University of Southampton

Faculty of Medicine

Human Development and Health

Trajectories of Muscle Strength, Muscle Function, Body Composition and Bone Mineral Density in Later Life: Analysis of Determinants, Interrelationships and Consequences Using Data from the Health ABC Study

by

Leo David Westbury

Thesis for the degree of Doctor of Philosophy

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Abstract

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Musculoskeletal disorders, such as sarcopenia and osteoporosis, are common among older people. Preventive strategies require understanding of the determinants, interrelationships and consequences of changes in muscle strength, function and body composition in older age.

Considering novel statistical techniques and using data from 3075 men and women (aged 70-79 years) from the Health, Aging and Body Composition Study, this thesis describes 9-year changes in grip strength, gait speed, appendicular lean mass (ALM), whole body fat mass and total hip BMD, and identifies determinants and consequences of lower levels and greater declines in these characteristics.

Declines were linear for ALM but accelerated with age for other characteristics. Declines in characteristics were positively correlated, suggesting they co-occur. Determinants of lower levels of most characteristics included older age, shorter stature and lower physical activity; older age and poorer diet quality predicted greater declines in some characteristics. Lower levels and greater declines in all characteristics predicted hospital admission (excluding ALM and fat mass) and mortality. Lower levels of all characteristics and greater hip BMD declines predicted fragility fracture. Lower grip strength, greater declines in ALM and hip BMD, and lower levels and greater declines in gait speed predicted falls.

These results have clinical implications. First, healthier lifestyles, represented by higher diet quality and physical activity, predicted higher levels and reduced declines in musculoskeletal characteristics. Therefore, encouraging healthier lifestyles may improve musculoskeletal health in older age. Second, interventions to maximize peak levels of musculoskeletal parameters in early adulthood, and to delay age-related declines, may reduce the burden of musculoskeletal morbidity in later life.

Statistical implications of this thesis are that latent class trajectory and growth mixture models were of limited use for identifying groups of participants with varying rates of decline in characteristics. Applying a linear mixed effects model to z-scores obtained from the LMS method and then extracting the random slopes was a feasible method for deriving change measures in these characteristics. Bivariate dual change score models were unsuitable for examining

interrelationships between changes in characteristics as many failed to converge. Longitudinal cohort studies of musculoskeletal parameters should ascertain these at many time-points and implement statistical methods to characterise change which use all repeated measurements.

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Research Thesis: Declaration of Authorship

Print name: Leo David Westbury

Title of thesis: Trajectories of Muscle Strength, Muscle Function, Body Composition and Bone Mineral Density in Later Life: Analysis of Determinants, Interrelationships and Consequences Using Data from the Health ABC Study

I declare that this thesis and the work presented in it is my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
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Definitions and Abbreviations

ADL	Activities of daily living
ALM	Appendicular lean mass
AWGS	Asian Working Group for Sarcopenia
BCCG	Box-Cox Cole and Green
BCPE	Box-Cox power exponential
BCT	Box-Cox t
BDCSM	Bivariate dual change score models
BI	Bioelectrical impedance
BIC	Bayesian information criterion
BMD	Bone mineral density
BMI	Body mass index
CFI	Comparative fit index
CG	Cole and Green
CHAMP	Concord Health and Ageing in Men Project
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computed tomography
DXA	Dual-energy x-ray absorptiometry
EMBASE	Excerpta Medica Database
EWGSOP	Original European Working Group on Sarcopenia in Older People
EWGSOP2	Revised European Working Group on Sarcopenia in Older People
FFQ	Food frequency questionnaire

FIML	Full information maximum likelihood
FNIH	Foundation for the National Institutes of Health
GAIC	Generalised Akaike information criterion
GAMLSS	Generalised additive models for location, scale, and shape
GDP	Gross domestic product
GEE	Generalised estimating equations
HCS	Hertfordshire Cohort Study
Health ABC	Health, Aging and Body Composition Study
HEI	Healthy eating index
IADL	Independent activities of daily living
Il-1Ra	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
IRP	Intramural Research Program
IWGS	International Working Group on Sarcopenia
LCT	Latent class trajectory
LGC	Latent growth curve
LME	Linear mixed effects
MCMC	Markov chain Monte Carlo
MEDLINE	Medical Literature Analysis and Retrieval System Online
MET	Metabolic equivalent unit
MrOS	Osteoporotic Fractures in Men Study
NIA	National Institute on Aging
OA	Osteoarthritis
OAI	Osteoarthritis Initiative

