*

Appendix 5.6 Longitudinal associations of cognitive tests at age 53 with log-transformed standing balance (sec) in sex-adjusted models, re-centred at ages 60-64 and 69 using multilevel models [a] (corresponds to models shown in Table 5.8)

	Sex-adjusted change in balance time at age 60-64 and 69 per change in cognition (max)				**Fully-adjusted change in balance time at age 60-64 and 69 per change in cognition**			
	Age 60-64		Age 69		Age 60-64		Age 69	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
i. Verbal memory (per SD)	0.07 (0.05, 0.09)	<0.001	0.04 (0.02, 0.07)	<0.01	0.03 (0.005, 0.05)	0.02	0.01 (-0.02, 0.04)	0.59
ii. Search speed								
Men (per SD)	0.05 (0.02, 0.08)	<0.001	0.03 (-0.01, 0.06)	<0.01	0.03 (-0.003, 0.05)	0.08	0.01 (-0.03, 0.05)	0.50
Women (per SD)	0.03 (0.002, 0.05)	0.03	0.01 (-0.03)	0.62	0.003 (-0.02, 0.03)	0.81	-0.01 (-0.04, 0.03)	0.66
iii. Verbal fluency (per SD)	0.06 (0.05, 0.08)	<0.001	0.04 (0.02, 0.06)	<0.001	0.03 (0.01, 0.05)	<0.01	0.01 (-0.01, 0.04)	0.32
iv. Prospective memory [b]	-		-					
v. NART Linear term[c] (per SD)	0.08 (0.06, 0.10)	<0.001	0.05 (0.03, 0.08)	<0.001	0.02 (-0.01, 0.04)	0.19	-0.004 (-0.04, 0.03)	0.80

max =maximal available sample

[a] *Sample sizes do not change (see Table 5.8) as estimates were re-centred at ages 6*

[b] *As there was no significant age interaction, coefficients estimates are the same at ages 60-64 and 69.*

[c] *As there was no significant age interaction for the quadratic term, the quadratic term estimates are the same as shown in Table 5.8*

Appendix 6.1 Standardized results from the autoregressive cross-lagged model of balance and verbal memory grouped by sex

		MEN (n=1346)		**WOMEN (n=1389)**	
		Change in balance time per SD change in cognition (95% CI)	**p-value**	**Change in balance time per SD change in cognition (95% CI)**	**p-value**
AUTOREGRESSIVE ESTIMATES					
Balance at age 60-64	*ON* Balance age 53	0.305 (0.226, 0.384)	<0.001	0.272 (0.243, 0.358)	<0.001
Balance at age 69	*ON* Balance age 60-64	0.295 (0.182, 0.409)	<0.001	0.244 (0.159, 0.329)	<0.001
	ON Balance age 53	0.198 (0.117, 0.279)	<0.001	0.133 (0.068, 0.198)	<0.001
Verbal memory at age 53	*ON* Verbal memory age 53	0.640 (0.606, 0.674)	<0.001	0.655 (0.621, 0.689)	<0.001
Verbal memory at age 60-64	*ON* Verbal memory age 53	0.361 (0.298, 0.423)	<0.001	0.435 (0.381, 0.489)	<0.001
	ON Verbal memory age 43	0.437 (0.378, 0.497)	<0.001	0.391 (0.337, 0.444)	<0.001
Verbal memory at age 69	*ON* Verbal memory age 60-64	0.385 (0.325, 0.444)	<0.001	0.426 (0.365, 0.486)	<0.001
	ON Verbal memory age 53	0.445 (0.389, 0.501)	<0.001	0.361 (0.300, 0.422)	<0.001
CROSS-LAGGED ESTIMATES					
Balance at age 53	*ON* Verbal memory age 43	0.161 (0.104, 0.218)	<0.001	0.154 (0.102, 0.206)	<0.001
Balance at age 60-64	*ON* Verbal memory age 53	0.028 (-0.032, 0.088)	0.37	0.102 (0.012, 0.098)	<0.005
Balance at age 69	*ON* Verbal memory age 60-64	0.054 (0.007, 0.087)	0.06	0.065 (0.008, 0.121)	0.03
Verbal memory at age 60-64	*ON* Balance age 53	0.024 (-0.024, 0.073)	0.33	0.021 (-0.014, 0.057)	0.24
Verbal memory at age 69	*ON* Balance age 60-64	0.019 (-0.029, 0.067)	0.44	-0.002 (-0.044, 0.040)	0.92
COVARIANCE ESTIMATES					
Verbal memory age 53 *WITH* Balance age 53		0.092 (0.032, 0.153)	<0.005	0.111 (0.057, 0.165)	<0.001
Verbal memory age 60-64 *WITH* Balance age 60-64		0.150 (0.087, 0.214)	<0.001	0.025 (-0.046, 0.095)	0.49
Verbal memory age 69 *WITH* Balance age 69		0.017 (-0.053, 0.087)	0.64	0.001 (-0.054, 0.057)	0.96

Appendix 7.1 Number of falls in last 12 months (0, 1-2, ≥3) amongst men and women at ages 60-64 and 68

	Total N	Men	Women	Tests of sex difference (p-value)
Number of recurrent falls (amongst fallers)				
Age 60-64				
1-2 falls	408	86/144 (59.72%)	143/264 (54.17%)	0.37
≥3 falls		55/144 (38.19%)	118/264 (44.70%)	
Unknown		3/144 (2.08%)	3/264 (1.14%)	
Age 68				
1-2 falls	532	102/207 (49.28%)	177/325 (54.46%)	0.45
≥3 falls		101/207 (48.79%)	144/325 (44.31%)	
Unknown		4/207 (1.93%)	4/325 (1.23%)	

Appendix 7.2 Descriptive characteristics of analytical sample with balance and falls data at age 60-64 (n=2182)

	Non-fallers (n=1790)	**1 fall** (n=225)	**≥2 falls** (n=167)	**p-value between groups**
BALANCE ABILITY, median (Q1, Q3)	3.47 (2.35, 5.35)	3.06 (2.13, 4.43)	2.36 (1.06, 4.21)	<0.001
ANTHROPOMETRY, mean (SD)				
Height (m)	1.68 (0.09)	1.67 (0.09)	1.66 (0.08)	<0.001
BMI (kg/m^2)	27.9 (4.9)	27.8 (4.6)	28.8 (5.5)	0.06
SOCIOECONOMIC INDICATORS, n (%)				
Paternal occupational class				
I Professional/II Intermediate	499 (29.3)	71 (32.7)	38 (24.5)	0.51
III Skilled (non-manual or manual)	796 (46.8)	100 (46.1)	79 (51.0)	
IV Partly skilled/V Unskilled	407 (23.9)	46 (21.2)	38 (24.5)	
Maternal education				
Secondary and further education	210 (13.1)	33 (16.2)	24 (16.3)	0.30
Secondary only	203 (12.7)	22 (10.8)	20 (13.6)	
Primary and further education	247 (15.5)	40 (19.6)	17 (12.6)	
Primary only	939 (58.7)	109 (53.4)	86 (58.5)	
Highest household occupational class				
I Professional/II Intermediate	833 (46.8)	111 (49.3)	73 (44.0)	0.28
III Skilled (non-manual or manual)	709 (39.8)	85 (37.8)	61 (36.8)	
IV Partly skilled/V Unskilled	238 (13.4)	29 (12.9)	32 (19.3)	
Educational attainment at age 26				
Degree or higher	204 (12.0)	21 (9.8)	9 (5.7)	0.02
GCE A level or Burnham B	485 (28.6)	66 (30.7)	39 (24.8)	
GCE O level or Burnham C	334 (20.0)	55 (25.6)	45 (28.7)	
Sub GCE	126 (7.4)	18 (8.4)	15 (9.6)	
None attempted	548 (32.3)	55 (25.6)	49 (31.2)	
BEHAVIOURAL RISK FACTORS, n (%)				
Leisure time physical activity				
None	1113 (48.7)	126 (57.5)	115 (71.9)	0.03
1-4 times/month	236 (18.1)	41 (18.7)	14 (8.8)	
≥5 times/month	389 (33.2)	52 (23.7)	31 (19.4)	
Smoking status				
Current	184 (11.3)	24 (11.4)	16 (11.0)	0.60
Previous smoker	918 (56.3)	111 (52.6)	89 (61.0)	
Never smoker	530 (32.5)	76 (36.0)	41 (28.1)	
CURRENT HEALTH STATUS				
History of diabetes, n (%)	143 (8.0)	13 (5.8)	17 (10.2)	0.27
History of CVD events, n (%)	115 (7.4)	18 (8.7)	19 (13.5)	0.03
Respiratory symptoms, n (%)	265 (16.9)	46 (22.1)	46 (32.9)	<0.001
Knee pain, n (%)	361 (20.2)	52 (23.1)	77 (46.1)	<0.001
Symptoms of anxiety/ depression, mean(SD)	16.0 (7.9)	17.4 (8.6)	21.2 (10.3)	<0.001
OTHER, mean (SD)				
Verbal memory	24.2 (6.0)	25.1 (6.5)	23.5 (6.6)	0.05

Q1= quartile 1 (25th percentile); Q3= quartile 3 (75th percentile)

Appendix 7.3 Descriptive characteristics of analytical sample with balance and falls data at age 69 (n=1928)

	Non-fallers (n=1790)	**1 fall** (n=225)	**≥2 falls** (n=167)	**p-value between groups**
BALANCE ABILITY, median (Q1, Q3)	2.97 (1.90, 4.50)	2.97 (1.85, 5.22)	2.12 (0.94, 3.41)	<0.001
ANTHROPOMETRY, mean (SD)				
Height (m)	1.67 (0.09)	1.66 (0.09)	1.66 (0.09)	<0.01
BMI (kg/m^2)	27.9 (4.9)	27.6 (4.9)	29.5 (6.0)	<0.001
SOCIOECONOMIC INDICATORS, n (%)				
Paternal occupational class				
I Professional/II Intermediate	426 (30.0)	77 (35.3)	55 (29.9)	0.35
III Skilled (non-manual or manual)	686 (48.2)	105 (48.2)	88 (47.8)	
IV Partly skilled/V Unskilled	310 (21.8)	36 (16.5)	41 (22.3)	
Maternal education				
Secondary and further education	185 (13.9)	30 (15.0)	27 (15.5)	0.47
Secondary only	175 (13.1)	33 (16.5)	22 (12.6)	
Primary and further education	200 (15.0)	31 (15.5)	18 (10.3)	
Primary only	775 (58.1)	106 (53.0)	107 (61.5)	
Highest household occupational class				
I Professional/II Intermediate	727 (48.6)	119 (51.7)	93 (49.0)	0.14
III Skilled (non-manual or manual)	585 (39.1)	92 (40.00)	66 (34.7)	
IV Partly skilled/V Unskilled	185 (12.4)	19 (8.3)	31 (16.3)	
Educational attainment at age 26				
Degree or higher	170 (11.9)	27 (12.4)	26 (14.1)	0.06
GCE A level or Burnham B	413 (29.0)	79 (36.4)	48 (26.1)	
GCE O level or Burnham C	294 (20.6)	51 (23.5)	38 (20.7)	
Sub GCE	102 (7.2)	17 (7.8)	16 (8.7)	
None attempted	447 (31.4)	43 (19.8)	56 (30.4)	
BEHAVIOURAL RISK FACTORS, n (%)				
Leisure time physical activity				
None	856 (57.5)	117 (51.8)	117 (61.6)	0.25
1-4 times/month	196 (13.2)	39 (17.3)	23 (12.1)	
≥5 times/month	437 (29.4)	70 (31.0)	50 (26.3)	
Smoking status				
Current	121 (8.1)	16 (7.1)	14 (7.4)	0.96
Previous smoker	913 (61.2)	136 (60.2)	117 (61.6)	
Never smoker	459 (30.7)	74 (32.7)	59 (31.1)	
CURRENT HEALTH STATUS				
History of diabetes, n (%)	157 (10.4)	18 (7.8)	32 (16.6)	0.01
History of CVD events, n (%)	170 (11.3)	25 (10.9)	37 (10.17)	<0.01
Respiratory symptoms, n (%)	299 (21.3)	46 (21.5)	65 (37.1)	<0.001
Knee pain, n (%)	276 (18.4)	45 (19.6)	62 (32.1)	<0.001
Symptoms of anxiety/ depression, mean (SD)	14.4 (7.1)	15.3 (18.6)	18.6 (11.1)	<0.001
OTHER, mean (SD)				
Verbal memory	21.4 (7.8)	21.5 (8.1)	20.5 (9.9)	0.33

Q1= quartile 1 (25th percentile); Q3= quartile 3 (75th percentile)

Appendix 7.4 Cross-sectional associations between balance ability and falls (number of falls, injurious falls) at age 53 and 60-64 (per 1 second increase in balance ability). Adjusted for sex if not stratified.

	Sex-adjusted (max)		**Sex-adjusted (ccs)**		**Fully-adjusted [c]**	
	RRR (95% CI)	**p-value**	**RRR (95% CI)**	**p-value**	**RRR (95% CI)**	**p-value**
BALANCE AND FALLS AT AGE 53						
Model 1: Outcome: 0 falls (ref)[a]	n=2896		n=2311		n=2311	
1-2 falls	0.99 (0.97, 1.00)	0.10	0.99 (0.99, 1.01)	0.50	0.99 (0.96, 1.01)	0.57
≥3 falls	0.93 (0.89, 0.97)	<0.005	0.96 (0.92, 1.00)	0.08	0.98 (0.94, 1.03)	0.43
BALANCE AND FALLS AT AGE 60-64						
Model 2: Outcome: 0 falls (ref)[b]	n=1049; n=1139		n=686; n=748		n=686; n=748	
Men: 1 fall	0.93 (0.87, 0.99)	0.04	0.93 (0.85, 1.01)	0.07	0.93 (0.85, 1.01)	0.08
≥2 falls	0.68 (0.57, 0.80)	<0.001	0.72 (0.58, 0.89)	<0.005	0.81 (0.67, 0.97)	0.02
Women: 1 fall	0.95 (0.90, 1.00)	0.06	0.97 (0.92, 1.03)	0.35	0.95 (0.90, 1.01)	0.13
≥2 falls	0.89 (0.82, 0.96)	<0.005	0.89 (0.80, 0.99)	0.03	0.90 (0.81, 1.00)	<0.05
Model 3: Outcome: 0 falls (ref)[b]	n=1046; n =1136		n=687; n=751		n=687; n=751	
Men: Non-injurious falls	0.90 (0.84, 0.97)	<0.005	0.91 (0.84, 0.99)	0.03	0.92 (0.85, 1.00)	0.04
Injurious falls	0.65 (0.52, 0.82)	<0.001	0.65 (0.50, 0.86)	<0.005	0.74 (0.57, 0.96)	<0.01
Women: Non-injurious falls	0.91 (0.86, 0.97)	<0.005	0.95 (0.90, 1.01)	0.12	0.94 (0.88, 1.00)	0.05
Injurious falls	0.95 (0.88, 1.02)	0.15	0.92 (0.83, 1.02)	0.12	0.91 (0.81, 1.02)	0.11

max = maximal available sample; ccs = complete cases sample; RRR = relative risk ratio of fall outcome relative to reference category

[a] No sex interaction(p=0.63); [b] Sex interaction (p<0.05); [c] Models adjusted for death, attrition, height, BMI, depression, diabetes, CVD history, respiratory events, knee pain, smoking status, leisure time physical activity, maternal education, paternal occupational class, own occupation, education, verbal memory.

Appendix 7.5 Cross-sectional associations between inability to complete balance test and falls (number of falls, injurious falls) at age 53 and 60-64

	Sex-adjusted (max)		Sex-adjusted (max)		Fully-adjusted [c]	
	RRR (95% CI)	**p-value**	**RRR (95% CI)**	**p-value**	**RRR (95% CI)**	**p-value**
BALANCE AND FALLS AT AGE 53						
Model 10: Outcome: 0 falls (ref)	n=2896		n=2264		n=2264	
1-2 falls	1.86 (1.09, 3.16)	0.10	1.53 (0.74, 3.13)	0.25	1.22 (0.57, 2.62)	0.60
≥3 falls	11.81 (7.04, 19.80)	<0.001	9.21 (4.45, 19.06)	<0.001	5.27 (2.27, 12.26)	<0.001
BALANCE AND FALLS AT AGE 60-64						
Model 11: Outcome: 0 falls (ref)	n=1046; n=1136		n=686; n=748		n=686; n=748	
<u>Men</u>: 1 fall	2.66 (0.87, 8.10)	0.09	2.63 (0.55, 12.71)	0.09	2.06 (0.40, 10.56)	0.39
≥2 falls	24.81 (11.71, 52.52)	<0.001	31.61 (11.09, 90.06)	<0.001	10.24 (2.79, 37.5)	<0.001
<u>Women</u>: 1 fall	1.20 (0.45, 3.17)	0.72	1.65 (0.45, 6.10)	0.45	2.34 (0.60, 9.18)	0.22
≥2 falls	6.16 (3.26, 11.64)	<0.001	7.96 (3.02, 20.97)	<0.001	6.47 (2.16, 19.3)	<0.005
Model 12: Outcome: 0 falls (ref)	n=1049; n=1139		n=687; n=751		n=687; n=751	
<u>Men</u>: Non-injurious falls	8.56 (4.14, 17.71)	<0.001	9.83 (3.56, 27.14)	<0.001	5.83 (1.89, 17.92)	<0.005
Injurious falls	17.51 (6.89, 44.51)	<0.001	17.35 (4.76, 63.26)	<0.001	8.64 (1.71, 43.71)	<0.01
<u>Women</u>: Non-injurious falls	2.67 (1.37, 5.22)	<0.005	2.91 (1.04, 8.16)	0.04	2.98 (1.00, 8.90)	0.05
Injurious falls	4.62 (2.08, 10.27)	<0.001	6.16 (2.08, 18.79)	<0.005	10.19 (2.77, 37.50)	<0.001

max = maximal available sample; ccs = complete cases sample; RRR= relative risk ratio of fall outcome relative to reference category

PUBLICATIONS

Chapter 3:

Blodgett JM, Cooper R, Kuh D, Davis DHJ, Hardy R. Associations between factors across life and balance ability in mid and later life: evidence from a British birth cohort study. *Frontiers in Sports and Active Living.* Special research topic: Balance and Ageing. 2020, 2:1-28 [pg 321]

Chapter 4:

Blodgett JM, Kuh D, Hardy R, Davis DHJ, Cooper R. Childhood cognition and age-related change in standing balance performance from mid to later life: findings from a British birth cohort. *J Gerontol A Biol Sci Med Sci*. 2020, 75(1): 155-161 [pg 335]

Chapter 5:

Blodgett JM, Cooper R, Davis DHJ, Kuh D, Hardy R. Memory, processing speed, fluency and overall intelligence: associations with balance performance in mid and later life. *J Gerontol A Biol Sci Med Sci*, under review January 2021 [pg 352]

Chapter 6:

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Associations Between Factors Across Life and One-Legged Balance Performance in Mid and Later Life: Evidence From a British Birth Cohort Study

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Introduction: Despite its associations with falls, disability, and mortality, balance is an under-recognized and frequently overlooked aspect of aging. Studies investigating associations between factors across life and balance are limited. Understanding the factors related to balance performance could help identify protective factors and appropriate interventions across the life course. This study aimed to: (i) identify socioeconomic, anthropometric, behavioral, health, and cognitive factors that are associated with one-legged balance performance; and (ii) explore how these associations change with age.