OFELY	Os des Femmes de Lyon Study
OSTPRE	Finnish Osteoporosis Risk Factor and Prevention study cohort
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RMSEA	Root mean squared error of approximation
RS	Rigby and Stasinopoulos
SD	Standard deviation
SDOC	Sarcopenia Definitions and Outcomes Consortium
SEP	Socioeconomic position
SOF	Study of Osteoporotic Fractures
SPPB	Short physical performance battery
SRMSE	Standardized root mean squared error
TLI	Tucker–Lewis index
TNFα	Tumor necrosis factor alpha
TUG	Timed up-and-go
WHAS	Women's Health and Aging Study
WHO	World Health Organisation

Chapter 1 Introduction

1.1 Chapter summary

This chapter includes the following information: rationale for this thesis; background information on scientific topics relevant to this thesis such as the musculoskeletal system, sarcopenia, osteoporosis, body composition and obesity; a review of the epidemiological literature on this thesis topic; a statement of the thesis aims and objectives; and a summary of the content in this thesis.

1.2 Rationale

Musculoskeletal disorders are prevalent in older people and are a leading cause of morbidity worldwide. Preventative strategies for age-related musculoskeletal conditions require better understanding of risk factors for accelerated loss of muscle strength and physical function, and changes in body composition (including bone), as well as knowledge about how these parameters interrelate.

Using data from the Health, Aging and Body Composition (Health ABC) Study, this thesis: uses statistical techniques to describe change in muscle strength, physical function and body composition; examines interrelationships between these changes; and identifies risk factors for, and health-related consequences of, lower levels and greater declines in these characteristics.

1.3 The musculoskeletal system

The musculoskeletal system, comprising bone, muscle and connective tissue such as cartilage, ligaments and tendons, provides support, protection and movement for the body[1]. Consequently, a healthy musculoskeletal system in older age is crucial for physical functioning and mobility and for maintaining independence[2]. However, musculoskeletal disorders are common, particularly among older people, with around one in three people currently living with a chronic musculoskeletal condition worldwide[3]; musculoskeletal disorders represented a sizeable proportion (17.1%, 95% CI: 15.3–18.9) of the Global Burden of Disease in 2016[4]. Musculoskeletal conditions confer considerable economic costs to society, including direct healthcare costs as well

as indirect costs relating to unemployment and lower productivity; these are likely to increase in Western countries due to aging populations. For example, the total cost of musculoskeletal conditions in the US increased from 3.4% of gross domestic product (GDP) in 1996 to 5.8% of GDP in 2014[5]. Common musculoskeletal conditions include osteoporosis, osteoarthritis and sarcopenia. Further background information about sarcopenia and osteoporosis is provided below as these are particularly relevant for this thesis.

1.3.1 Sarcopenia

Sarcopenia is the aggressive loss of skeletal muscle mass, strength and function in older age[6]. It is associated with increased risk of physical frailty, disability and mortality and is now regarded as a specific condition by the International Classification of Diseases[7]. Sarcopenia is also a major contributor to health care costs; in the year 2000, annual estimated medical costs attributable to sarcopenia in the United States, based on the extent to which sarcopenia increased risk of physical disability, were $18.5 billion, representing approximately 1.5% of annual healthcare expenditure[8]. Using data from the Hertfordshire Cohort Study (HCS), estimated UK healthcare costs associated with sarcopenia were £2.5 billion annually[9]. Established determinants of sarcopenia include older age, female sex, low physical activity, poor diet quality[10] and developmental influences such as low birth weight[11].

There is currently no consensus algorithm for defining sarcopenia. However, various diagnostic criteria for sarcopenia have been suggested, primarily based on muscle mass, strength, and function[12]. For example, the revised European Working Group on Sarcopenia in Older People (EWGSOP2), defines probable sarcopenia as having low grip strength, confirmed sarcopenia as low grip strength and lean mass and severe sarcopenia as low grip strength and lean mass and slow gait speed[13]. In contrast, the International Working Group on Sarcopenia (IWGS), proposes a combination of only low lean mass and slow gait speed[14]. Standardised measurement protocols exist for the ascertainment of grip strength and gait speed in clinical and community settings[15 16].

The prevalence of sarcopenia varies depending on the age, ethnicity and setting of the population sampled and on the diagnostic tools used to define the condition[6]. A systematic review of 35 studies which estimated the prevalence of sarcopenia among community-dwelling older individuals (aged 60 and older) using the original European Working Group on Sarcopenia in Older People (EWGSOP), IWGS or Asian Working Group for Sarcopenia (AWGS) definitions, reported an overall prevalence of sarcopenia of 10% among men and women[17]. Higher prevalences of sarcopenia according to the EWGSOP algorithm have been observed across care settings, for

example, among geriatric outpatients (26%)[18], older adults admitted to acute hospital wards (34.7%)[19] and in long term care homes (63.0%)[20].

1.3.2 Osteoporosis

Osteoporosis is a disorder characterized by micro-architectural deterioration of bone tissue and low bone mass which increases bone fragility and fracture risk[21]. Osteoporotic fractures are associated with increased risk of morbidity, mortality, and reduced physical function, resulting in huge individual and societal costs, especially as 20% of men and 50% of women over 50 are likely to suffer from an osteoporotic fracture[22]. Hip fractures are the most common type and have the greatest economic costs out of all osteoporotic fractures[23 24]. The overall economic burden associated with osteoporotic fractures has been estimated at $17 billion in the US in 2005[25] and €37.4 billion in the European Union in 2010[26]. FRAX®, a fracture risk assessment tool for estimating an individual's 10-year likelihood of hip and major osteoporotic fracture (hip, distal forearm, proximal humerus or clinical spine) was released in 2008 and is based on age, BMI and clinical risk factors (femoral neck BMD can also be used in the calculation if available)[27 28]. Clinical risk factors in the FRAX® algorithm include current smoking, excessive alcohol intake, long term glucocorticoid use, prior fragility fracture, parental hip fracture, rheumatoid arthritis, and secondary osteoporosis[29].

The World Health Organisation (WHO) classifies an individual as osteoporotic if their bone mineral density (BMD), assessed using dual-energy x-ray absorptiometry (DXA), is at least 2.5 standard deviations below that of a young adult of the same sex[30]. Using this definition, the estimated UK prevalence of osteoporosis at either the total hip or lumbar spine among individuals aged 50 or older was 7% among men and 27% among women in 2010; corresponding estimates in the US were 4% and 16% among men and women respectively[31].

1.3.3 The muscle-bone unit

Muscle and bone are regarded as part of a single operational unit according to the Mechanostat hypothesis[32]. This hypothesis explains how bones respond to the forces exerted on them through muscle contraction and relaxation to ensure sufficient bone strength is maintained. Modelling (addition of bone to the outer surface) and remodelling (removal and repair of defective bone along with the formation of new bone) are the two processes influenced by muscle loading which

affect bone strength[33]. Aspects of bone which may be influenced in this framework include bone mass, stiffness, shape and size. Whilst not directly related to the forces impacting on bone, factors such as hormones and nutrition may influence the ability of bone to respond to these forces. The Mechanostat hypothesis underpins how bones adapt to the changes in muscle loading across the lifecourse. This interconnectedness of muscle and bone at the physiological level may partly explain why musculoskeletal disorders, such as sarcopenia and osteoporosis, often co-occur and share similar risk factors.

1.4 Body composition and obesity

Body composition refers to the distribution and amount of lean and fat mass in the body and has a substantial effect on health among people of all ages[34]. Simple assessments of body composition include BMI for general adiposity and the use of skinfolds, waist circumference and waist-to-hip ratio for fat distribution. More complex techniques, such as DXA, allow total mass to be partitioned into lean, fat and bone mass.

Aging is associated with decreases in lean mass and increases in fat mass (particularly in the abdominal area)[35] which can increase the risk of sarcopenia and obesity respectively. Sarcopenic obesity, the presence of both sarcopenia and obesity, can arise which is related to greater risk of disability and adverse health outcomes than sarcopenia or obesity in isolation[36]. Obesity (often defined as a BMI $\geq$30 kg/m^2) in older age has been related to higher risks of: cardiovascular disease; diabetes; various cancers; physical disability and mortality[37]. Higher levels of fat mass have also been related to increased risk of subsequent disability[38] and all-cause mortality[39]. A recent meta-analysis found that annual medical spending attributable to obesity in the US was approximately $149.4 billion[40]. Determinants of overweight and obesity in older populations have been examined previously[41-43] and include male sex, low educational attainment, being married, not currently smoking, physical inactivity, functional limitations and comorbidity.