Methods: Data came from 3,111 members of the MRC National Survey of Health and Development, a British birth cohort study. Multilevel models examined how one-legged standing balance times (assessed at ages 53, 60–64, and 69) were associated with 15 factors across life: sex, maternal education (4 years), paternal occupation (4 years), own education (26 years), own occupation (53 years), and contemporaneous measures (53, 60–64, 69 years) of height, BMI, physical activity, smoking, diabetes, respiratory symptoms, cardiovascular events, knee pain, depression and verbal memory. Age and sex interactions with each variable were assessed.

Results: Men had 18.8% (95%CI: 13.6, 23.9) longer balance times than women at age 53, although this difference decreased with age (11.8% at age 60–64 and 7.6% at age 69). Disadvantaged socioeconomic position in childhood and adulthood, low educational attainment, less healthy behaviors, poor health status, lower cognition, higher body mass index (BMI), and shorter height were associated with poorer balance at all three ages. For example, at age 53, those from the lowest paternal occupational classes had 29.6% (22.2, 38.8) worse balance than those from the highest classes. Associations of balance with socioeconomic indicators, cognition and physical activity became smaller with age, while associations with knee pain and depression became larger. There were no sex differences in these associations. In a combined model, the majority of factors remained associated with balance.

Discussion: This study identified numerous risk factors across life that are associated with one-legged balance performance and highlighted diverse patterns of association with age, suggesting that there are opportunities to intervene in early, mid and later life. A multifactorial approach to intervention, at both societal and individual levels, may have more benefit than focusing on a single risk factor.

Keywords: balance, aging, life course, risk factor, epidemiology

INTRODUCTION

From getting out of bed in the morning to sitting, standing and walking throughout the day, balance is a crucial component of everyday life (Muir et al., 2010). Poor balance is linked with several adverse health outcomes, perhaps most notably increased falls risk (Ganz et al., 2007), but also with increased risk of disability, fractures, hospitalization, and premature mortality (Cooper et al., 2011b, 2014; Nofuji et al., 2016; Keevil et al., 2018). Despite the growing awareness of the importance of balance in aging—as reflected in recent physical activity guidelines (Centre for Ageing Better, 2018; US Department of Health Human Services., 2018; Department of Health Social Care., 2019)—the life course epidemiology of balance performance has been under-investigated compared with other measures of physical capability such as grip strength and chair rise performance.

In the few studies that have examined factors across life in relation to balance performance, several associations have been found. Across a range of ages, males tend to have better balance performance than females (Wolfson et al., 1994; Schultz et al., 1997; Cooper et al., 2011a; Kim et al., 2012). Low socioeconomic position (SEP) has been found to have a negative cumulative association with balance performance, with an additive effect of low SEP in childhood and adulthood on risk for poor balance in later life (Birnie et al., 2011b; Strand et al., 2011a). Smoking history (Strand et al., 2011b), low cognitive ability in both childhood and adulthood (Kuh et al., 2009a; Blodgett et al., 2020), higher levels of depression (Nitz et al., 2005), and low levels of physical activity (Cooper et al., 2011c, 2015; Chang et al., 2013), have also been shown to be associated with poor balance.

These previous studies have primarily examined associations between a single risk factor and balance ability at one time point. With the exception of our recent study of the association between childhood cognitive ability and balance performance (Blodgett et al., 2020), to our knowledge, no study has examined whether associations change with age. This is a limitation, given that balance is a complex process that relies on sensory input including visual cues, proprioception, vestibular processes as well as muscular strength and cognitive processing (Merla and Spaulding, 1997), and so may be affected by age-related changes, such as increased levels of morbidity and decline in cognitive functioning. In addition, few studies have investigated sex differences in the associations between risk factors and balance ability. This is despite the fact that investigating sex differences in the relationships between different risk factors and balance may help elucidate why men have better average balance performance than women, as the reasons for this are still not fully understood (Maki et al., 1990; Wolfson et al., 1994; Hageman et al., 1995; Schultz et al., 1997; Bryant et al., 2005).

Using a British birth cohort study, previously used to study factors associated with balance at a single age (Kuh et al., 2006, 2009a; Birnie et al., 2011a; Cooper et al., 2011a,c, 2015; Strand et al., 2011a,b; Mulla et al., 2013; Murray et al., 2013; Blodgett et al., 2020), we aimed to investigate associations of socioeconomic, behavioral, health and cognitive risk factors across life with one-legged balance performance over 16 years and assess if these associations change with age or sex. We hypothesized that positive factors such as high SEP, low BMI, participation in healthy behaviors, absence of poor physical and mental health as well as higher adult cognitive ability would be associated with better balance performance. As physical and mental comorbidities become more common with age, we hypothesized that the associations of health status with balance performance would get stronger with age. Conversely, as health status becomes more important, the relative contributions of SEP were hypothesized to decrease.

METHODS

Sample

The MRC National Survey of Health and Development (NSHD) is an ongoing study of 5,362 individuals born in England, Scotland, or Wales within 1 week in March 1946. Since 1946, study members have been followed up to 24 times in infancy, across childhood, adolescence, and adulthood, most recently at ages 53 ($n = 2{,}988$), 60–64 ($n = 2{,}229$), and 69 ($n = 2{,}149$) using a combination of questionnaires, interviews, and clinical examinations (Kuh et al., 2016). Details of loss to follow-up (e.g., death, emigration, refusal, incapacity) in this sample have been previously described (Blodgett et al., 2020). Ethical approval for the most recent data collection wave (2015) was obtained from Queen Square Research Ethics Committee (14/ LO/1073) and Scotland A Research Ethics Committee (14/SS/1009).

Assessment of Balance Ability

One-legged balance performance was assessed by trained nurses during clinical assessments at ages 53, 60–64, and 69 using standardized protocols. Study members were asked to fold their arms and stand on their preferred leg with their eyes closed for as long as possible up to a maximum of 30 s. If individuals were unable to perform the test, the reason was recorded. In these analyses, individuals who could not perform the test due to health reasons and those who attempted but could not maintain the balance position were given a score of zero. The final analytical sample consisted of individuals with a balance time at one or more ages ($n = 3{,}111$). The one-legged balance test is considered to be a reliable and valid measure of static balance and has been shown to have high inter-rater and test-retest reliability (Giorgetti et al., 1998; Bohannon, 2006; Springer et al., 2007; Michikawa et al., 2009; Choi et al., 2014; Ortega-Pérez de Villar et al., 2018). Many studies have consistently demonstrated associations between poor one-legged balance performance and higher risk of falls, disability, poor gait speed, frailty and premature mortality (Drusini et al., 2002; Michikawa et al., 2009; Cooper et al., 2010, 2014; Delbaere et al., 2010; Oliveira et al., 2018).

Assessment of Risk Factors

We selected a set of risk factors *a priori* that had previously been shown to be associated with balance or other measures of physical capability at a single time point in NSHD and other studies (Kuh et al., 2006, 2009a; Birnie et al., 2011b; Cooper et al., 2011a,c, 2015; Strand et al., 2011a,b; Welmer et al., 2012; D'Andréa Greve et al., 2013; Amemiya et al., 2019; Thomas et al., 2019).

Socioeconomic Indicators

Paternal occupational class (at age 4) and *own occupational class* (reported at age 53 years) were grouped into three categories as distinguished by the Registrar General's Social Classification (Galobardes et al., 2006): (1) I Professional and II Intermediate; (2) III Skilled (non-manual) and III Skilled (manual); and (3) IV Partly skilled and V Unskilled manual. *Maternal education* was classified into four categories: (1) Primary only; (2) Primary and further education; (3) Secondary only; (4) Secondary and further education. Participants reported their highest level of *educational attainment* by age 26, which was categorized as degree or higher, advanced secondary qualifications generally attained at 18 years (GCE A level or Burnham B), ordinary secondary qualifications generally attained at 16 years, (e.g., GCE O level or Burnham C), below ordinary secondary qualifications, or none.

Anthropometric Indicators (Ages 53, 60–64, 69)

Height (m) and *BMI* (kg/m^2), derived from height and weight measurements ascertained by nurses using standardized protocols, were used (Braddon et al., 1986).

Behavioral Risk Factors (Ages 53, 60–64, 69)

Individuals self-reported their *leisure time physical activity participation* (never, 1–4 times/month, 5+ times/month) and their *smoking status* (never, past smoker, current smoker) (Kuh et al., 2009b; Strand et al., 2011b). Current and past smokers were defined as those who smoked at least one cigarette a day for 12 months or more.

Health Status (Ages 53, 60–64, 69)

Current health conditions (yes/no for each) were ascertained using a series of self-reported questions on *history of diabetes, cardiovascular events, respiratory symptoms, and knee pain* (Kuh et al., 2005; Cooper et al., 2014). *Symptoms of depression and anxiety* were assessed using the 28-item self-reported General Health Questionnaire; each item was scored from 1 to 4 and summed together (range: 0–84) (Goldberg and Hillier, 1979).

Cognitive Ability (Ages 53, 60–64, 69)

Verbal memory was assessed using a 15-item word list. Each word was presented for 2 s before individuals were instructed to write down as many words as they could remember. This was repeated over three identical trials and the number of words recalled during each trial were summed (range: 0–45). To minimize any practice effects, two word lists were rotated between follow-up assessments (Davis et al., 2017).

Statistical Analyses

Sex differences in each risk factor were assessed using *t*-tests or chi-square tests, as appropriate, and described by the mean (±SD) or proportion (*n*). Separate multilevel models were used to examine the associations between each risk factor (independent variable) and log transformed balance time (dependent variable) in the maximal available sample size. Cross-sectional associations were assessed for time-varying covariates (e.g., anthropometric, behavioral, health, cognitive factors), whereas SEP measures were based on reports from one age. Balance times at each age (level 1) were nested within individuals (level 2) and both the intercept and slope were modeled as random effects. As the sample was age-homogenous, age was employed as a linear time metric and was centered at age 53 (intercept); age 63 was utilized as the time integer for age 60–64 (Kuh et al., 2019; Blodgett et al., 2020). Balance times were log-transformed due to the skewed distribution of balance. Non-linearity of the association between each risk factor and balance was assessed using likelihood ratio tests.

A variable-by-sex interaction term was estimated, with subsequent models stratified by sex if there was evidence of an interaction. An interaction between age and each risk factor was added to the model to test whether the association between each risk factor and balance changes with age. Age interactions were considered if $p < 0.05$; an alpha of 0.05 was used for both age and sex interactions in order to parsimoniously build each model. Finally, all risk factors and significant interaction terms were included in a combined model. To account for the non-random events of mortality and attrition (not due to death), the model was adjusted for separate binary indicators of both death and attrition (not due to death) between ages 53 and 69. This approach minimizes the correlation between non-random loss to follow up and poorer performance on the balance test, thus reducing bias in the other estimates (Botoseneanu and Liang, 2012; Botoseneanu et al., 2013). All estimates are presented as sympercents (i.e., as % change) to aid interpretation (Cole and Kryakin, 2000). Stata 14 was used for all statistical analyses.

RESULTS

Characteristics of the sample are described in **Table 1**. Men were taller than women, had higher adult SEP, higher educational attainment, lower verbal memory, and were more likely to have a history of smoking. Men also had a higher prevalence of diabetes and CVD events, although women reported higher prevalence of knee pain and symptoms of anxiety and depression.

TABLE 1 | Characteristics of analytical sample ($n = 3{,}111$), MRC National Survey of Health and Development.

		Men ($n = 1{,}550$)	Women ($n = 1{,}561$)	Tests of sex differences (p-value)
ONE-LEGGED BALANCE TIME (s), MEDIAN (Q1, Q3), *n*				
Age 53		5 (3, 10), $n = 1421$	4 (3, 7), $n = 1{,}476$	<0.001
Age 60-64		3.57 (2.35, 5.53), $n = 1{,}055$	3.16 (2.16, 4.72), $n = 1{,}148$	<0.001
Age 69		2.94 (1.84, 4.78), $n = 1{,}037$	2.72 (1.69, 4.15), $n = 1{,}079$	<0.005
SOCIOECONOMIC INDICATORS, *n* (%)				
Paternal occupational class				
I Professional/II Intermediate		407 (27.6)	383 (26.0)	0.56
III Skilled (non-manual or manual)		692 (46.9)	716 (48.7)	
IV Partly skilled/V Unskilled		377 (25.5)	372 (25.3)	
Maternal education				
Secondary and further education		162 (11.74)	169 (12.2)	0.49
Secondary only		167 (12.1)	153 (11.0)	
Primary and further education		213 (15.4)	193 (13.90)	
Primary only		838 (60.7)	873 (62.9)	
Highest household occupational class				
I Professional/II Intermediate		788 (51.6)	559 (36.1)	<0.001
III Skilled (non-manual or manual)		578 (37.8)	659 (42.6)	
IV Partly skilled/V Unskilled		162 (10.6)	329 (21.3)	
Educational attainment at age 26				
Degree or higher		212 (14.5)	81 (5.5)	<0.001
GCE A level or Burnham B		408 (27.9)	343 (23.3)	
GCE O level or Burnham C		211 (14.4)	377 (25.6)	
Sub GCE		92 (6.3)	134 (9.1)	
None attempted		540 (36.9)	537 (36.5)	
ANTHROPOMETRY, MEAN (SD)				
Height (m)				
Age 53		1.75 (0.07), $n = 1{,}436$	1.62 (0.06), $n = 1{,}498$	<0.001
Age 60–64		1.75 (0.09), n=1062	1.62 (0.06), n=1159	<0.001
Age 69		1.73 (0.09), $n = 1{,}023$	1.61 (0.06), $n = 1{,}077$	<0.001
BMI (kg/m^2)				
Age 53		27.4 (4.0), $n = 1{,}435$	27.4 (5.5), $n = 1{,}486$	0.89
Age 60–64		27.9 (4.1), $n = 1{,}061$	27.9 (5.5), $n = 1{,}158$	0.92
Age 69		28.2 (4.6), $n = 1{,}040$	28.2 (5.7), $n = 1{,}081$	0.91
BEHAVIORAL RISK FACTORS, *n* (%)				
Leisure time physical activity				
Age 53	None	693 (47.9)	761 (50.4)	0.18
	1–4 times/month	270 (18.7)	245 (16.2)	
	5+ times/month	485 (33.5)	503 (33.3)	
Age 60–64	None	681 (65.2)	716 (62.9)	0.52
	1–4 times/month	137 (13.1)	162 (14.2)	
	5+ times/month	227 (21.7)	261 (22.9)	
Age 69	None	711 (59.9)	777 (61.33)	0.08
	1–4 times/month	135 (11.4)	170 (13.42)	
	5+ times/month	341 (28.7)	320 (25.3)	
Smoking status				
Age 53	Current	343 (23.6)	339 (22.5)	<0.001
	Previous smoker	737 (50.8)	671 (44.5)	
	Never smoker	371 (25.6)	499 (33.1)	
Age 60–64	Current	137 (12.3)	142 (11.8)	<0.001

(Continued)

TABLE 1 | Continued

		Men ($n = 1,550$)	Women ($n = 1,561$)	Tests of sex differences (p-value)
	Previous smoker	663 (59.5)	629 (52.1)	
	Never smoker	314 (28.2)	436 (36.1)	
Age 69	Current	123 (10.3)	111 (8.8)	<0.001
	Previous smoker	756 (63.5)	723 (57.2)	
	Never smoker	311 (26.1)	430 (34.0)	
HEALTH STATUS, n (%)				
Diabetes	Age53	57 (3.1)	43 (2.4)	0.18
	Age60–64	129 (10.1)	99 (7.2)	<0.01
	Age69	175 (13.7)	136 (10.0)	<0.005
CVD events	Age53	85 (5.8)	48 (3.2)	<0.01
	Age60–64	131 (11.5)	62 (5.1)	<0.001
	Age69	193 (17.6)	114 (10.0)	<0.001
Respiratory symptoms	Age 53	292 (19.9)	276 (18.2)	0.22
	Age 60–64	233 (20.1)	224 (18.2)	0.15
	Age 69	264 (24.5)	266 (22.4)	0.23
Knee pain	Age 53	226 (15.5)	310 (20.6)	<0.001
	Age 60–64	216 (20.3)	288 (24.6)	0.01
	Age 69	190 (18.1)	241 (22.1)	0.02
Depression/anxiety	Age 53	15.2 (7.3), $n = 1,051$	17.8 (8.9), $n = 1,137$	<0.001
	Age 60–64	15.7 (8.6), $n = 1,407$	18.9 (10.3), $n = 1,470$	<0.001
	Age 69	14.1 (7.5), $n = 1025$	16.2 (8.2), $n = 1068$	<0.001
VERBAL MEMORY SCORES, MEAN (SD)				
	Age 53	23.0 (6.2), $n = 1,397$	24.9 (6.2), $n = 1473$	<0.001
	Age 60–64	23.0 (5.9), $n = 1,023$	25.4 (6.1), $n = 1,127$	<0.001
	Age 69	21.2 (6.0), $n = 1,005$	23.1 (6.0), $n = 1057$	<0.001

Sex, Age, and Balance

Women had 18.8% (95%CI: 13.6, 23.9%; **Table 2**, **Figure 1**) worse balance performance than men at age 53. The interaction between age and sex indicated that for every additional year increase in age, the sex difference in balance decreased by 0.7% (0.3, 1.2%). Thus, at ages 63 and 69, respectively, women had 11.4% (7.6, 15.2%) and 7.0% (2.1, 11.9%) lower balance times than men. Despite the sex differences in balance performance across time, there were no interactions between sex and any of the risk factors investigated.

Socioeconomic Indicators and Balance

The results of the likelihood ratio tests for deviations from linearity suggested that all four socioeconomic indicators could be modeled as continuous variables. More disadvantaged SEP for all four indicators—paternal occupation, maternal education, own education, own occupation—was associated with worse balance times (**Table 2**, **Figure 2**). For example, more disadvantaged paternal occupational class was associated with 14.8% (11.1, 18.4%; **Table 2**, **Figure 2A**) poorer balance time for each subsequent level. The associations with paternal occupational class, maternal education and own educational attainment all became smaller with age (all $p < 0.001$, **Table 2**, **Figure 2**), however there was no interaction between own occupational class and age ($p = 0.1$).

Anthropometric Indicators and Balance

Height had a quadratic association with balance such that taller individuals had better balance times than shorter individuals although this association plateaued at the tallest heights (see **Table 2**, **Figure 3**). BMI had an inverse linear association with balance, where every additional kg/m^2 was associated with 2.8% (2.5, 3.1%) poorer balance time (**Table 2**, **Figure 4**). There was no evidence of an interaction with age for either height ($p = 0.1$) or BMI ($p = 0.6$) suggesting that the association stayed constant over time (**Table 3**).

Health Behaviors and Balance

Those who participated in leisure time physical activity 1–4 times [23.9% (17.3, 30.5%)] or 5+ times [23.3% (18.0, 28.7%)] per month had better balance times than those who did not participate at age 53 (**Table 2**, **Figure 5A**). There was no difference in balance between those who participated in leisure time physical activity 1–4 times/month and those who participated 5+ times/month. There was evidence that the association got smaller with age, as shown by the age-interaction for those who participated 1–4 times/month. Individuals who had a past history of smoking or who were current smokers had worse balance ability than those who had never smoked [6.1% (3.3, 8.9%); **Table 2**, participating in leisure time physical activity, reporting a history of CVD events, higher levels of anxiety and depression and lower verbal memory remained associated with lower balance time. Nearly all age interaction terms weakened and were no longer statistically significant (at the 5% level) in this model, although there remained evidence that the associations with sex and verbal memory decreased with age.

DISCUSSION

Main Findings

We quantified associations between a range of risk factors across life and balance performance at ages 53, 60–64, and 69. Individuals with better balance were more likely to be male, have higher SEP in both childhood and adulthood,

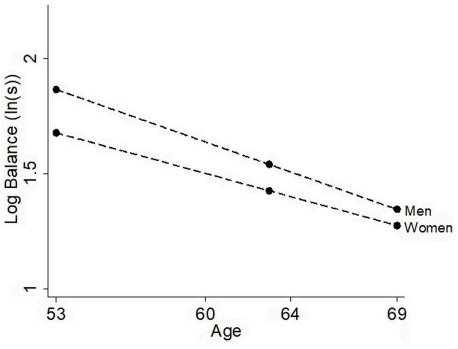

FIGURE 1 | Differences in balance time at ages 53, 60–64, and 69 years by sex.

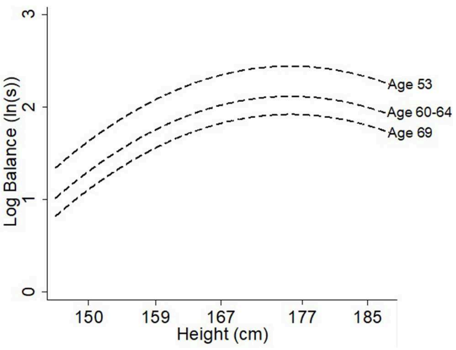

FIGURE 3 | Differences in balance time at ages 53, 60–64, and 69 years by height (cm).

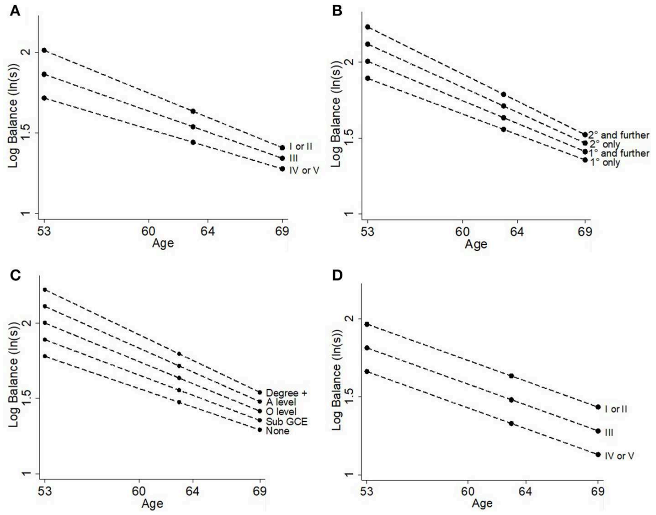

FIGURE 2 | Differences in balance time at ages 53, 60–64, and 69 years by **(A)** paternal occupational class, **(B)** maternal education, **(C)** own education, and **(D)** own occupational class.

be taller, have lower BMI, partake in leisure time physical activity and were less likely to smoke. Individuals with better balance were also more likely to be healthier (no history of diabetes or CVD, not currently experiencing respiratory symptoms or knee pain), less likely to be experiencing symptoms of depression and anxiety, and more likely to have higher verbal memory. In a combined model, the majority of risk factors remained independently associated with balance, indicating that the factors across life that are associated with one-legged balance performance are multifaceted and complex.

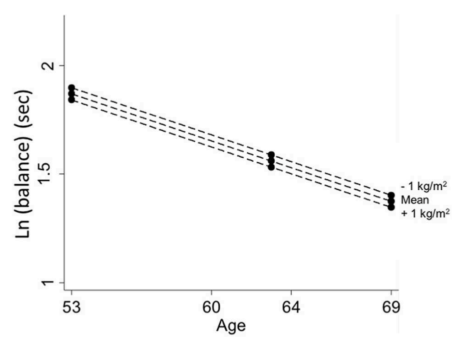

FIGURE 4 | Differences in balance time at ages 53, 60–64, and 69 years by BMI (kg/m^2).

Sex differences in balance performance were not explained by adjustment for other risk factors. Furthermore, there was no evidence to suggest that the associations between these risk factors and balance differed by sex, although several associations did change with age. Associations of balance performance with sex, socioeconomic indicators, physical activity and verbal memory became smaller with increasing age, while associations with anthropometric indicators, smoking, and physical health status stayed constant. Two associations became larger with age; associations of both knee pain and symptoms of anxiety and depression with balance doubled from age 53–69.

Comparison With Other Studies and Explanation of Findings

Socioeconomic Indicators

A systematic review and meta-analysis of over 22 000 individuals from 11 separate studies reported that lower childhood SEP (as indicated by parental occupation and education) was associated with inability to balance with eyes open for ≥5 s (Birnie et al., 2011b); adjustment for adult SEP fully attenuated the effect of childhood SEP (paternal occupation used if available). However, maternal education and both indicators of adulthood SEP remained independently associated with balance time in our fully-adjusted model. In addition to differing operationalisations of one-legged balance performance (continuous vs. binary; eyes closed vs. eyes open), a possible explanation for these differing results is that 9 of the 11 studies included in the meta-analysis relied upon retrospective reports of childhood SEP (Birnie et al.,

TABLE 3 | Summary of tests of non-linearity, sex interactions and age interactions of all covariates with balance performance.

	Description of how variable is modeled	Sex interaction *p*-value	Age interaction effect on size of association
Sex (female)	n/a[a]	n/a	↓ with age
Socioeconomic indicators			
Paternal occupational class	Continuously	0.9	Effect ↓ with age
Maternal education	Continuously	0.7	Effect ↓ with age
Education	Continuously	0.5	Effect ↓ with age
Own occupational class	Continuously	0.4	Constant with age
Anthropometry			
Height	Quadratic term	0.9	Constant with age
BMI	Linear term only	0.1	Constant with age
Health behaviors			
Leisure time physical activity	Categorically	0.7	Effect ↓ with age
Smoking	Continuously	0.1	Constant with age
Current health status			
History of diabetes	n/a[a]	0.5	Constant with age
History of cardiovascular events	n/a[a]	0.2	Constant with age
Respiratory symptoms	n/a[a]	0.6	Constant with age
Knee pain	n/a[a]	0.8	Effect ↑ with age
Symptoms of anxiety & depression	Linear term only	0.4	Effect ↑ with age
Other			
Verbal memory	Linear term only	0.2	Effect ↓ with age

[a] *Unable to test non-linearity in dichotomous indicators.*

2011a). A strength of NSHD is that data on SEP and other risk factors were prospectively ascertained and so not prone to recall bias. As previously shown in relation to cognitive outcomes (Kaplan et al., 2001; Guralnik et al., 2006), paternal occupational class and maternal education may have distinctive associations with balance performance; further exploration of these differences are required.

While childhood SEP is hypothesized to be associated with balance ability via a complex pathway of health behaviors, education, adult SEP, cognitive ability and/or health conditions, the association remained when these factors were included in the model. Thus, childhood may also represent a sensitive period of development for balance ability, as previously hypothesized when testing associations of childhood cognition and midlife balance performance in NSHD (Blodgett et al., 2020). Adult SEP may also be associated with balance through a pathway of current physical and cognitive health or health behaviors. That both childhood and adult SEP indicators remained independently associated with balance suggests that accumulation of low SEP across the life course may be a greater risk factor than low SEP at any one particular life stage.

Notably, the relationship between most SEP indicators and balance time weakened with increasing age. This suggests that SEP may be more strongly associated with balance in midlife than at older ages when substantial age-related decline begins and chronic diseases manifest. Nevertheless, the association between the most recent measure of SEP (occupational class at age 53) and balance did not change with age.

Anthropometric Indicators

Higher body mass may influence the stability of an individual and the motor mechanisms involved in the balance process. For example, individuals with higher BMI often require more movement in order to maintain their balance, thus frequently demonstrate high levels of postural sway and reduced balance performance (D'Andréa Greve et al., 2013; Hita-Contreras et al., 2013). Studies have suggested that body stability is inversely related to the height of the center of gravity (D'Andréa Greve et al., 2013) and that shorter individuals are better able to maintain their balance. However, we found that taller individuals had better balance than shorter individuals though this effect appeared to plateau above a certain height.

Previous evidence has suggested that sex differences in balance performance disappear when scores are normalized to height (Maki et al., 1990; Hageman et al., 1995; Era et al., 2002; Bryant et al., 2005), while other studies have shown that anthropometric factors are major determinants of balance performance in women only (Kim et al., 2012). However, we found no sex differences in the association of either height or BMI with balance ability and adjustment for these measures did not explain sex differences (as seen in the combined model). Given that men have higher average strength and mobility compared to women (Miller et al., 1993; Sugimoto et al., 2014; Zunzunegui et al., 2015), further investigation into whether more detailed assessment of body composition (e.g., lean mass, fat mass) explains sex differences is warranted.

Health Behaviors

It is well-recognized that low levels of physical activity (de Rezende et al., 2014; Cooper et al., 2016; Olanrewaju et al., 2016; Schwingshackl et al., 2017) and current or past smoking (Cooper et al., 2016; Daskalopoulou et al., 2018) have negative consequences for an individual's physical capability, including their balance performance. Some studies have shown increasing levels of physical activity are associated with better balance (Powell et al., 2011; Cooper et al., 2015), while others have shown that there is no difference in health benefit between moderately active and maximally active groups (Cooper et al., 2016). In this study, participation in leisure time physical activity was associated with better balance performance. Although there was little additional benefit for balance ability beyond 1–4 times per month at age 53, a graded association between increasing levels of physical activity and balance performance emerged by age 69 (see **Figure 5A**).

Individuals who currently smoked had worse balance performance compared with those who were ex-smokers; ex-smokers also had worse balance compared with those who had never smoked. Although not previously examined in balance ability, this is consistent with increasing severity of poor physical capability seen amongst categories of smoking history (North et al., 2015; Cooper et al., 2016), suggesting that quitting smoking may have a positive association with balance performance.

Current Health Status

The presence of each physical and mental health condition (diabetes, CVD, respiratory symptoms, knee pain, symptoms of anxiety, and depression) was associated with poorer balance performance. This is consistent with the literature on how current health impacts an individual's physical capability or functional decline (Welmer et al., 2012; Kuh et al., 2014; Ryan et al., 2015). Each health condition likely has a direct biological pathway impacting balance. For example, diabetes is related to both peripheral neuropathy (Greene et al., 1992) and age-related visual impairment (Lutty, 2013; Pelletier et al., 2016) while knee pain can have a direct impact on proprioception and musculoskeletal function (Sanchez-Ramirez et al., 2013). Individuals with a history of CVD events or respiratory symptoms often demonstrate shared pathophysiological features common in those with balance impairment including increased postural sway due to physical displacement of breathing (Jeong, 1991), decreased blood flow in specific functional areas (Abate et al., 2009) and decreased musculoskeletal capacity (Crisan et al., 2015). Finally, increased inflammatory markers that are common in arthritis, such as C-reactive protein or nitric oxide (Cepeda et al., 2016) are also more common in individuals with depression than those without. In addition to this inflammation pathway, individuals with depression also tend to restrict their physical activity, have reduced motivation to perform well and exhibit psychomotor impedance such as a slowing in musculoskeletal components (Bennabi et al., 2013); all of these factors can influence balance performance.

The associations of diabetes, CVD and respiratory symptoms with balance performance were constant. However, the associations of knee pain and symptoms of anxiety and

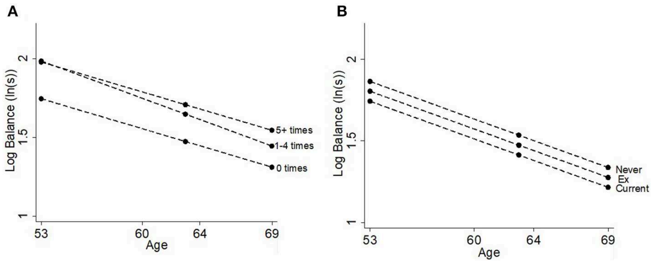

FIGURE 5 | Differences in balance time at ages 53, 60–64, and 69 years by **(A)** leisure time physical activity and **(B)** smoking status.

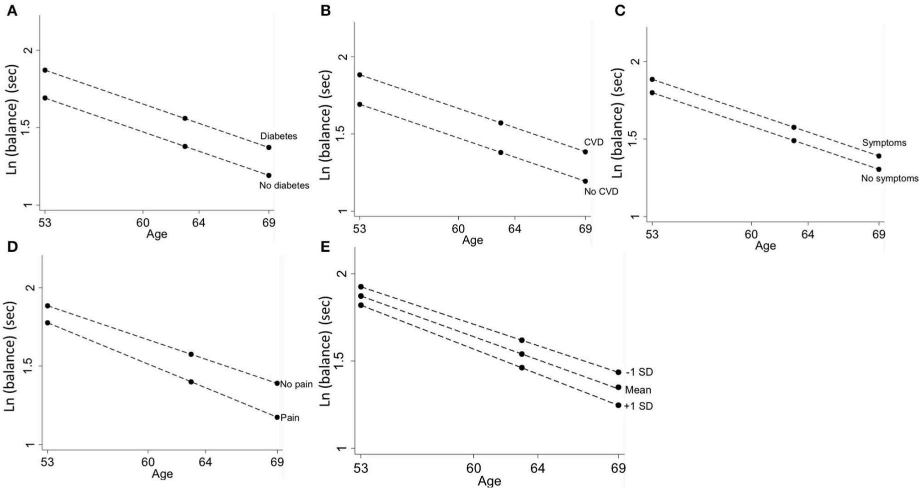

FIGURE 6 | Differences in balance time at ages 53, 60–64, and 69 years by **(A)** diabetes, **(B)** CVD events, **(C)** respiratory symptoms, **(D)** knee pain, and **(E)** symptoms of depression and anxiety.

depression with balance got stronger at older ages. The constant or increasing associations between health conditions and balance ability with age suggests that overall health becomes relatively more important for balance ability in later life; this could in part explain why the strength of associations with many other risk factors decreased with increasing age.

Cognitive Ability

As expected given previous findings in NSHD (Kuh et al., 2009a; Blodgett et al., 2020), higher verbal memory was associated with higher levels of balance performance. Cognitive processing of sensory and motor input is an important component of the balancing process (Li et al., 2018). Previous evidence in NSHD has shown that childhood cognitive ability is associated with adult balance performance; this is primarily via an adult cognition and education pathway that is independent of most of the other risk factors examined here (Blodgett et al., 2020). As suggested above, the decreasing strength of association with age suggests that cognitive ability becomes less important with age, as other factors in the aging process, in particular health conditions, become more important.

Methodological Considerations

A major strength of this paper is the assessment of balance performance at three ages, which facilitated our novel investigation into whether associations between risk factors and balance ability change over 16 years, from mid to later life. A second strength is the comprehensive investigation, in separate and combined models, of the associations between 14 different factors across life and balance performance. These risk factors were all prospectively ascertained which increases reliability of response and limits recall bias. A third strength was the methods used to include those individuals who had missing balance scores for health reasons or because of death or loss to follow up between ages 53 and 69. These combined strengths provided novel evidence on how the associations between these risk factors and balance ability change with age. Finally, the age homogeneity of the sample eliminated any confounding by age that is common when examining physical capability in mid and later life (Seeman and Chen, 2002; Garber et al., 2010).

One potential limitation of our study is that we were unable to include participants in analyses if they had been lost to follow up before age 53 (i.e., the age at which balance was first assessed). Characteristics of study members who were lost to follow up before the first clinical assessment at age 53 were more likely to be male (Stafford et al., 2013), have lower childhood and adulthood occupational class (Stafford et al., 2013; Kuh et al., 2016), demonstrate unhealthy behaviors (smoking, physical inactivity) (Stafford et al., 2013), have lower verbal memory (Stafford et al., 2013) and have poorer overall

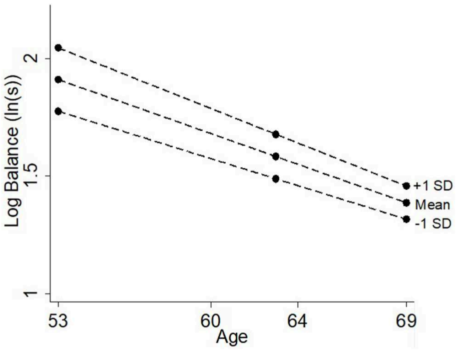

FIGURE 7 | Differences in balance time at ages 53, 60–64, and 69 years by verbal memory.

TABLE 4 | Combined model of all risk factors and all significant age interactions from individual models additionally adjusting for death and attrition, $n = 2,465$ (obs = 5,150).

	Mean difference in % balance time at age 53 (intercept)		Age (years)*risk factor interaction	
Risk factors[a]	**Coefficient (%) (95% CI)**	***p-value***	**Coefficient (%) (95% CI)**	***p-value***
Sex (female)	−21.7 (−28.7, −14.7)	<0.001	0.9 (0.4, 1.3)	<0.001
Paternal occupational class[b] (per 1 level change)	−2.7 (−6.8, 1.5)	0.21	0.3 (−0.1, 0.7)	0.11
Maternal education[c] (per 1 level change)	−3.9 (−6.7, −1.0)	<0.01	0.1 (−0.2, 0.3)	0.51
Education at age 26[d] (per 1 level change)	−3.8 (−6.2, −1.3)	<0.005	−0.2 (−0.4, 0.02)	0.08
Own occupational class[b] (per 1 level change)	−4.9 (−8.2, −1.7)	<0.005	–	–
Height (m)				
linear term	5.0 (−1.6, 11.6)	0.13	–	–
quadratic term	−0.02 (−0.04, 0.004)	0.12		
BMI (per kg/m^2)	−2.1 (−2.5, −1.7)	<0.001	–	–
Leisure time physical activity[e]				
1–4 times/week	9.1 (1.9, 16.3)	<0.001	0.1 (−0.6, 0.8)	0.28
5+ times/week	5.8 (−0.2, 11.8)		0.3 (−0.3, 0.9)	
Smoking[f] (per 1 level change)	1.4 (−1.6, 4.4)	0.36	–	–
Diabetes[g]	−6.9 (−14.1, 0.5)	0.07	–	–
CVD events[g]	−7.1 (−14.0, −0.3)	0.04	–	–
Respiratory symptoms[g]	−2.5 (−7.0, 2.0)	0.28	–	–
Knee pain[g]	−4.5 (−11.2, 2.1)	0.18	−0.2 (−0.8, 0.4)	0.55
Symptoms of depression/anxiety[h] (per 1 SD)	−3.1 (−5.8, −0.4)	0.02	−0.1 (−0.4, 0.2)	0.46
Verbal memory[h] (per 1SD)	5.9 (2.8, 8.9)	<0.001	−0.4 (−0.7, −0.1)	<0.01

[a] *all models adjusted for sex as no evidence of sex interactions (see **Table 3**).*
[b] *ref: I Professional or II Intermediate.*
[c] *ref: Secondary and further education.*
[d] *ref: Degree or higher.*
[e] *ref: none in last 4 weeks.*
[f] *ref: current smoker.*
[g] *ref: individuals with no health condition.*
[h] *SD estimates at each age are provided in **Table 1**.*

health (Kuh et al., 2016). Participants who were followed up to age 53 but could not be included in analyses due to missing data on risk factors had similar characteristics to those lost to follow-up before age 53. Many of these characteristics (i.e., low SEP, unhealthy behaviors, lower cognition, and poorer health) were negatively associated with balance ability, thus it is hypothesized that those with lost to follow up before age 53 or with missing risk factor data may have had poorer balance. This likely resulted in an underestimation of the size and strength of associations.