Obesity is common among older people in Europe with an estimated prevalence of 19.2% in 2013 according to the Survey of Health, Ageing and Retirement in Europe, a study of individuals aged $\geq$50 years from 10 European countries[44]; the prevalence in the US among individuals aged $\geq$60 years was estimated at 35.4% in 2011-2012 according to the National Health and Nutrition Examination Survey[45].

In summary, sarcopenia, osteoporosis and obesity are common among older people, impose a heavy burden on individuals and on society and are underpinned by parameters relating to

muscle strength, function and body composition (including bone density). Therefore, preventive strategies for these conditions require understanding of the determinants, interrelationships and health-related consequences of changes in these parameters which this thesis addresses.

1.5 Epidemiological literature review

Scoping literature searches were conducted to identify determinants, interrelationships and health-related consequences of change in grip strength, gait speed as a measure of physical function, lean mass, fat mass and BMD. Although methodical in nature, literature reviews conducted in this thesis were not formally systematic and, therefore, did not follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Grip strength, gait speed and lean mass are key components of sarcopenia and are more commonly used as predictors and outcomes in epidemiological studies instead of sarcopenia as they are measureable across a continuum; similarly BMD is an important continuous measure relating to osteoporosis and both fat and lean mass are important measures of body composition. These searches were conducted in December 2017 in OVID using the Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica Database (EMBASE) databases. Observational studies in the English language among cohorts of older people were eligible for inclusion. Measures of fat mass and lean mass included in this review were those ascertained using DXA, computed tomography (CT) or bioelectrical impedance (BI); articles including fat distribution measures such as waist circumference and waist-to-hip ratio were also deemed eligible whereas measures of adiposity based on weight and BMI were not. The exclusion of these more simplistic measures of adiposity was performed to focus on more sophisticated measures which calculate fat mass or account for its distribution.

Overall, three literature searches were implemented to identify articles using the following measures: grip strength, gait speed and lean mass (Table 1); fat mass (Table 2) and BMD (Table 3). Articles deemed relevant based on the title were then carried forward and the abstracts of these articles were then screened by one reviewer (myself) to identify relevant publications with the full text being examined if a decision could not be made using the abstract alone. Articles were then grouped into those examining determinants of change and those examining health-related consequences of change. In total, 206 relevant publications were identified.

Table 1: OVID literature search for articles examining change in grip strength, gait speed and lean mass

Stage	Search terms used	Articles returned
1	**Articles exploring change in grip strength, gait speed or lean mass** (change* or decline* or attenuation or loss or lost or gain* or trajectories or trajectory).ti,ab. **and** (hand strength/ **or** (grip strength or hand strength or hand-grip strength or hand grip strength).ti,ab. **or** (muscle mass or lean mass or lean body mass or appendicular skeletal mass).ti,ab. **or** (gait speed or gait speed or gait-speed or gait velocity).ti,ab.)	48142
2	**Articles on cohort studies of older people** ((cohort or cohort analysis or follow up or follow-up or cohort studies or follow-up studies or prospective).ti,ab. or cohort studies/ or follow-up studies/ or prospective studies/ or longitudinal studies.mp.) **and** ((older adults or elderly or old or seniors or adult or middle aged).ti,ab. or exp Aged/ or middle aged/)	2175822
3	**Articles relevant to both Stage 1 and 2 which are in the English language and were published from 1980 to 2017** 1 and 2 limit to English language and human.mp limit to yr=1980-2017 remove duplicates	2751
4	**Potentially relevant publications (based on the title and abstract)**	101
5	**Relevant publications (based on the title, abstract and full-text if the relevance could not be determined by the title and abstract)**	85