Two further limitations are the assumptions of the model: that the change in balance over time is linear and that all individuals follow the same mean trajectory of decline. Individuals are likely to exhibit heterogonous aging trajectories as they demonstrate different patterns of change in balance performance with age (e.g., steeper decline, delayed decline, maintenance of balance ability). As there were only three time points for balance, it was not appropriate to test for non-linearity in balance trajectories. Identifying polynomial time terms can help identify the age at which decline begins or accelerates. Further research, with at least four measures of balance performance, should address these differences across time and between individuals. We also need to consider the possibility that other factors not considered in our analyses such as alcohol consumption and medication use may also be important and need to be considered in future research.

Although there were multiple comparisons, the risk of Type 1 error remains low as all of the primary associations in **Table 2** were significant at $p < 0.001$ and an alpha of 0.05 was intentionally used for interaction terms to ensure a parsimonious model. Finally, one-legged balance ability measures a specific aspect of static balance that does not directly represent the dynamic balance relied upon in everyday situations (Owings et al., 2000; Mackey and Robinovitch, 2005; Bhatt et al., 2011). Further research should consider if associations between the risk factors identified in this study are consistent for tests of dynamic balance or for more sensitive measures of postural sway, as assessed with a force plate.

Implications and Conclusions

We investigated 14 different factors across life that are associated with balance performance. These findings are important in considering appropriate interventions to minimize balance decline or when identifying high-risk individuals. That multiple risk factors were identified suggests that a multifactorial approach including behavioral, health and cognitive factors (amongst others) may have more benefit than a focus on a single risk factor. As several of these risk factors have different associations with balance at different ages, there may be benefit in targeting different factors at different ages. Knee pain and symptoms of depression and anxiety both appear to become more important with age and may represent important targets for intervention in midlife before their potential association with balance performance increases. While not all of the factors identified (e.g., socioeconomic, height, smoking history) may be easily modified, they are likely to have utility in helping to identify individuals at high risk of future balance difficulties who may require more support than others to maintain balance ability as they age.

In summary, this study identified many anthropometric, behavioral, socioeconomic, health and cognitive risk factors across life that are associated with balance ability. The majority of variables remained independently associated with one-legged balance performance, suggesting that the range of risk factors associated with poor balance ability is diverse and complex. This highlights the importance of considering both type (i.e., multifactorial approach) and timing (i.e., early, mid, and later life) of interventions that target balance performance in adulthood.

DATA AVAILABILITY STATEMENT

The datasets used in this study will not be made publicly available. Access to NSHD data adheres to strict confidentiality guidelines but these data are available to bonafide researchers upon request to the NSHD Data Sharing Committee via a standard application procedure. Further details can be found at http://www.nshd.mrc.ac.uk/data. doi: 10.5522/NSHD/Q101; doi: 10.5522/NSHD/Q102; doi: 10.5522/NSHD/Q103.

ETHICS STATEMENT

At each wave of data collection, relevant ethical approval has been received. Ethical approval for the most recent data collection (2014–2015) was obtained from Queen Square Research Ethics Committee (13/LO/1073) and Scotland A Research Ethics Committee (14/SS/1009). All participants have provided written informed consent.

AUTHOR CONTRIBUTIONS

JB performed statistical analyses and wrote the first draft of the manuscript. All authors contributed to the conception and design of the study, to manuscript revision, read, and approved the submitted version.

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Research Article

Childhood Cognition and Age-Related Change in Standing Balance Performance From Mid to Later Life: Findings From a British Birth Cohort

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Abstract

Background: Cognitive processing plays a crucial role in the integration of sensory input and motor output that facilitates balance. However, whether balance ability in adulthood is influenced by cognitive pathways established in childhood is unclear, especially as no study has examined if these relationships change with age. We aimed to investigate associations between childhood cognition and age-related change in standing balance between mid and later life.

Methods: Data on 2,380 participants from the MRC National Survey of Health and Development were included in analyses. Repeated measures multilevel models estimated the association between childhood cognition, assessed at age 15, and log-transformed balance time, assessed at ages 53, 60–64, and 69 using the one-legged stand with eyes closed. Adjustments were made for sex, death, attrition, anthropometric measures, health conditions, health behaviors, education, other indicators of socioeconomic position (SEP), and adult verbal memory.

Results: In a sex-adjusted model, 1 standard deviation increase in childhood cognition was associated with a 13% (95% confidence interval: 10, 16; $p < .001$) increase in balance time at age 53, and this association got smaller with age (cognition × age interaction: $p < .001$). Adjustments for education, adult verbal memory, and SEP largely explained these associations.

Conclusions: Higher childhood cognition was associated with better balance performance in midlife, with diminishing associations with increasing age. The impact of adjustment for education, cognition and other indicators of SEP suggested a common pathway through which cognition is associated with balance across life. Further research is needed to understand underlying mechanisms, which may have important implications for falls risk and maintenance of physical capability.

Keywords: Life course, Balance, Cognition, Age-related decline

The ability to balance underlies nearly all physical movement at each stage of life from an infant learning to stand to an older adult trying to avoid a fall. Age-related decline in balance ability is a particular concern due to high incidence of falls in older individuals (1), and growing evidence that poor balance performance is also associated with higher disability, morbidity, and mortality rates (2,3). Yet balance remains an under-recognized and frequently overlooked aspect of physical health (4,5).

Neural processing plays a crucial role in integrating the sensory input and motor output involved in successfully balancing (6). Given that the brain undergoes significant development throughout childhood and adolescence (7), the neural processes involved in balance could be a result of early establishment of synapses and neural connectivity (8). Further investigation of neurological development and its contribution to balance could identify a period in early life, during which cognitive processes involved in balance may be formed.

Previous analyses of the MRC National Survey of Health and Development (NSHD) (9,10) and a Danish cohort study (11) have demonstrated that higher cognition in early life (at ages 8–18) was associated with better balance performance at ages 53 and 50, respectively. However, no study has investigated these associations with balance in later life nor investigated serial measures of balance ability to see if these associations change with age. Studies examining age-related decline in physical capability have prioritized more proximal age-related factors, such as chronic health conditions, health care utilization, and other psychosocial factors (12–14). Conversely, the life course approach suggests that physical and social factors in early and midlife contribute to health and disease risk in later life (15). Here, childhood cognition may be associated with peak balance ability and subsequent age-related change for several reasons: childhood cognition is considered to be an initial indicator of lifetime cognitive ability, it is associated with lifelong socioeconomic pathways and it is predictive of health behaviors, all of which relate to balance ability (16–18).

The objectives of this analysis were to (a) examine the associations between childhood cognition and standing balance at three ages in mid and later life; (b) assess whether these associations change with age; and (c) investigate the impact of adjusting for adult cognition, education, anthropometric measures, and sociobehavioural factors.

Methods

Study Sample

The NSHD is a nationally representative study of 5,362 males and females born within 1 week in March 1946 in England, Scotland, and Wales. Study members have been assessed up to 24 times since birth and were most recently examined by trained research nurses at ages 53 (n = 2,988), 60–64 (n = 2,229) and 69 (n = 2,149). Reasons for nonparticipation include death, emigration, refusal, and incapacity [(19) Supplementary Figure 1]. Participants provided written consent at each data collection. Ethical approval for the most recent visit (at age 69) was given by Queen Square Research Ethics Committee (13/LO/1073) and Scotland A Research Ethics Committee (14/SS/1009).

Measurement of Balance

At ages 53, 60–64, and 69, participants were asked to fold their arms across their chest and, when indicated by the nurse, stand on their preferred leg and raise the contralateral foot off the floor for a maximum of 30 seconds. The test was undertaken first with eyes open and then repeated with eyes closed, with the eyes closed score used in these analyses due to a ceiling effect with eyes open. Balance time was measured in seconds at age 53 and in milliseconds at ages 60–64 and 69. At age 53, 93.4% of participants who underwent assessment completed an eyes closed balance test, 94.8% completed the test at age 60–64, while 92.3% completed the test at age 69. Reasons for noncompletion of tests were recorded by the nurse. Those who were unable to complete the test due to health reasons were excluded from primary analyses.

Childhood Cognition

Childhood cognition was ascertained at age 15 when participants completed the Alice Heim (AH4) test of fluid intelligence, the Watts–Vernon reading test, and a study-specific test of mathematical ability (17,20). Each test score was standardized and then summed to create an overall cognitive score which was then standardized to the analytical sample (mean of 0, *SD* [standard deviation] of 1). Consistent with other NSHD analyses, if the score was missing at age 15, scores from comparable examinations of global cognition at ages 11 or 8 (n = 165) were used (17,21,22).

Covariates

Covariates were chosen based on a review of the literature and previous NSHD findings (2,17,22–26). Anthropometric measures, health conditions, and behaviors were assessed at ages 53, 60–64, and 69. Height and BMI (kg/m^2), derived from nurse-measured height and weight, were considered as continuous measures (23). Four chronic health conditions were ascertained using a series of self-reported questions on knee pain, respiratory symptoms, history of diabetes, and cardiovascular events (2). Individuals reported the frequency they participated in sports, vigorous leisure activities or exercise (never, 1–4 times/month, 5+ times/month) and whether they smoked cigarettes (never, past smoker, current smoker) (24).

Paternal occupational class, reported at age 4 (or ages 11 or 15 if missing at age 4 [n = 45]), and own occupational class, reported at age 53 (or ages 43 or 36 if missing at age 53 [n = 83]), were based on the Registrar General's Social Classification (25) and were grouped into three categories: I (professional) and II (intermediate); IIINM (skilled nonmanual) and IIIM (skilled manual); IV (partly skilled manual) and V (unskilled manual) (27). Maternal education was classified into four categories: primary only; primary and further education; secondary only; secondary and further education.

Educational attainment by age 26 was categorized into five groups: degree or higher; A levels or equivalent (typically attained at age 18); O levels or equivalent (typically attained at age 16); clerical course or equivalent; and none. While education is often conceptualized as a measure of socioeconomic position (SEP) (28), here, it is considered separately as a mediator due to the clearly established pathway from childhood cognition to education and adult cognition (17). Adult verbal memory was measured at each age using a 15-item word-learning task that assesses fluid ability (17,22). The total score (max: 45 over three trials) was standardized to the analytical sample such that the mean was 0 and the *SD* was 1. As multilevel models assume that any missing data are missing at random, we also adjusted for binary indicators for mortality (ie, died between ages 53 and 69) and attrition (ie, permanent attrition between ages 53 and 69 not due to death) (26).

Statistical Analyses

Repeated measures multilevel models (MLMs) were used to examine the associations between childhood cognition and balance time and to assess if this changed with age. MLMs, with fitted random intercepts and slopes, allow for variation both between individuals and within individuals over time (29). The age intercept was set to zero at age 53 for all models. Due to the skewed distribution of balance times, balance was log-transformed and all estimates are presented as percent change in balance time (30). Initial models tested if the association between childhood cognition and balance deviated from linearity and if there were any interactions between childhood cognition and sex or age. This selected model was then adjusted for sex, death, attrition, and anthropometric measures. The following covariates were then added sequentially: chronic health conditions, health behaviors, socioeconomic indicators, education, and verbal memory. Any nonlinear and sex by age interaction terms were included where relevant.

The analytical sample included individuals with a balance time at one or more ages, childhood cognition score and complete covariate data (n = 2,380; Supplementary Figure 1). Sensitivity analyses were conducted to test the sex-adjusted association in the maximal available sample and to test all models in the sample with a value of zero imputed where scores were missing due to health reasons (166 additional observations, but only n = 49 additional participants) in keeping with previous analyses in NSHD (16).

Results

Men had higher childhood cognition, educational attainment, occupational class, and balance times at all ages than women, but lower

Table 1. Characteristics of Analytical Sample (Those With Data on Childhood Cognition, One or More Measure of Balance Ability, Complete Covariates) in NSHD (*n* = 2,380) by Sex

Variable		Men (*n* = 1,185)	Women (*n* = 1,195)
Childhood cognition, mean (*SD*)		0.12 (1.01)	−0.04 (0.95)
Balance time (s), median (IQR)			
Age 53		5 (3–10), *n* = 1,101	4 (3–7), *n* = 1,134
Age 60–64		3.79 (2.53–5.73), *n* = 829	3.27 (2.25–4.83), *n* = 902
Age 69		2.98 (1.98–4.87), *n* = 803	2.91 (1.91–4.31), *n* = 817
Height (m), mean (*SD*)			
Age 53		1.75 (0.06), *n* = 1,126	1.62 (0.06), *n* = 1,170
Age 60–64		1.75 (0.07), *n* = 862	1.62 (0.06), *n* = 935
Age 69		1.74 (0.06), *n* = 830	1.60 (0.06), *n* = 869
BMI (kg/m^2), mean (*SD*)			
Age 53		27.4 (4.1), *n* = 1,126	27.3(5.2), *n* = 1,167
Age 60–64		27.9 (4.1), *n* = 861	28.0(5.5), *n* = 935
Age 69		28.1 (4.5), *n* = 842	28.2(5.7), *n* = 873
Paternal occupational class, *n* (%)			
I professional/II intermediate		320 (27.0)	308 (25.8)
III skilled (nonmanual or manual)		583 (49.2)	586 (49.0)
IV partly skilled/V unskilled		282 (23.8)	301 (25.2)
Maternal education, *n* (%)			
Secondary and further education		141 (11.9)	143 (12.0)
Secondary only		143 (12.1)	131 (11.0)
Primary and further education		190 (16.0)	164 (13.7)
Primary only		711 (60.0)	757 (63.3)
Own occupational class, *n* (%)			
I professional/II intermediate		620 (52.3)	444 (37.2)
III skilled (non-manual or manual)		440 (37.1)	509 (42.6)
IV partly skilled/V unskilled		125 (10.6)	242 (20.3)
Knee pain, n (%)			
Age 53		169 (15.1)	237 (20.4)
Age 60–64		172 (19.9)	224 (23.8)
Age 69		147 (17.4)	187 (21.4)
Respiratory symptoms, *n* (%)			
Age 53		219 (19.4)	211 (18.0)
Age 60–64		173 (19.8)	174 (18.1)
Age 69		205 (25.2	200 (21.9)
History of angina, stroke or MI, *n* (%)			
Age 53		65 (5.8)	34 (2.9)
Age 60–64		103 (11.7)	46 (4.9)
Age 69		142 (16.3)	87 (9.6)
History of diabetes, *n* (%)			
Age 53		37 (3.1)	26 (2.2)
Age 60–64		92 (9.4)	74 (7.0)
Age 69		128 (13.3)	104 (10.2)
Leisure time physical activity, *n* (%)			
Age 53	None	513 (45.5)	573 (48.9)
	1–4 times/month	222 (19.7)	198 (16.9)
	5+ times/month	393 (34.8)	402 (34.3)
Age 60–64	None	546 (64.5)	574 (62.1)
	1–4 times/month	110 (13.0)	142 (15.4)
	5+ times/month	191 (22.6)	208 (22.5)
Age 69	None	520 (59.4)	578 (60.0)
	1–4 times/month	99 (11.3)	128 (13.3)
	5+ times/month	257 (29.3)	258 (26.8)
Smoking status, *n* (%)[a]			
Age 53	Current	254 (22.5)	259 (22.1)
	Previous smoker	575 (51.0)	527 (44.9)
	Never smoker	299 (26.5)	387 (33.0)
Age 60–64	Current	111 (12.4)	117 (12.1)
	Previous smoker	519 (58.2)	507 (52.3)
	Never smoker	262 (29.4)	346 (35.7)

Table 1. *Continued*

Variable		Men (n = 1,185)	Women (n = 1,195)
Age 69	Current	98 (10.4)	91 (9.0)
	Previous smoker	590 (62.3)	573 (56.8)
	Never smoker	259 (27.4)	345 (34.2)
Educational attainment, n (%)			
Degree or higher		174 (14.7)	70 (5.9)
GCE A level or Burnham B		343 (29.0)	284 (23.8)
GCE O level or Burnham C		176 (14.9)	308 (25.8)
Sub GCE		72 (6.1)	110 (9.1)
None attempted		420 (35.4)	423 (35.4)
Verbal memory, mean (SD)			
Age 53		23.0 (6.2), n = 1,126	24.9 (6.2), n = 1,164
Age 60–64		23.1 (5.91), n = 839	25.2 (6.03), n = 914
Age 69		21.2 (5.99), n = 821	23.2 (6.02), n = 852
Death by age 69, n (%)		116 (9.8)	78 (6.5)
Attrition by age 69 (excl. death), n (%)		218 (18.4)	217 (18.2)

verbal memory (all $p < .001$; Table 1). Men were also less likely to have respiratory symptoms and more likely to have a history of diabetes and cardiovascular events and to have died between ages 53 and 69 (all $p < .05$; Table 1). Those excluded due to missing covariate data (n = 405) were similar to the main analytical group (n = 2,380), but were more likely to have a lower childhood SEP ($p < .01$), to be a current or ex-smoker ($p < .05$) and to have lower childhood cognition ($p < .001$).

In men, median balance time decreased from 5 seconds (Q1, Q3: 3, 10; n = 1,101) at age 53–3.79 seconds (2.53, 5.73; n = 829) at age 60–64 and 2.98 seconds (1.98, 4.87; n = 803) at age 69. In women, median balance time decreased from 4 seconds (3, 7; n = 1,134) at age 53–3.27 seconds (2.25, 4.83; n = 902) at age 60–64 and 2.91 seconds (1.91, 4.31; n = 817) at age 69 (Table 1).

Sex-adjusted multilevel models (n = 2,380, obs = 4,926), including a childhood cognition by age interaction, demonstrated that a 1 SD increase in childhood cognition was associated with a 13% (95% confidence interval [CI]: 10%, 16%) increase in balance time at age 53 ($p < .001$; Table 2, Model 1). The interaction between childhood cognition and age indicated that this association weakened over time (childhood cognition × age interaction term: by −0.6% per SD cognition for every year increase in age [95% CI: 0.3%, 0.8%], $p < .001$; Table 2, Model 1; Figure 1). Thus, a 1 SD increase in childhood cognition was associated, in sex-adjusted models, with 7% (5%, 9%) and 4% (1%, 7%) increases in balance times at ages 60–64 and 69, respectively.

The associations between higher childhood cognition and better balance times at the intercept (age 53) remained fairly constant with the addition of death and attrition (Table 2, Model 2), anthropometric indicators (Table 2, Model 3), chronic health conditions (Table 2, Model 4) and health behaviors (Table 2, Model 5). The addition of socioeconomic indicators (Table 2, Model 6), educational attainment (Table 2, Model 7) and verbal memory (Table 2, Model 8) partially attenuated the association between childhood cognition and balance, with the lowest intercept estimate of 6% ([3%, 10%], $p < .001$; Model 7) in the education-adjusted model. In the fully adjusted model, the estimates were further attenuated (3% [−1%, 7%] at 53 y/intercept, $p = .15$; Model 9).

When the sex-adjusted model was repeated in the maximal available sample (n = 2,785; obs = 6,379), the estimates remained consistent with those in the restricted sample (Figure 1). When scores that were missing due to health reasons were included (imputed with balance time of 0 second), the main findings did not change (Supplementary Table 1).

Discussion

Higher childhood cognition was associated with better balance performance in midlife, with diminishing associations with increasing age. This association remained robust to adjustment for death, attrition, anthropometric factors, chronic health conditions, and health behaviors. It was largely explained by education, adult verbal memory, and other socioeconomic indicators, suggesting that the association between childhood cognition and later life balance acts largely via cognitive and socioeconomic pathways.

Our findings are consistent with two previous sets of analyses in NSHD and one other Danish study demonstrating an association between higher cognition in early life and better balance performance in midlife (10,11,23). Our study builds on this evidence by demonstrating that although the sex-adjusted association is strongest in midlife (at age 53), it remains at later ages (ages 60–64 and 69). The attenuation in effect size after adjustment for SEP, education, and verbal memory suggests that these factors may mediate the association between childhood cognition and balance.

Explanations of Findings

The reliance of balance on higher level cognitive processes could extend back past current cognitive ability to the initial formation of neural connections in early life. The cerebellum, an area of the brain heavily involved in balance, undergoes substantial development early in life (7,31) with continual maturation until approximately 15 years of age (32). Childhood may represent a sensitive period necessary for the development of important synapses and neural connectivity involved in successfully balancing. As cognitive ability in childhood is the start of a lifelong cognitive pathway (16–18), it may provide the earliest opportunity for successful interventions.

Our findings suggest that the associations between early life cognition and balance may be mediated by education, adult verbal memory, and SEP. First, balance ability across life is strongly dependent on cognitive processes involved in sensori-motor integration of the nervous system. This is consistent with partial attenuation of the estimates when education and adult verbal memory were added to the model. It is known that cognitive ranking remains fairly consistent

Table 2. Results from Multilevel Models Demonstrating Percent (%) Difference in Mean Balance Time by Childhood Cognition (*n* = 2,380 Individuals, 4,926 Observations)

	Percent Difference in Balance Score at Age 53 Per *SD* of Childhood Cognition [intercept]		Childhood Cognition (*SD*) × Age (Year) Interaction	
Model	Coefficient (%) (95% CI)	*p* Value	Coefficient (%) (95% CI)	*p* Value
1: age[a], sex[b]	13 (10, 16)	<.001	−0.6 (−0.8, −0.3)	<.001
2: model 1+ death + attrition[c]	12 (10, 15)	<.001	−0.5 (−0.8, −0.3)	<.001
3: model 2 + anthropometric[d]	12 (9, 15)	<.001	−0.6 (−0.8, −0.3)	<.001
4: model 3 + chronic health conditions[e]	12 (9, 14)	<.001	−0.6 (−0.8, −0.3)	<.001
5: model 3 + health behaviors[f]	11 (8, 13)	<.001	−0.5 (−0.8, −0.3)	<.001
6: model 3 + SEP[g]	8 (5, 11)	<.001	−0.6 (−0.8, −0.3)	<.001
7: model 3 + education[h]	6 (3, 10)	<.001	−0.4 (−0.7, −0.04)	.03
8: model 3 + verbal memory[i]	9 (6, 12)	<.001	−0.6 (−0.8, −0.3)	<.001
9: fully adjusted[j]	3 (−1, 7)	.15	−0.3 (−0.7, −0.02)	.04

[a] Age is centered at age 53 = 0 in all models. [b] Adjusted for age, sex, age × sex (note: age × sex interaction indicates that sex differences in balance ability decreased with age). [c] Adjusted for model 1 + death, attrition, death × age, death × sex, death × age × sex. [d] Adjusted for model 2 + height, height^2, BMI. [e] Adjusted for model 3 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events. [f] Adjusted for model 3 + smoking history, leisure time physical activity. [g] Adjusted for model 3 + maternal education, paternal social class, adulthood social class. [h] Adjusted for model 3 + educational attainment by age 26, age × educational attainment by age 26. [i] Adjusted for model 3 + verbal memory. [j] Adjusted for all covariates in Models 1–8.

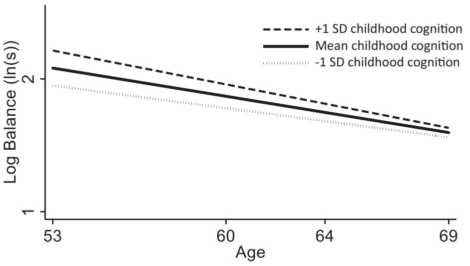

Figure 1. Predicted mean log-transformed balance by age for different levels of childhood cognition from a sex-adjusted multilevel model (*n* = 2,785, obs = 6,379)

across the life course (17,18,33), as such cognition in adulthood may play a role on the pathway between childhood cognition and balance. Education is also likely to play a role on the pathway between childhood and adult verbal memory, as higher cognitive ability in early life correlates with higher educational attainment and subsequent higher fluid ability in adulthood (17).

Second, SEP also attenuated the association when added to the model. Education and adult verbal memory are highly correlated with other indicators of SEP (such as adult occupational class in this study) (25) and as such, these effects are likely to act on the same cognitive-education pathway described above. The association between low SEP and balance impairment could also be mediated by unhealthy behaviors, decreased access to material resources and services to maintain health or increased cumulative life stress (34). However, the addition of health behaviors and chronic health conditions into earlier models had little impact on the main association. Other studies in NSHD and elsewhere have reported associations between lower childhood cognition and poorer physical capability (9,10,22), higher morbidities (33) and premature mortality (35,36) in later life. Thus, in addition to childhood cognition acting as an indicator of neurological function involved in the balance process, this evidence suggests that it is also a predictor of overall health in older age.

We observed that the association between childhood cognition and balance was smaller at older ages. This suggests that there is an advantage of higher childhood cognition on midlife balance but that this advantage gets smaller with age, or equivalently that those with higher cognition in childhood having a steeper decline in balance ability. This advantage in midlife may decrease as age-related impairments in visual, vestibular, or musculoskeletal cues begin to emerge. These age-related impairments may lead to differences in balance ability between older adults that are not observed in younger adults. Individual variation in these more proximal factors, such as sarcopenia and multiple morbidities may thus begin to outweigh balance capability, and its reliance on cognition, developed earlier in life. Further consideration of age-related change in the sensory input systems involved in balance is needed.

Strengths and Limitations

This study has several important strengths. Firstly, the availability of longitudinal, prospectively ascertained data on cognitive ability and multiple measures of balance performance offered a novel opportunity to investigate this association. As the sample was age homogenous, there was no confounding by age. Cognitive ability and other covariates were prospectively collected, thus limiting recall bias. The use of multilevel models in the analyses increased the statistical power by allowing us to include individuals with any balance data over the three clinical visits from ages 53 to 69 (three balance scores: *n* = 1,329, two balance scores: *n* = 548, one balance score: *n* = 503).

Missing data due to loss to follow-up, death, inability to complete balance assessments due to health reasons and incomplete data on covariates could bias the results as it is known that those who were lost to follow-up tended to have poorer health than those included in the study sample (19,37,38). We did adjust for indicators of death and attrition, examined the sex-adjusted model in the maximal available sample and conducted a sensitivity analysis that included those who were unable to complete the assessment due to health reasons; the results did not change. We modeled the association in various stages to identify factors that may mediate the association between childhood cognition and balance. Consequently, we adjusted for intermediate variables on the causal pathway (i.e., education, adult verbal memory); as such, the impact of adjustment needs to be interpreted with caution.

Implications

Establishing neural pathways early in life may influence peak balance ability and have long-term advantages in the face of age-related decline in the systems underlying balance ability. Understanding how cognition across all stages of life may impact balance ability and its decline could help inform interventions to combat physical decline (39,40). This could contribute to improving peak balance ability, delaying the onset of balance decline and minimizing rate of decline in mid and later life. Early life intervention studies designed to improve childhood cognitive potential and its long-term consequences (41) should include adult balance ability as an outcome. Ongoing research is currently investigating bidirectional associations between adult cognition and balance ability to better understand the mechanism by which cognition may impact balance.

In conclusion, understanding the mechanisms underlying the positive association between higher childhood cognition and better midlife balance performance may have important implications for falls risk and the maintenance of physical capability.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest Statement

None declared.

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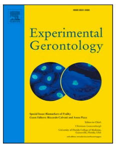

Bidirectional associations between word memory and one-legged balance performance in mid and later life

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ABSTRACT

Background: Age-related changes in cognitive and balance capabilities are well-established, as is their correlation with one another. Given limited evidence regarding the directionality of associations, we aimed to explore the direction and potential explanations of associations between word memory and one-legged balance performance in mid-later life.

Methods: A total of 3062 participants in the Medical Research Council National Survey of Health and Development, a British birth cohort study, were included. One-legged balance times (eyes closed) were measured at ages 53, 60–64 and 69 years. Word memory was assessed at ages 43, 53, 60–64 and 69 with three 15-item word-recall trials. Autoregressive cross-lagged and dual change score models assessed bidirectional associations between word memory and balance. Random-effects models quantified the extent to which these associations were explained by adjustment for anthropometric, socioeconomic, behavioural and health status indicators.

Results: Autoregressive cross-lagged and dual change score models suggested a unidirectional association between word memory and subsequent balance performance. In a sex-adjusted random-effects model, 1 standard deviation increase in word memory was associated with 9% (7,12%) higher balance performance at age 53. This association decreased with age (−0.4% /year (−0.6,-0.1%). Education partially attenuated the association, although it remained in the fully-adjusted model (3% (0.1,6%)).

Conclusions: There was consistent evidence that word memory is associated with subsequent balance performance but no evidence of the reverse association. Cognitive processing plays an important role in the balance process, with educational attainment providing some contribution. These findings have important implications for understanding cognitive-motor associations and for interventions aimed at improving cognitive and physical capability in the ageing population.

1. Introduction

As both cognitive and balance abilities decline with age, associations between measures are frequently found. Whether these associations are simply an artefact of their correlations with age or whether changes in cognitive capability precipitate changes in balance ability or vice versa has not been established. Understanding the temporality and direction of the relationship between these measures has important implications for interventions aimed at improving cognitive and balance outcomes. Previous research on this topic has been limited by a focus on aggregate physical or cognitive measures (Clouston et al., 2013), the application of traditional regression models that only allow the investigation of unidirectional associations (Chen et al., 2016; Tolea et al., 2015), and little consideration of underlying pathways of associations (Finkel et al., 2016). Evidence on bidirectional associations is sparse, despite plausible reasons to expect that associations may act in one or both directions.

Firstly, there may be shared underlying factors driving decline in cognitive and balance abilities (Christensen et al., 2001) such that any observed associations could simply be a consequence of simultaneous declines with age. Equally, functional decline in areas of the brain responsible for integrating sensory and motor information could impact an individual's balance ability. This may include fronto-parietal areas, the right cerebellum, and basal ganglia structures (Emch et al., 2019). The cerebellum is the coordination centre of the brain and regulates

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posture, movement and balance (Morton and Bastian, 2004), while the basal ganglia are primarily responsible for regulating motor control, but also play a key role in learning and executive function (Bostan and Strick, 2010). Similar to the cerebellum, the basal ganglia form iterative synaptic loops with the cerebral cortex, which are involved in movement and cognitive function (Leisman et al., 2014; Middleton and Middleton and Strick, 2000).

There may also be indirect pathways that act in both directions. Those with higher cognitive ability are more likely to have more advantaged socioeconomic position, healthier behaviours and positive health outcomes, each of which are associated with better balance (Birnie et al., 2011; Blodgett et al., 2020b; Richards and Richards and Sacker, 2011; Singh-Manoux et al., 2005). Equally, poor balance could lead to activity restriction, decreased social activity and lower physical health, which could subsequently impact cognitive ability (McDermott and McDermott and Ebmeier, 2009; Singh-Manoux et al., 2003; Zunzunegui et al., 2002).

We used longitudinal data from the MRC National Survey of Health and Development to test i) bidirectional associations between balance performance and word memory between ages 43 and 69 years and ii) potential explanatory socioeconomic, behavioural or health pathways. We hypothesised that there would be bidirectional associations between word memory and balance and that associations between memory and subsequent balance would be independent of other pathways, while associations between balance and subsequent memory would be largely explained by socioeconomic, behavioural and health pathways.

2. Materials and methods

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al., 2007).

2.1. Study sample

The MRC National Survey of Health and Development (NSHD) is a nationally representative, age-homogenous sample of 5362 individuals born within one week in March 1946 in England, Scotland and Wales. Study members have been followed from birth, for up to 24 waves, with the most recent data collection at age 69 years. Study member retention has been high and reasons for non-participation have been previously described (Kuh et al., 2016; Stafford et al., 2013). Briefly, of 5362 study members at birth, 3062 (57.1%) had at least one measure of balance and one measure of word memory at any age and were included in analyses. By age 69, the remaining study members had either died (n = 726;13.5%), emigrated (n = 543;10.1%), permanently or temporarily refused to participate (n = 1012;18.9%) or had missing balance (n = 11;0.2%) or word memory data (n = 8;0.1%) at all ages. Relevant ethical approval and written informed consent was provided at all waves. Approval for the most recent visit at age 69 was given by Queen Square Research Ethics Committee (13/ LO/1073) and Scotland A Research Ethics Committee (14/SS/1009).

2.2. Measurement of word memory and balance

Word memory, historically called *verbal memory* in NSHD (Richards and Sacker, 2003), was assessed at ages 43, 53, 60–64 and 69 years by research nurses using a 15-item word-learning task devised by the NSHD team. Using a rotating card index, each word was presented by the nurse to the participant for 2 seconds. Once all fifteen words had been presented, participants had 1 minute to write down all of the words that they could remember. The score (range: 0–45) represents the number of words correctly recalled over three identical trials. To minimise any practice effects, two word lists were rotated such that a different list was used at the subsequent follow-up. Each of the fifteen words were unrelated to one another; examples include imagine, wheat and hotel. This test was chosen a priori as the measure of cognition because repeat data were available over four waves in NSHD and previous evidence demonstrated robust associations of this specific cognitive measure with balance performance (Blodgett et al., 2020a; Kuh et al., 2009; Saverino et al., 2016).

Balance performance was assessed by research nurses at ages 53, 60–64 and 69 using a one-legged balance test. Individuals were instructed to cross their arms, stand on their preferred foot and raise their other leg a few inches off the ground. Participants were given the opportunity to practice once. The nurse stopped timing a) when the raised leg touched the floor as the participant lost their balance or b) after a maximum of 30 s. One trial was completed with eyes open followed by a trial with eyes closed. Due to a ceiling effect for balance times with eyes open in NSHD as in other studies of middle-aged adults (Morioka et al., 2012; Springer et al., 2007), eyes closed scores were used for analysis. The one-legged balance test with eyes closed is a reliable measure of static balance, with high inter-rater (ICC: 0.98–1.00) and test-retest reliability (ICC: 0.72–0.74) (Franchignoni et al., 1998; Kammerlind et al., 2005; Michikawa et al., 2009; Springer et al., 2007) and is associated with a range of adverse outcomes (Choy et al., 2007; Cooper et al., 2010; Cooper et al., 2014; El-Sobkey, 2011). Individuals who were unable to complete the test due to health reasons were allocated a balance time of 0 s (Blodgett et al., 2020a).

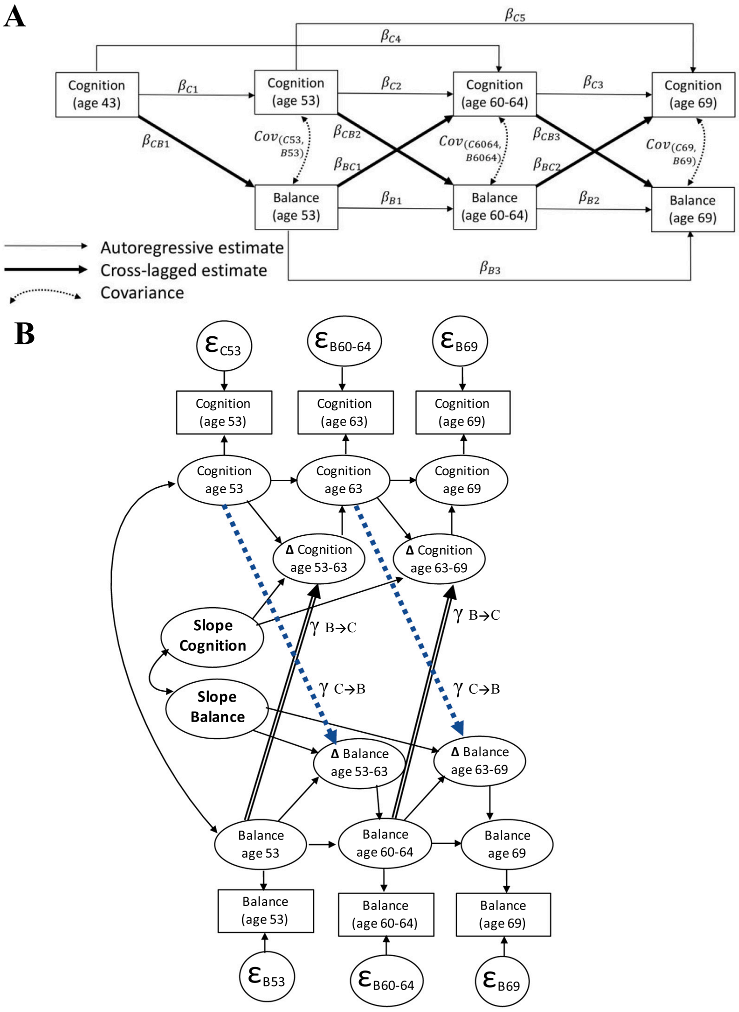
2.3. Measurement of covariates

Time-varying covariates were measured at ages 53, 60–64 and 69 years. This includes ascertainment of height (cm) and weight (kg) using standard protocols by research nurses (Braddon et al., 1986), which were used to calculate BMI (kg/m^2), as well as self-reported measures of leisure-time physical activity (never, 1–4 times/month, 5+ times/ month), smoking status (never, ex, current smoker), history of diabetes (yes, no), history of cardiovascular events (yes, no), respiratory symptoms (yes, no)(Cooper et al., 2014) and symptoms of depression and anxiety (28-item General Health Questionnaire; range: 0–84)(Goldberg and Hillier, 1979). Occupational class was self-reported at age 53 using the Registrar General's Social Classification (I-Professional/ II-Intermediate, III-Skilled non-manual or manual, IV-Partly skilled/ V-Unskilled manual) (Galobardes et al., 2006). The highest level of educational attainment by age 26 was self-reported as degree or higher, advanced secondary qualifications (generally attained at 18 years), ordinary secondary qualifications (generally attained at 16 years), below ordinary secondary qualifications, or none. Binary indicators of death and non-death attrition were included to minimise bias resulting from poorer performance in those lost to follow-up (Botoseneanu et al., 2013). Death was dichotomised as alive at age 69 or died between ages 53 and 69. Attrition was dichotomised as participating in the study at age 69 or attrition not due to death between ages 53 and 69.

2.4. Statistical analyses

Sample characteristics by sex are described for median balance times, mean word memory scores and all covariates at each age, with differences assessed by Kruskal-Wallis, *t*-tests or chi-square tests respectively. Three distinct modelling techniques were employed: autoregressive cross-lagged models, bivariate dual change score models and random-effects models. Analyses were conducted in Stata 14.0 and Mplus v6.1 (maximum likelihood estimator with robust standard errors (Grimm et al., 2017)).

Autoregressive cross-lagged models assessed directional associations between word memory and balance over time. Auto-regressive components describe the stability of each construct over time, cross-lagged components describe reciprocal associations over time and covariance estimates allow for the expected correlation of variance between cognition and balance at each age (Fig. 1A) (Selig and Selig and Little, 2012). Satorra-Bentler Scaled chi-square difference tests are used to



ε represents error term (or residual variance) for each measure of word memory or balance

▭ represents observed scores.

⬭ represents latent scores (either latent scores or latent change scores)

···▶ represents coupling mechanism of verbal memory to subsequent change in balance

⇒ represents coupling mechanism of balance to subsequent change in word memory.

Model 1: All coupling parameters (γ) are freely estimated

Model 2: No coupling (models constrained such that $\gamma_{B\to C} = 0$; $\gamma_{B\to C} = 0$).

Model 3: Unidirectional word memory → balance only ($\gamma_{B\to C} = 0$)

Model 4: Unidirectional balance → word memory only ($\gamma_{C\to B} = 0$)

Fig. 1. Analytical model demonstrating A. all pathways of the autoregressive cross-lagged model and B. all model terms and coupling mechanisms of the bivariate dual change model.

compare pathways (e.g. reciprocal cross-lagged pathways at the same age, unidirectional pathways at multiple ages, pathways between males and females) (Satorra and Bentler, 2001). Standardised estimates (per 1SD) are presented. Full information maximum likelihood, assumes that data are missing at random, and utilises all available variables to estimate the model regardless of an individual's missing data (Collins et al., 2001).

Bivariate dual change score models combine aspects of growth modelling and autoregressive cross-lagged models to evaluate the extent to which balance performance or word memory can predict change in the other (Grimm et al., 2017). Latent scores, latent change scores (e.g. Δ between two ages) and growth curves (based on the change scores) are estimated for each of balance performance and word memory, while the addition of coupling parameters ($\gamma_{B \rightarrow C}$ and $\gamma_{C \rightarrow B}$) allows change in one construct to depend on previous scores in the other (e.g. change in balance from age 53 to 60–64, word memory at age 53) (Fig. 1B). First, a full model with all coupling parameters is freely estimated. Next, the coupling parameters are constrained to be zero, denoting no association between constructs. The third model tests the unidirectional association of word memory to balance and the fourth the unidirectional association in the opposite direction. By constraining coupling parameters, hypotheses about the direction of association are tested by examining the fit of four different models; the model with the best fit can provide hypotheses about the direction of association. The following indices are used to assess model fit: Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), Standardised Root Mean Square Residual (SRMR), Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

Random-effects models use random intercepts and slopes to partition the total variation into that attributable to individual factors and to changes over time within the same individual (Lininger et al., 2015). Dependent on the results of the bidirectional models, lagged random-effects models assessed the association between the independent variable at *time x* (e.g. age 53) with the dependent variable at *time x + 1* (e.g. age 60–64), with age centred at age 53 (e.g. intercept). Initial models assessed for non-linearity and age or sex interactions of the independent variable and any covariates; interactions or non-linear terms were included if $p < 0.05$. An initial sex-adjusted model adjusted for death and attrition between ages 53 and 69, followed by anthropometric measures. Using this base model, each stage of adjustment additionally considered health status indicators, health behaviours, adult social class and education. A final fully-adjusted model is also presented.

3. Results

3.1. Sample characteristics

The distribution of balance times was right skewed as the majority of individuals could not maintain the position with eyes closed for more than 10 s (Fig. A.1). At all ages, males had higher median balance times than females, while females had higher mean word memory scores. Males were also more likely than females to be taller, be a current or ex-smoker, have a history of CVD events, and have higher occupational class and educational attainment. Conversely, females were more likely to have knee pain and more symptoms of depression/anxiety (Table 1).

Table 1
Characteristics of maximal analytical sample (up to $n = 3062$), MRC National Survey of Health and Development.

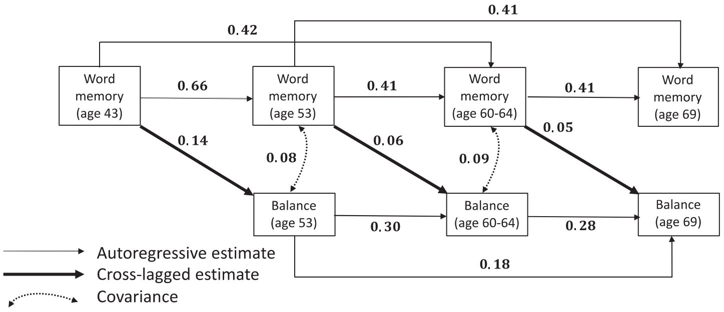
	Males ($n = 1515$)	Females ($n = 1547$)	Tests of sex differences (p-value)
Balance time (S), median (Q1, Q3), n			[a]
Age 53	5 (3,10), $n = 1389$	4 (3, 7), $n = 1464$	<0.001
Age 60–64	3.57 (2.35, 5.53), $n = 1047$	3.16 (2.16, 4.72), $n = 1146$	<0.001
Age 69	2.94 (1.85, 4.78), $n = 1028$	2.72 (1.69, 4.15), $n = 1076$	<0.005
Word memory, mean ± SD, n			[b]
Age 43	24.1 ± 6.1, $n = 1335$	25.7 ± 6.4, $n = 1385$	<0.001
Age 53	23.0 ± 6.2, $n = 1397$	24.9 ± 6.2, $n = 1473$	<0.001
Age 60–64	23.0 ± 5.9, $n = 1023$	25.4 ± 6.1, $n = 1127$	<0.001
Age 69	21.2 ± 6.0, $n = 1005$	23.1 ± 6.0, $n = 1056$	<0.001
Anthropometry[d], mean ± SD, n			[b]
Height (m)	1.75 ± 0.06, $n = 1409$	1.62 ± 0.06, $n = 1485$	<0.001
BMI (kg/m^2)	27.4 ± 4.0, $n = 1408$	27.4 ± 5.4, n = 1473	0.83
Behavioural risk factors[d], n (%)			
Leisure time physical activity			[c]
None	665 (47.0)	754 (50.4)	0.09
1–4 times/month	267 (18.9)	242 (16.2)	
5+ times/month	484 (34.2)	500 (33.4)	
Smoking status			[c]
Current	329 (23.2)	338 (22.6)	<0.001
Previous smoker	728 (51.3)	669 (44.7)	
Never smoker	361 (25.5)	489 (32.7)	
Health status[d], n(%) or mean ± SD			[c]
History of diabetes	45 (3.0)	39 (2.5)	0.44
History of CVD events	83 (5.9)	46 (3.2)	<0.001
Experiencing respiratory symptoms	276 (19.5)	274 (18.3)	0.42
Experiencing knee pain	217 (15.5)	306 (20.7)	<0.001
Symptoms of depression/anxiety	15.6 ± 8.5, $n = 1386$	18.9 ± 10.3, $n = 1463$	<0.001[b]
Highest household occupational class[d], n (%)			[c]
I Professional/II intermediate	781 (52.1)	559 (36.4)	<0.001
III Skilled (non-manual or manual)	566 (37.7)	655 (42.6)	
IV Partly skilled/V unskilled	153 (10.2)	323 (21.0)	
Educational attainment[e], n(%)			[c]
Degree or higher	211 (14.7)	81 (5.5)	<0.001
GCE A level or Burnham B	405 (28.2)	343 (23.5)	
GCE O level or Burnham C	207 (14.4)	377 (25.6)	
Sub GCE	91 (6.3)	133 (9.1)	
None attempted	521 (36.3)	528 (36.1)	

[a] Kruskal-Wallis equality of populations rank test for non-parametric data.
[b] One-way ANOVA.
[c] Chi-square test.
[d] At age 53 years.
[e] At age 26 years.

3.2. Autoregressive cross-lagged model

A total of 2735 individuals had at least one lagged association between memory and balance at any age and in either direction and thus were included in the autoregressive cross-lagged model. Satorra-Bentler scaled chi-square difference tests revealed no sex differences in pathways, thus the main model results include males and females. All presented estimates are standardised. Autoregressive effects suggested low-to-moderate stability of balance over time [β = 0.30 (95%CI: 0.24,0.36), 0.28(0.20,0.36)] and moderate-to-high stability of word memory [β = 0.66(0.63,0.68), 0.41(0.37,0.45), 0.41(0.37,0.45)] (Fig. 2, Table A.1)]. There was evidence of a cross-lagged association between word memory and subsequent balance at all ages, but no association of balance performance with subsequent word memory at any age.

The effect size was bigger for word memory at age 43 to balance time at age 53 [β = 0.14(0.10,0.17); $p < 0.001$] than for associations with



Model fit: CFI=0.98, TLI=0.94, RMSEA =0.068, SRMR =0.018, chi-square test value =68.07 (df=5), p<0.0001). Only significant pathways (p<0.05) are shown here, while all pathways including estimates, p-values and 95% CI are presented in Table A.1.

Fig. 2. Autoregressive cross-lagged model of the associations between word memory and balance.

balance time at ages 60–64 [β = 0.055(0.012,0.098)] or 69 [β = 0.05 (0.01,0.09)]. There was no difference in effect size between the two later ages. Covariance between balance and word memory suggested a correlation at ages 53 and 60–64 ($p < 0.001$), however, this weakened over time and was no longer present at age 69 ($p = 0.7$). The model was an excellent fit (CFI = 0.98, TLI = 0.94, RMSEA = 0.068, SRMR = 0.018) (see Fig. 2).

3.3. *Dual change score models*

Due to the complexity of the dual change score models, they failed to converge in the main sample, forcing the sample to be restricted to those with complete data on balance time and word memory at all ages (n = 1641). As expected, the freely estimated model (Model 1) had the best fit. Notably, the unidirectional word memory to balance model (Model 3) also demonstrated an excellent fit for the data (Table 2) and across all six model fit indices, had a similar fit to the freely estimated model. Conversely, the no-coupling model (Model 2) and the unidirectional balance to word memory model (Model 4) were similar to one another and were a worse fit compared to Models 1 and 3 (Table 2). The optimal fit of Model 3 and the poor fit of Models 2 and 4 indicate support for a unidirectional relationship between word memory and subsequent change in balance.

3.4. *Random-effects models*

As both the autoregressive cross-lagged model and the dual change score model suggested a unidirectional association between word memory and subsequent balance performance, word memory (at ages 43, 53 and 60–64) was considered as the independent variable and balance performance (at ages 53, 60–64 and 69) was the dependent variable in lagged random-effects models. Individuals were included if they had at least one measure of word memory at age t and balance at age $t + 1$ (n = 2783). Due to the skewed balance times, balance was log-transformed. In a sex-adjusted model, a 1SD increase in word memory was associated with a 9% (95% CI: 7, 12%) increase in subsequent balance time (Table 3). The negative age-interaction suggested that this association became smaller with age (e.g. by −0.4% (−0.6, −0.1) per year).

Adjustment for death, attrition, anthropometric, health and behavioural factors had little impact on the estimates (Table 3). Education partly explained the association between word memory and balance as indicated by partial attenuation of both the intercept and slope estimates. In the fully-adjusted model, a 1SD change in word memory remained associated with a 3% (0.1,6%) change in balance time.

4. Discussion

In a large nationally representative study with multiple measurements of word memory and balance performance over 26 years, there was consistent evidence that higher word memory was associated with better subsequent balance performance. This association was strongest in midlife and weakened with age, with no evidence of associations operating in the opposite direction. When the model was adjusted for covariates, only education had a meaningful impact on estimates. These results suggest that cognition, as assessed by word memory, may play an important role in balance ability, with educational attainment partially explaining this association.

In previous longitudinal studies, balance performance is most commonly modelled as a function of cognitive ability (Kuh et al., 2009; Kuh et al., 2006; Saverino et al., 2016; Tabbarah et al., 2002), with few studies examining balance and subsequent cognitive outcomes (Bullain

Table 2
Model fit parameters for dual change score model between balance ability and word memory from age 53 to 69, complete cases only (n = 1641).

Model fit parameter	Adequate fit	Excellent fit	Model 1: Freely estimated	Model 2: No coupling	Model 3: VM➔ Bal only	Model 4: Bal➔ VM only
CFI	≥0.90	≥0.95	0.99	0.96	0.99	0.96
TLI	≥0.90	≥0.95	0.97	0.93	0.97	0.91
RMSEA	≤0.08	≤0.06	0.046	0.069	0.041	0.077
SRMR	≤0.08	≤0.06	0.032	0.084	0.032	0.084
AIC	The model with a lower AIC/ BIC of ≥10 is more likely to be the true model (e.g. a better fit)		−3727.874	−3728	−3680	−3728
BIC			−3609.007	−3609	−3586	−3620

CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; RMSEA = Root Mean Square Error of Approximation; SMR = Standardised Root Mean Square Residual; AIC = Akaike Information Criterion; BIC=Bayesian Information Criterion.

Table 3
Associations between word memory (per 1SD) and subsequent log-transformed balance time (s) in random-effects models.

Model:	Percent change in lagged ln (balance time) at age 53 per SD of word memory [intercept]		Word memory (SD) *age (year) interaction [slope]	
	Coefficient (%) (95% CI)	*p*-Value	Coefficient (%) (95% CI)	*p*-Value
Maximal available sample n = 2783 (obs = 6195)				
0: age[a], sex[b]	9 (7, 12)	<0.001	−0.4 (−0.6, −0.1)	<0.005
Complete cases sample *n* = 2551 (obs = 5167)				
1: age, sex[b]	9 (7, 12)	<0.001	−0.4 (−0.7, −0.2)	<0.005
2: model 1 + death + attrition[c]	9 (6, 11)	<0.001	−0.4 (−0.6, −0.1)	<0.005
3: model 2 + anthropometric[d]	8 (6, 11)	<0.001	−0.4 (−0.6, −0.2)	<0.005
4: model 3 + health status[e]	8 (6, 11)	<0.001	−0.4 (−0.6, −0.2)	<0.005
5: model 3 + health behaviours[f]	7 (5, 10)	<0.001	−0.4 (−0.6, −0.2)	<0.005
6: model 3 + SEP[g]	7 (4, 9)	<0.001	−0.4 (−0.6, −0.2)	<0.005
7: model 3 + education[h]	4 (1, 7)	<0.01	−0.2 (−0.5, 0.1)	0.13
8: fully adjusted[i]	3 (0.1, 6)	0.04	−0.2 (−0.5, 0.1)	0.13

[a] Age is centred at age 53 = 0 in all models.
[b] Adjusted for age, sex, age*sex.
[c] Adjusted for model 1 + death, attrition.
[d] Adjusted for model 2 + height, height^2, BMI.
[e] Adjusted for model 3 + respiratory symptoms, knee pain, history of diabetes, history of cardiovascular events, symptoms of anxiety/depression, age*knee pain, age*symptoms of anxiety/depression.
[f] Adjusted for model 3 + smoking history, leisure time physical activity, age* leisure time physical activity.
[g] Adjusted for model 3 + maternal education, paternal social class, adulthood social class, age*maternal education, age*paternal social class.
[h] Adjusted for model 3 + education, age*education.
[i] Adjusted for all covariates in Models 1–7.

et al., 2016; Ursin et al., 2015) and only three studies investigating bidirectional balance-cognition associations (Chen et al., 2016; Finkel et al., 2016; Tolea et al., 2015). One study visually compared estimates from two separate unidirectional regression models concluding that baseline balance 'predicted' cognitive function at a later age (Chen T 2016), while another study concluded that baseline cognitive impairment had a unidirectional association with declining balance-gait performance (Tolea et al., 2015); as such, neither study appropriately addressed the question of directionality. As above, the third study applied bivariate dual change score models to capture the extent to which change in balance or cognition was a function of the other and identified an association between balance performance and subsequent changes in processing speed (Finkel et al., 2016). These studies examined older samples (mean age 65 or 75 at baseline) (Chen et al., 2016; Finkel et al., 2016). Age differences may explain the contrasting findings, especially as our study findings suggest that the association may be age-dependent. The studies were conducted in the USA, Sweden and Japan and included adults born earlier in the 20th century than the NSHD cohort. Thus, differences may also be a result of country or cohort effects, especially as there are regional and temporal differences in longevity and patterns of age-related change in cognitive and physical capability (Ahrenfeldt et al., 2018; Varnum et al., 2010).

Previous work from our group has suggested that childhood cognitive ability is associated with midlife balance performance (Blodgett et al., 2020b), although this association was primarily explained by education, social class and adult cognition. Here, we extend these results to suggest that adult cognitive ability plays an important role in balance performance, with education only partially explaining the association.

Cognitive integration of sensory input and motor output is crucial for postural equilibrium (Menant et al., 2014). Individuals with higher cognitive ability, in particular working memory, often have greater white matter volume (Lazar, 2017), increased hippocampal activity (Leszczynski, 2011) and sustained activation in the prefrontal cortex (Funahashi, 2017); this neural activity is relevant to maintaining balance. Current evidence has not distinguished if memory plays a direct role in balance performance or if both abilities rely on functionality of shared neural structures. Our findings suggest that components of memory may be involved in balance mechanisms, rather than an age-related correlation between the neural structure and functions involved in both processes.

In addition to the physiological mechanism of association between word memory and balance ability, education may play a role. Education can beneficially impact cognitive ability; equally, higher cognitive ability can lead to higher educational attainment (Ritchie and Tucker-Drob, 2018). Higher educational attainment is linked to better health status, which may be a result of better access to healthcare or improved health behaviours and has a positive association with balance performance (Blodgett et al., 2020a; Hahn and Truman, 2015).

Consistent across models, the association between word memory and balance was strongest in midlife and weakened with age. While cognitive processing involved in balance remains important in later life, physical health-related factors may become more dominant. For example, as musculoskeletal problems (e.g. hip/knee pain, sarcopenia) become more common with age (Anderson and Anderson and Loeser, 2010; Walston, 2012), changes in physical health at older ages may have a greater impact on balance than cognitive pathways. Previous evidence in NSHD is consistent with this explanation, demonstrating that associations between knee pain and balance performance increase with age (Blodgett et al., 2020a). As balance ability relies on input from visual, vestibular and proprioceptive sources, age-related changes in the ability to perceive these sensory inputs could also explain a weakening association between cognition and balance at older ages. Given that balance may have a greater reliance on visual input at older ages (Púcik et al., 2014; Saftari and Kwon, 2018; Yeh et al., 2014), one would expect that visual acuity would explain more variation in balance performance compared with cognitive processes. Replication of these analyses in older adults with eyes open tests may inform how the roles of visual input and subsequent processing in balance change with age.

This is one of few studies to specifically examine the direction of associations between word memory and balance. It utilises more than 25 years of data on word memory and 15 years of balance data in 3000 individuals. Using repeated measures of word memory and balance performance and approaches which model bidirectional associations simultaneously, we have overcome limitations in analytical methodology of previous studies. This is the first study to examine the directionality in associations between cognitive and balance abilities in an age homogenous sample in mid-life, thus identifying changes with age without any confounding by age or birth cohort. There are limitations to our analyses. Despite the advantage of repeated measures of balance, with only three time points, balance performance could only be modelled linearly in the dual change score and random-effects models. Utilising data with more waves of follow-up could allow piecewise trajectories that reflect potential changes in cognitive-balance mechanisms with age to be considered. The autoregressive cross-lagged models enabled four measures of cognition to be included, while equal numbers of each measure were required for the dual change score models. Visual acuity at relevant ages in adulthood has not been assessed in the main NSHD sample, thus we were unable to investigate how vision may have contributed to these associations and their changes with age.

Another important limitation is missing data both from individuals lost to follow-up before age 43 and incomplete data between ages 43 and 69; this is important in interpretation of dual change score models whereby only individuals with complete data on word memory and balance tests could be included. Across all models, the sample size was maximised, resulting in slightly different samples for each model, however findings were consistent across all models despite different sample sizes. Importantly, for all comparisons between pathways (autoregressive cross-lagged model), models (dual change score model) and stages of adjustment (random-effects model), the same sample was compared. Representativeness of the NSHD cohort has been extensively examined (Kuh et al., 2016; Stafford et al., 2013), demonstrating that those lost to follow-up are more likely to have poor physical and cognitive health compared to those who remained in the study. Individuals with complete cognitive and balance data also tend to perform better than those with any missing data. Thus, it is hypothesised that the associations assessed here are conservative and potentially underestimated the true strength of association. Finally, word memory may have been measured with more precision than balance time due to differences in test sensitivity; replication of analyses with a more sensitive balance test (e.g. postural sway as assessed by a force plate) is recommended.

5. Conclusions

This paper provides evidence of a unidirectional association between word memory and balance and suggests that education may partly explain this association. Evidence in this research area remains limited; further investigation into these relationships are required and replication of findings is critical. Future research should examine longer trajectories from early to late adulthood and across a wider range of cognitive measures to assess if these associations differ with age (as suggested here) or by cognitive domain. Many cohort studies have collected data on balance and cognitive performance across numerous waves; secondary analysis of these data would be valuable in contributing to the current evidence on the topic.

The association between word memory and subsequent balance performance may have later implications for interventions aimed at improving balance ability. Interventions tend to be limited to physical training programs such as flexibility, balance or resistance training. Few interventions have included a cognitive component, although there is evidence suggesting that dual or multi-task training (that combines cognitive and physical training) can improve balance ability and minimise falls risk (Halvarsson et al., 2015; Halvarsson et al., 2013). Word memory may be a proxy for overall cognitive function; further research must assess if findings can be extended to other cognitive areas to better understand which cognitive processes contribute to changes in balance with age. This, along with insights from functional magnetic resonance imaging data during one-legged balance tests, could aid in the design of cognitive training that targets balance ability.

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Data available

The datasets used in this study will not be made publicly available. Access to NSHD data adheres to strict confidentiality guidelines but these data are available to bona fide researchers upon request to the NSHD Data Sharing Committee via a standard application procedure. Further details can be found at http://www.nshd.mrc.ac.uk/data. doi: https://doi.org/10.5522/NSHD/Q101; doi: https://doi.org/10.5522/NSHD/Q102; doi: https://doi.org/10.5522/NSHD/Q103.

CRediT authorship contribution statement

Joanna M Blodgett: Conceptualization, Methodology, Formal analysis, Visualization, Writing - Original Draft, Writing - Review & Editing. **Rachel Cooper:** Conceptualization, Writing - Review & Editing, Supervision. **Daniel HJ Davis:** Conceptualization, Writing - Review & Editing, Supervision. **Diana Kuh:** Conceptualization, Writing - Review & Editing, Supervision. **Rebecca Hardy:** Conceptualization, Methodology, Writing - Review & Editing, Supervision.

Declaration of competing interest

None.

Appendix A

Fig. A.1. Distribution of balance times among maximal sample at ages 53, 60–64 and 69 years.

Table A.1
Standardised results from the autoregressive cross-lagged model of balance and word memory, n = 2735; corresponding estimates in Fig. 2.

Dependent variable	Independent variable	Change in standardised balance per 1SD change in cognition (95% CI)	*p*-Value
Autoregressive estimates			
Balance at age 60–64	*ON* Word age 53	0.30 (0.24, 0.36)	<0.001
Balance at age 69	*ON* Word age 60–64	0.28 (0.20, 0.36)	<0.001
	ON Word age 53		<0.001
Word memory at age 53	*ON* Word memory age 43	0.66 (0.63, 0.68)	<0.001
Word memory at age 60–64	*ON* Word memory age 53	0.41 (0.37, 0.45)	<0.001
	ON Word memory age 43	0.42 (0.38, 0.46)	<0.001
Word memory at age 69	*ON* Word memory age 60–64	0.41 (0.37, 0.45)	<0.001
	ON Word memory age 53	0.41 (0.36, 0.45)	<0.001
Cross-lagged estimates			
Balance at age 53	*ON* Word memory age 43	0.14 (0.10, 0.17)	<0.001
Balance at age 60–64	*ON* Word memory age 53	0.06 (0.01, 0.10)	0.01
Balance at age 69	*ON* Word memory age 60–64	0.05 (0.01, 0.09)	0.02
Word memory at age 60–64	*ON* Balance age 53	0.01 (−0.02, 0.04)	0.49

(*continued on next page*)

Table A.1 (*continued*)

Dependent variable	Independent variable	Change in standardised balance per 1SD change in cognition (95% CI)	*p*-Value
Word memory at age 69	*ON* Balance age 60–64	0.01 (−0.03, 0.04)	0.77
Covariance estimates			
Word memory age 53	*WITH* Balance age 53	0.08 (0.04, 0.13)	<0.001
Word memory age 60–64	*WITH* Balance age 60–64	0.09 (0.04, 0.13)	<0.001
Word memory age 69	*WITH* Balance age 69	0.01 (−0.04, 0.05)	0.69

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Associations of working memory, processing speed, executive function and crystallised cognitive ability with balance performance in mid and later life

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ABSTRACT

Background: Cognitive integration of sensory input and motor output plays an important role in balance. Despite this, it is not well understood if specific cognitive processes are associated with balance and how these associations change with age. We examined longitudinal associations of word memory, verbal fluency, search speed and reading ability with repeated balance performance measures.

Methods: Up to 2934 participants in the MRC National Survey of Health and Development, a British birth cohort study, were included. At age 53, word memory, verbal fluency, search speed and reading ability were assessed. One-legged balance times (eyes closed) were measured at ages 53, 60-64 and 69 years. Associations between each cognitive measure and balance time were assessed using random-effects models. Adjustments were made for sex, death, attrition, height, body mass index, health conditions, health behaviours, education, and occupational class.

Results: In sex-adjusted models, one SD higher scores in word memory, search speed and verbal fluency were associated with 14.1% (95%CI: 11.3,16.8), 7.2% (4.4,9.9) and 10.3% (7.5,13.0) better balance times at age 53, respectively. Higher reading scores were associated with better balance, although this association plateaued. Associations were partially attenuated in mutually-adjusted models and effect sizes were smaller at ages 60-64 and 69. In fully-adjusted models, associations were largely explained by education, although remained for word memory and search speed.

Conclusions: Higher cognitive performance across all measures was independently associated with better balance performance in midlife. Identification of individual cognitive mechanisms involved in balance could provide opportunities for targeted cognitive interventions in midlife.

Key words: cognitive ageing; physical performance; epidemiology; life course; birth cohort

INTRODUCTION

Age-related declines in cognitive and physical capability from mid-life onwards are common, with increasing recognition of the interdependency of these two domains [1]. This includes theories of an underlying common cause of ageing [2] and evidence that declines in one domain may contribute directly to declines in the other [3-6]. Balance is one of the physical capability measures most closely linked to cognitive ability, given the crucial neural integration of sensory input and motor response required to maintain balance [7]. Recent analyses from our group provided evidence of a unidirectional association between midlife working memory and subsequent balance performance and identified research gaps which need addressing to further understand this association [6].

Although better overall cognition is associated with better balance performance [4, 8-11], the role of specific cortical processes in maintaining balance is not well established. Given the complexity of neural circuits involved in balance and gait tasks [7], specific cognitive processes may play independent roles in maintaining balance. For example, poor functioning in areas of the brain responsible for working memory, executive function or processing speed could partially explain poor balance [7, 12, 13]. Existing evidence suggests that there are conflicting patterns of association between different cognitive processes and balance performance [9-11, 14], lending support to the involvement of distinct cognitive pathways.

Most evidence on individual cognitive measures (e.g. working memory, executive function) and balance has relied on cross-sectional data, small sample sizes and/or older, age-heterogeneous samples (≥65 years) [4, 8-11]. Furthermore, studies have not investigated if specific cognitive processes have independent roles in maintaining balance nor assessed alternate pathways that may explain the association such as socioeconomic position (SEP), health status or health behaviours.

Previous findings from the MRC National Survey of Health and Development (NSHD) have identified positive associations between general cognitive performance in childhood and balance performance over three time points in midlife [15] and between individual cognitive measures in adulthood with balance at age 53 [14]. In our most recent analyses, we found a unidirectional association between word memory and balance performance that weakened between ages 53 and 69 years; in these analyses, other cognitive measures were not examined [6]. Investigating longitudinal cognitive-balance associations across multiple cognitive measures could have important implications for understanding age-related decline in balance performance. For example, single cognitive tests could identify individuals at risk of poor balance and subsequent related outcomes such as falls, providing opportunities for both screening and interventions.

To address important limitations within the current evidence base, our primary aim was to examine longitudinal associations between four cognitive measures (working memory, executive function, processing speed, crystallised cognitive ability) at age 53 with balance performance at ages 53, 60-64 and 69. We also sought to test if these associations differed by i) age using repeated balance assessments; or ii) sex; and if they remained after iii) mutual adjustment for other cognitive measures; and iv) adjustment for education, other indicators of SEP, health status and health behaviours.

METHODS

Study sample

Data from the MRC National Survey of Health and Development (NSHD) were used. NSHD is a birth cohort of 5 362 individuals born in England, Scotland and Wales in one week in March 1946. Study members have been followed up to 24 times from birth to the most recent data collection in 2015 (age 69). The cohort profile, participation rates and characteristics of those lost to follow-up have been previously detailed [16-18]. As the main focus of the analyses is on cognitive measures at age 53, we considered participants who had participated in a nurse home visit at this age. By age 53, 469 of the original cohort had died, 580 had emigrated or were temporarily living abroad, 610 were unable to be traced, 668 refused to participate and 47 responded to a questionnaire only. Of the 2988 study members who participated at age 53, 32 (1.1%) individuals were missing cognitive data at this age and 22 (0.7%) had no balance data at any age. The final analytical sample (n=2934) consisted of those who had cognitive data at age 53 and at least one balance score at ages 53, 60-64 or 69 (see Figure 1).

Assessment of balance and cognition

Balance performance was assessed at ages 53, 60-64 and 69 using the one-legged stand test according to a standardised protocol. Individuals were instructed by a research nurse to cross their arms, close their eyes and stand on one leg and maintain this position for as long as possible up to a maximum of 30 seconds. Time was recorded in seconds at age 53 and milliseconds at ages 60-64 and 69. Timing stopped when the suspended leg touched the ground or after the maximum time was reached. If participants fell over straight away or were unable to complete the test due to health reasons, they were allocated a score of zero for the purpose of these analyses (n=335 scores in 277 individuals).

Working memory was assessed at age 53 using a *word memory* recall task. Participants were presented with 15 words at a rate of one word every two seconds. They were then immediately asked to write down all of the words that they could recall. Three trials were administered with the total score representing the number of words correctly recalled across all trials (maximum score: 45).

Executive function was assessed at age 53 using a *verbal fluency* test. Study members were asked to name as many animals as possible within one minute. Species (e.g. bird, snowy owl, blue jay, etc.), sex and generation-specific names (e.g. bull, cow, calf) were considered as different names, while repetitions and redundancies (e.g. black cow, brown cow) were not. The score was the number of different animals named.

Processing speed was assessed at age 53 using a visual *search speed* task. Study members were given a grid of letters and, starting at the top left corner of the grid, were asked to go through each line and cross out as many "P"s and "W"s as they could, as quickly and as accurately as possible, in 1 minute. The score represents the total number of letters searched (maximum: 600).

Crystallised cognitive ability was assessed at age 53 using the *National Adult Reading Test* (NART), a test of general verbal knowledge that is commonly used to assess premorbid intelligence levels [19]. Study members were asked to pronounce a set of 50 words and responses were scored as correct or incorrect (maximum score: 50). These words are all atypical in grapheme-phoneme correspondence, such that they are only likely to be pronounced correctly if the study member has previous knowledge of the word. Examples include 'hiatus', 'syncope' and 'placebo'.

Assessment of covariates

Health status, health behaviours, height and BMI were each assessed at ages 53, 60-64 and 69 and thus were treated as time-varying covariates. Measures of health status included binary indicators of *diabetes*, *knee pain*, history of *cardiovascular events* and *respiratory symptoms* and a continuous measure of *symptoms of depression and anxiety* (28-item General Health Questionnaire; range: 0-84). Health behaviours included self-reported *leisure time physical activity* (never, 1-4 times/month, 5+ times/month) and *smoking status* (never, past smoker, current smoker). *Height* (cm) and *BMI* (kg/m^2; derived from height and weight measurements) were ascertained by research nurses. *Adult occupational class* was recorded at age 53 using the

Registrar General's Social Classification (I Professional/ II Intermediate, III Skilled non-manual or manual, IV Partly skilled/ V Unskilled manual). Highest level of *educational attainment* (degree or higher; advanced secondary qualifications generally attained at 18 years; ordinary secondary qualifications generally attained at 16 years; below ordinary secondary qualifications; none) was self-reported at age 26.

Statistical analyses

Mann-Whitney U and t-tests were used to examine sex differences in median (interquartile range (IQR)) balance and mean (SD) cognitive scores. Pearson's correlation coefficients assessed correlations between scores on each of the different cognitive tests. Due to its right skew, balance times were log-transformed for all regression analyses and all estimates are presented as sympercents (% change) [20]. One second was added to all balance times prior to log-transformation to circumvent log values of zero.

Associations between each cognitive score at age 53 and balance performance at ages 53, 60-64 and 69 were assessed with random-effects models which account for repeated balance scores at three different ages nested within individuals. The intercept represents balance performance at age 53, with the intercept and the slope modelled as random effects. Age-by-cognitive test interaction terms were included to assess if the associations between cognitive scores and balance performance changed with age. Interactions between sex and each cognitive measure were also assessed and models were stratified by men and women where significant (at $p<0.05$). Quadratic cognitive terms were tested for all scores (also at $p<0.05$) to check for evidence of deviation from linearity. First, sex-adjusted (or stratified) models were used to investigate the association between cognition at age 53 (word memory, search speed, verbal fluency and NART) and balance performance in four individual models. Next, all cognitive scores were included in a mutually-adjusted model to assess independent associations with balance performance. Finally, covariates were added in five stages (anthropometric measures, health status, health behaviours, adult occupational class, education), with a final model that was fully-adjusted for all covariates. At each stage, quadratic covariate terms, sex by covariate and age by covariate interactions were included where significant at p<0.05. Binary indicators of death and attrition between ages 53 and 69 were included in these analyses to minimise bias that may have been introduced by loss to follow-up in those with poorer balance performance [18, 21].

Characteristics of those with missing cognitive scores or covariate data at age 53 were compared with the main analytical sample and cognitive scores were compared between individuals with missing balance data at any age. Sensitivity analyses replicated the initial sex-adjusted (or stratified) models using the maximal available sample for each cognitive test. Sensitivity analyses were also undertaken in the final fully-adjusted model, where non-significant age*cognitive terms were removed from the model. All analyses were conducted in Stata 15.1.

RESULTS

Descriptive characteristics

Median (Q1, Q3) balance times and mean (SD) cognitive scores are shown in Table 1. Balance times declined with age in both men and women, although men had better balance times than women at all ages (p<0.001 for all ages). Women performed better than men on the visual search speed and word memory tests (both p<0.001). There were no sex differences in verbal fluency (p=0.3) or NART scores (p=0.7). In men and women, NART and word memory scores were the two most highly correlated tests (r=0.53), while NART and search speed scores were the least strongly correlated (r=0.15).

Individual sex-adjusted models (Models 1-4)

In random-effects models, 2549 individuals had complete balance and covariate data at one or more ages, contributing 5466 balance observations. There was no evidence of sex differences in associations between any of the cognitive tests and balance time ($p>0.15$). In sex-adjusted models containing each cognitive score separately, one SD higher scores in word memory, search speed and verbal fluency were associated with 14.1% (95% CI: 11.3, 16.8), 7.2% (4.4, 9.9) and 10.3% (7.5, 13.0) better balance times at age 53, respectively (Table 2 Models 1-3, Figure 2A-C). NART scores demonstrated a quadratic association with balance performance, such that better scores were associated with better balance but this effect plateaued above a certain score (Table 2 Model 4, Figure 2D).

For all cognitive scores, the association decreased with age as illustrated by the weaker estimated association between cognitive score and balance at later ages in Figure 2. For example, one SD increase in word memory was associated with 9.2% (7.0, 1.4) better balance performance at age 60-64, decreasing further to 6.2% (3.3, 9.2) at age 69 (Table 2 Model 1, Figure 2A). Similar changes in associations with age were observed for both search speed (Model 2, Figure 2B) and verbal fluency (Model 3, Figure 2C). The linear term for NART scores also decreased with age, however the quadratic term remained constant ($p=0.95$ for age*NART^2 interaction term); this suggests the association plateaued at lower scores with increasing age (Model 4, Figure 2D).

Adjusted models (Models 5 + 6)

In a mutually-adjusted model of all cognitive tests, estimates for each measure were attenuated by nearly half, although all cognitive scores remained associated with balance performance (Table 2 Model 5). Attenuation of age interaction terms suggests that associations for search speed and verbal fluency no longer became smaller at older ages. Figure 3 outlines the impact of adjustment for covariates at each stage (e.g. B. anthropometric measures, C. health status indicators, D. health behaviours, E. occupational class, F. education), demonstrating that associations between most cognitive tests and balance performance remained. Notably, adjustment for education largely explained the smaller NART coefficients and NART by age interaction terms.

In the fully-adjusted model, one SD increases in search speed and verbal fluency at age 53 were associated with 2.2% (0.2, 4.1) and 2.1% (-0.1, 4.2) better balance performance at all ages (53, 60-64, 69 years) (Table 2, Model 6). One SD increase in word memory was associated with 5.0% (1.7, 8.3) and 2.6% (0.04, 5.2) better balance performances at ages 53 and 60-64, although was no longer associated by age 69. Finally, the association between NART and balance performance was weak in fully-adjusted models and no longer present at ages 60-64 or 69.

Sensitivity analyses

Compared with the main analytical sample (n=2934), those with missing cognitive data (n=32) had worse balance performance at age 53 (p<0.001) and those with missing balance data at all ages (n=22) performed worse on all four cognitive tests (p<0.05 for all). Individuals with complete covariate data (n=2445) performed better on the balance, word memory and verbal fluency tests than those missing one or more covariates (n=429), although there were no differences in search speed (p=0.15) or NART scores (p=0.18).

In separate cognitive models, associations did not change when examined in the maximal available sample (eTable 1, Models 1-4). Sensitivity analyses in the final model removed both NART*age and word memory*age interaction terms and then each term in turn; results demonstrated that each interaction was stronger when only one was included (Supplementary Table 1 Models A-C). This contrasted with the final fully-adjusted model, which produced weaker evidence that associations attenuated with age.

DISCUSSION

Higher cognitive performance in all four tests in midlife was associated with better balance performance. Associations were strongest cross-sectionally at age 53 and became smaller with increasing age. Changes in the associations of search speed and verbal fluency with balance by age were considerably attenuated after adjustment for covariates, while associations of word memory and reading scores with balance performance continued to weaken over time. Estimates were attenuated by approximately half when all cognitive scores were included in the model. Fully-adjusted models suggested that working memory, executive function and processing speed were associated with balance performance independent of each other and of all covariates, while associations between NART scores and balance were largely explained by educational attainment.

Comparison with other studies

No previous study has investigated age-related changes in associations between specific cognitive processes and balance in midlife or considered mutual adjustment of multiple cognitive measures. As such, several of the study findings are novel and comparisons with other studies are limited. However, findings are generally consistent with evidence showing that individuals with higher overall cognitive ability have better balance performance [9, 11, 22, 23]. Fewer studies have examined specific cognitive measures, with mainly cross-sectional studies demonstrating different patterns of associations with balance across different processes [9-11, 24].

Associations between higher scores on both processing speed and executive function tasks and better balance performance are consistent with other studies [3, 9-11, 25]. Conversely, the results for word memory are inconsistent with existing evidence. Although previous analyses of cross-sectional or lagged associations between memory and balance at ages 43 and 53 in

NSHD are consistent with findings shown here [6, 14], other studies have either reported no associations [3] or found evidence of an association for visual but not word memory [10]. Only one non-NSHD study has examined crystallised cognition (measured with the Wechsler Adult Intelligence Scale-III), reporting no association with balance performance [10]. This is consistent with our findings that suggest that fluid cognitive measures may be more strongly associated with balance than crystallised measures.

Explanation of possible indirect and direct pathways

Differences in patterns of association support the hypothesis of direct and indirect pathways between cognition and balance. Attenuation of associations between NART (e.g. crystallised cognitive ability) and balance, particularly at later ages, suggests an indirect pathway that may largely act via educational attainment. Intelligence, education and socioeconomic position (SEP) are all highly correlated; those with higher overall cognitive ability are more likely to have higher educational attainment and a higher SEP, and vice versa [26, 27]. These individuals are also more likely to partake in healthy behaviours, have positive health outcomes, better psychosocial support and fewer physical impairments, including poorer balance performance [28-31]. Taken together, individuals with higher general cognitive ability may be better positioned to improve their health and maintain independent functioning [32]. This is consistent with evidence suggesting that positive associations between childhood cognitive ability and balance performance in later life [15, 33] are explained by socioeconomic, health and behavioural pathways [15].

Independent associations between all fluid cognitive measures – working memory, processing speed and executive function – suggests that balance relies on the integration of multiple cognitive processes. *Working memory* draws on a temporary storage system [34], which may allow selective utilisation of cognitive resources needed to maintain postural stability [35].

Additionally, some memory tasks heavily rely on attention, which can play a large role in maintaining balance, depending on the complexity of the task. For example, selective attention can be important to filter out unimportant stimulus information (e.g. distracting visual cues), while divided attention allows an individual to carry out more than one task at a time (e.g. walking and talking) [36]. Multiple dual task paradigms, that include simultaneous physical and cognitive tasks, have demonstrated the importance of attention in balance [12, 37]. Differing contribution of attention to memory tasks could explain different patterns of association with balance performance [6, 10, 14, 38].

Processing speed captures an underlying cognitive process that has an impact on the efficiency of all other cognitive operations [39]. Slower processing speed is linked to reduced activity in the prefrontal cortex and dopamine deficiency, both of which are thought to impact balance and motor abilities [40-43]. Individuals who are able to quickly process, react and provide an integrated motor response may demonstrate better balance abilities. Finally, two subcomponents of *executive function* involved in balance may explain positive associations between verbal fluency and balance performance: action inhibition and task switching [44]. Action inhibition is the ability to suppress a tendency to react to irrelevant stimuli, while task-switching is similar to divided attention and requires working memory in order to achieve the goals of each task [44, 45]. Evidence from dual task paradigms has shown that older adults are less able to divide their attention and working memory between multiple tasks than younger adults [46]; this could translate to difficulties maintaining balance in situations with competing cues.

Understanding changes with age

Associations between all cognitive measures and balance performance became weaker with increasing age in individual models. The relative contribution of cognitive mechanisms may decrease as more proximal physical factors associated with ageing such as visual impairment, muscular atrophy and reduced vestibular functioning emerge. Previous NSHD research has shown that associations between knee pain and symptoms of depression and anxiety and balance ability grew stronger at older ages [30]. Once all time-varying covariates, including health status indicators, were accounted for, associations between cognition and balance largely remained constant with age. This may suggest that the contribution of cognition to balance is similar at all ages, however as other physical factors become more important, cognition may have a lesser role in maintaining balance at later ages.

Strengths and limitations

The availability of longitudinal data in NSHD is a major strength of this paper. Ascertainment of multiple cognitive measures at age 53, repeated measures of balance performance and a range of prospectively ascertained covariates enabled the role of different cognitive processes to be examined, changes with age to be investigated and allowed exploration of factors that could confound or mediate the associations. However, there are several limitations that should be considered. First, previous NSHD analyses have shown that individuals with missing data or those lost to follow-up have lower SEP across life and are more likely than those with complete data to participate in unhealthy behaviours and be in poor health [17, 18]. Thus, associations may be underestimated as the analytical sample may include those with higher levels of cognition and balance. Several analytical steps were taken to minimise potential bias introduced by loss to follow up; this included the addition of death and attrition indicators, zero imputation of those unable to complete the balance test due to health reasons and sensitivity analyses in the maximal available sample. It is challenging to isolate single cognitive processes within each cognitive measure; however, the differing associations in mutually adjusted models suggests that distinct facets of each process were appropriately captured within each test. Finally, repeated assessment of balance performance throughout midlife is a major strength of the study, however there are limitations to using the one-legged stand test. The range of balance scores were limited by both floor and ceiling effects suggesting the test did not capture the full range of functional ability of the sample. More sensitive assessments of balance and posture, using posturography, may allow better understanding of associations between cognitive processes and balance in future studies.

Conclusions and implications

This study has shown evidence of associations of word memory, search speed, verbal fluency and, to a weaker extent, crystallised cognitive ability with balance performance that were not explained by other covariates or mutual adjustment of all cognitive measures. Research has begun to acknowledge the interactive nature of cognitive and physical domains in the ageing process. Much of this research has focused on aggregate measures of physical and cognitive capabilities, however it is important to consider individual mechanisms of associations. Given the evidence of independent cognitive mechanisms involved in balance performance, further research should consider how distinct areas of cognitive ageing may impact specific functional outcomes such as balance.

These findings could have widespread benefits across several areas of research including: understanding of biological mechanisms, identification of cognitive and physical impairments and organisation of targeted interventions. Interventions aimed at improving balance and mobility could target specific cognitive exercises in addition to a physical training program [47, 48]. This training should target multiple cognitive processes, including but not limited to memory, attention, processing speed and executive function. Understanding that lower cognitive performance in midlife may be a risk factor for subsequent poor balance ability could also help identify at-risk individuals providing further opportunities for intervention.

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Conflicts of interest:

None

Author contributions:

JB performed statistical analyses and wrote the first draft of the manuscript. All authors contributed to the conception and design of the study, to manuscript revision, read, and approved the submitted version.

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Table and figure captions:

Table 1. Mean balance performance and cognitive test scores by sex at age 53 in maximum available sample (up to n=2934)

Table 2. Random-effects models assessing longitudinal associations of each of four cognitive test scores at age 53 with log-transformed balance time (ln(sec)) at ages 53 to 69 (n=2549 (5466))

Figure 1. Derivation of analytical sample in MRC National Survey of Health and Development

Figure 2. Sex-adjusted models showing associations between cognitive score and balance performance at ages 53, 60-64 and 69 (n=2549, obs=5466) for A. word memory; B. search speed; C. verbal fluency; D. NART scores.

Figure 3 A. Mean percent difference in balance time for all cognitive scores at each stage of adjustment and **B.** cognitive*age interaction terms indicating the decreasing association of both word memory and NART with balance score over time

eTable 1. Random-effects models assessing longitudinal associations of cognitive tests at age 53 with log-transformed balance time (ln(sec)) at ages 53 to 69 in A. maximal-available samples and B. modified fully-adjusted models

Table 1. Mean balance performance and cognitive test scores by sex at age 53 in maximum available sample (up to n=2934)

		Men	**Women**	**Tests of sex difference (p-value)**
Balance time (eyes closed) (s)				
Age 53y	n	1405	1468	<0.001 [a]
	Median (Q1, Q3)	5 (3, 10)	4 (3, 7)	
Age 60-64y	n	982	1107	<0.001 [a]
	Median (Q1, Q3)	3.57 (2.34, 5.50)	3.17 (2.16, 4.78)	
Age 69y	n	956	1043	<0.001 [a]
	Median (Q1, Q3)	2.99 (1.89, 4.88)	2.72 (1.67, 4.15)	
Range at all ages (min-max)		0-30	0-30	
Word memory, n		1367	1442	
Mean (SD)		23.0 (6.2)	24.9 (6.2)	<0.001 [b]
Range		4-40	3-41	
Search speed, n		1396	1454	
Mean (SD)		272.9 (75.7)	289.9 (75.6)	<0.001 [b]
Range		91-591	64-591	
Verbal fluency, n		1400	1466	
Mean (SD)		23.8 (6.7)	23.5 (7.1)	0.27 [b]
Range		1-47	1-62	
NART, n		1330	1419	
Mean (SD)		34.5 (9.6)	34.3 (9.4)	0.72 [b]
Range		2-50	1-50	

Q1=quartile 1; Q3=quartile 3

[a] Mann Whitney U test

[b] t-test for comparison of mean (SD)

Table 2. Random-effects models assessing longitudinal associations of each of four cognitive test scores at age 53 with log-transformed balance time (ln(sec)) at ages 53 to 69 (n=2549 (5466))

		% change in association per 1 year		Mean % difference in balance time (s) per 1 SD change in cognition at:					
				Age 53		Age 60-64		Age 69	
		Age*cognition coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
SEX-ADJUSTED MODELS 1-4									
1. Word memory		-0.49 (-0.73, -0.25)	*<0.001*	14.1 (11.3, 16.8)	*<0.001*	9.2 (7.0, 1.4)	*<0.001*	6.2 (3.3, 9.2)	*<0.001*
2. Search speed		-0.20 (-0.44, 0.04)	*0.10*	7.2 (4.4, 9.9)	*<0.001*	5.2 (3.0, 7.3)	*<0.001*	4.0 (1.1, 6.9)	*<0.01*
3. Verbal fluency		-0.39 (-0.63, -0.15)	*<0.001*	10.3 (7.5, 13.0)	*<0.001*	6.4 (4.2, 8.5)	*<0.001*	4.0 (1.1, 6.9)	*<0.01*
4. NART	Linear term	-0.49 (-0.73, -0.25)	*<0.001*	14.7 (11.8, 17.7)	*<0.001*	9.8 (7.4, 12.2)	*<0.001*	6.9 (3.8, 10.0)	*<0.001*
	Quadratic term	-[a]		2.2 (0.6, 3.9)	*<0.01*	*Estimate constant* [e]			
MUTUALLY-ADJUSTED MODEL 5									
Word memory		-0.32 (-0.60, -0.03)	*0.03*	8.3 (5.0, 11.5)	*<0.001*	5.1 (2.5, 7.7)	*<0.001*	3.2 (-0.3, 6.7)	*0.07*
Search speed		-[b]		3.4 (1.3, 5.5)	*<0.005*	*Estimate constant* [e]			
Verbal fluency		-[b]		2.9 (0.7, 5.1)	*0.01*	*Estimate constant* [e]			
NART	Linear term	-0.32 (-0.60, -0.03)	*0.03*	8.7 (5.3, 12.1)	*<0.001*	5.5 (2.7, 8.3)	*<0.001*	3.5 (-0.1, 7.2)	*0.06*
	Quadratic term	-[b]		1.8 (0.1, 3.5)	*0.03*	*Estimate constant* [e]			
FULLY-ADJUSTED MODEL 6 [c]									
Word memory		-0.24 (-0.53, 0.05)	0.11[d]	5.0 (1.7, 8.3)	*<0.005*	2.6 (0.04, 5.2)	*0.05*	*1.2 (-2.3, 4.7)*	*0.51*
Search speed		-		2.2 (0.2, 4.1)	*0.03*	*Estimate constant* [e]			
Verbal fluency		-		2.1 (-0.1, 4.2)	*0.06*	*Estimate constant* [e]			
NART	Linear term	-0.23 (-0.54, 0.09)	0.16[d]	3.3 (-0.4, 7.1)	*0.08*	*1.1 (-2.0, 4.2)*	*0.48*	*-2.6 (-4.2, 3.7)*	*0.90*
	Quadratic term	-		0.6 (-1.0, 2.3)	*0.46*	*Estimate constant* [e]			

[a] *Interaction term for age*NART score^2 (p=0.95) was not significant and thus removed from the model.*

[b] *Interaction terms for age*search speed (p=0.50), age*verbal fluency (p=0.19) and age*NART^2 (p=0.88) were not significant and thus removed from the model.*

[c] *Adjusted for sex, sex*age, death, death*age*sex, attrition, height, height^2, BMI, CVD events, diabetes, respiratory symptoms, knee pain, knee pain*age, symptoms of depression and anxiety, depression/anxiety*age, smoking history, leisure time physical activity, physical activity*age, adult social class, education, education*age.*

[d] *See sensitivity analyses in eTable 1 for models without age*word memory and age*NART interaction terms*

[e] *Estimates at ages 60-64 and 69 are equivalent to those estimated at age 53*

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eTable 1. Random-effects models assessing longitudinal associations of cognitive tests at age 53 with log-transformed balance time (ln(sec)) at ages 53 to 69 in A. maximal-available samples and B. modified fully-adjusted models

		Change in association per 1 year		Mean % difference in balance time (s) per 1 SD change in cognition at:					
				Age 53		Age 60-64		Age 69	
		Age*cognition coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
SEX-ADJUSTED MODELS 1-4 [a]									
1. Word memory	n=2870 (6851)	-0.36 (-0.58, -0.14)	*<0.005*	14.2 (11.6, 16.7)	*<0.001*	10.6 (8.6, 12.5)	*<0.001*	8.4 (5.8, 11.0)	<0.001
2. Search speed	n=2912 (6922)	-0.26 (-0.48, -0.05)	*0.02*	8.5 (6.0, 11.1)	*<0.001*	5.9 (3.9, 7.9)	*<0.001*	4.3 (1.7, 6.9)	<0.005
3. Verbal fluency	n=2927 (6945)	-0.41 (-0.62, -0.20)	*<0.001*	12.5 (9.9, 15.0)	*<0.001*	8.4 (6.4, 10.3)	*<0.001*	5.9 (3.4, 8.5)	<0.001
4. NART	Linear term	-0.41 (-0.62, -0.19)	*<0.001*	15 (12, 18)	*<0.001*	11.0 (8.8, 13.2)	*<0.001*	8.5 (5.7, 11.3)	<0.001
	Quadratic term	-[a]	-	2.2 (0.6, 3.7)	*<0.01*	*Estimate constant* [b]			
MODIFIED FULLY-ADJUSTED MODELS	n=2934 (5466)								
A. No age interaction terms									
Word memory		-	-	3.2 (0.7, 5.7)	*0.01*	*Estimate constant* [b]			
Search speed		-	-	2.2 (0.2, 4.1)	*0.03*	*Estimate constant* [b]			
Verbal fluency		-	-	2.1 (-0.1, 4.2)	*0.06*	*Estimate constant* [b]			
NART	Linear term	-	-	1.6 (-1.3, 4.6)	*0.28*	*Estimate constant* [b]			
	Quadratic term			0.5 (-1.2, 2.2)	*0.56*	*Estimate constant* [b]			
B. Word memory*age only									
Word memory		-0.31 (-0.58, -0.04)	0.03	5.5 (2.3, 8.7)	*<0.005*	2.4 (-0.1, 5.0)	*0.06*	*0.6 (-2.8, 3.9)*	*0.74*
Search speed		-	-	2.1 (0.2, 4.1)	*0.03*	*Estimate constant* [b]			
Verbal fluency		-	-	2.1 (-0.1, 4.2)	*0.06*	*Estimate constant* [b]			
NART	Linear term	-	-	1.7 (-1.3, 4.6)	*0.27*	*Estimate constant* [b]			
	Quadratic term			0.6 (-1.1, 2.2)	*0.51*	*Estimate constant* [b]			
C. NART*age only									
Word memory		-	-	3.2 (0.7, 5.7)	*0.01*	*Estimate constant* [b]			
Search speed		-	-	2.2 (0.2, 4.2)	*0.03*	*Estimate constant* [b]			
Verbal fluency		-	-	2.1 (-0.1, 4.2)	*0.06*	*Estimate constant* [b]			
NART	Linear term	-0.31 (-0.61, -0.02)	0.04	4.0 (0.3, 7.7)	*0.03*	*0.9 (-2.2, 3.9)*	*0.58*	*-1.0 (-4.9, 2.9)*	*0.61*
	Quadratic term	-		0.6 (-1.1, 2.3)	*0.47*	*Estimate constant* [b]			

[a] *Interaction term for age*NART^2 (p=0.59) was not significant and thus removed from the model*

[b] *Estimates at ages 60-64 and 69 are equivalent to those estimated at age 53*

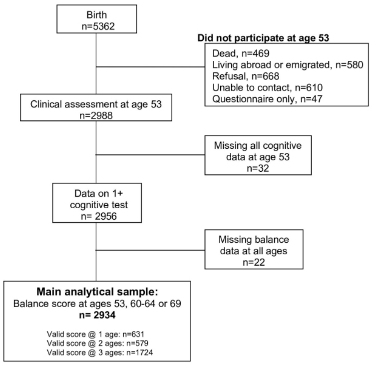


Figure 1. Derivation of analytical sample in MRC National Survey of Health and Development

210x297mm (300 x 300 DPI)

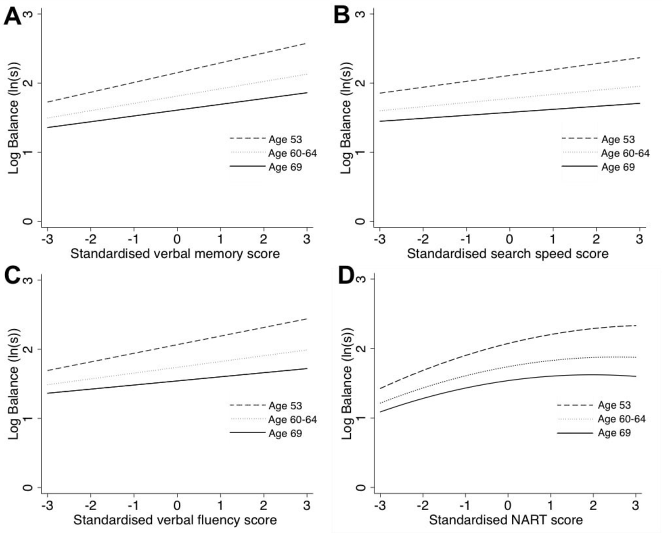
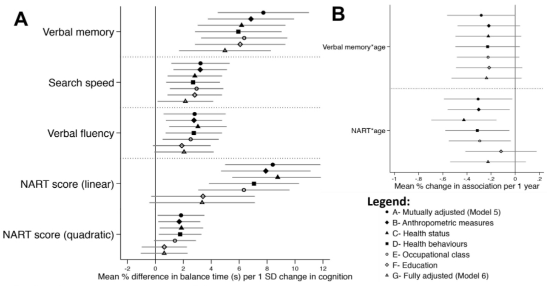


Figure 2. Sex-adjusted models showing associations between cognitive score and balance performance at ages 53, 60-64 and 69 (n=2549, obs=5466) for A. word memory; B. search speed; C. verbal fluency; D. NART scores.

373x293mm (72 x 72 DPI)



*Model A: Adjusted for sex, sex*age, death, death*age*sex, attrition*
Model B: Model A + height, height^2, BMI
*Model C: Model B + CVD events, diabetes, respiratory symptoms, knee pain, knee pain*age, symptoms of depression and anxiety, depression/anxiety*age*
*Model D: Model B + smoking history, leisure time physical activity, physical activity*age*
Model E: Model B +adult social class,
*Model F: Model B + education, education*age*
Model G: Adjusted for all covariates in Models A-F

Figure 3 A. Mean percent difference in balance time for all cognitive scores at each stage of adjustment and B. cognitive*age interaction terms indicating the decreasing association of both word memory and NART with balance score over time

297x210mm (300 x 300 DPI)