Table 2: OVID literature search for articles examining change in fat mass

Stage	Search terms used	Articles returned
1	**Articles exploring change in fat mass or measures of adiposity** (change* or decline* or attenuation or loss or lost or gain* or trajectories or trajectory).ti,ab. **adj5** (fat or fat mass or fatness or adipos*)	44862
2	**Articles on cohort studies of older people** ((cohort or cohort analysis or follow up or follow-up or cohort studies or follow-up studies or prospective).ti,ab. or cohort studies/ or follow-up studies/ or prospective studies/ or longitudinal studies.mp.) **and** ((older adults or elderly or old or seniors or adult or middle aged).ti,ab. or exp Aged/ or middle aged/)	2175822
3	**Articles relevant to both Stage 1 and 2 which are in the English language and were published from 1980 to 2017** 1 and 2 limit to English language and human.mp limit to yr=1980-2017 remove duplicates	1282
4	**Potentially relevant publications (based on the title and abstract)**	31
5	**Relevant publications (based on the title, abstract and full-text if the relevance could not be determined by the title and abstract)**	25

Table 3: OVID literature search for articles examining change in BMD

Stage	Search terms used	Articles returned
1	**Articles exploring change in bone mineral density** (change* or decline* or attenuation or loss or lost or gain* or trajectories or trajectory).ti,ab. **and** (bone density/ or (bone densit* or bone mineral densit* or bone mineral content or BMD or BMC or bone mass or bone strength).ti,ab.)	76579
2	**Articles on cohort studies of older people** ((cohort or cohort analysis or follow up or follow-up or cohort studies or follow-up studies or prospective).ti,ab. or cohort studies/ or follow-up studies/ or prospective studies/ or longitudinal studies.mp.) **and** ((older adults or elderly or old or seniors or adult or middle aged).ti,ab. or exp Aged/ or middle aged/)	2175822
3	**Articles relevant to both Stage 1 and 2 which are in the English language and were published from 1980 to 2017** 1 and 2 limit to English language and human.mp limit to yr=1980-2017 remove duplicates	3960
4	**Potentially relevant publications (based on the title and abstract)**	110
5	**Relevant publications (based on the title, abstract and full-text if the relevance could not be determined by the title and abstract)**	96

1.5.1 Determinants and health-related consequences of change in grip strength, gait speed, body composition and BMD

The determinants and consequences of change in grip strength, gait speed, lean mass, fat mass and BMD as identified from the epidemiological literature review are summarised in Table 4. Information on interrelationships between changes in these measures is not included in Table 4; this material is outlined in Section 1.5.2.

Some of the measures of interest had common determinants (Table 4). Older age, height loss, lower physical activity, poorer diet and comorbidity were each associated with greater decline in grip strength, gait speed and BMD. In addition to male sex, older age, lower physical activity and poorer diet were also determinants of increases in fat mass. Determinants of lean mass decline were broadly a subset of the determinants of grip strength decline.

Health-related consequences of changes in these parameters were also identified from the literature review (Table 4). For example, increases in fat mass and declines in grip strength, gait speed, lean mass and BMD were each associated with increased risk of mortality. Associations between decreases in fat mass among older people and increased risk of mortality and cognitive decline were also identified, suggesting that accelerated loss of fat may reflect poor underlying health status. Declines in grip strength and gait speed were also related to increased risk of physical disability. Declines in BMD shared some consequences with declines in gait speed (cognitive decline) and increases in fat mass (poorer cardiovascular health).

Table 4: Determinants and health-related consequences of change in grip strength, gait speed, body composition and BMD

Component	Determinants	Consequences
Grip strength decline	Older age[46-49] Male sex[46-49] Lower childhood SEP[50] Lower occupational position (M)[51] Shorter height[47] Height loss[52 53] Increased adiposity[54] Weight loss[52 53 55] Lower physical activity[49 52 56] Poorer diet quality[57] Lower protein intake[58] Lower 25-hydroxyvitamin D[59 60] Smoking (W)[49] Depressive symptoms (M)[61] Higher perceived stress (W)[49] Lower cognition[62 63] Dementia (W)[49] Stroke (M)[55] Diabetes (M)[55] Arthritis (M)[55] Coronary heart disease (M)[55] COPD (M)[55] Increased comorbidity[47] Higher inflammation (CRP, IL-6 and IL-1Ra)[64-66]	Mortality[67-72] Increased fall risk (W)[73] Frailty (W)[73] IADL disability (W)[73] ADL disability[72] Mobility disability[72]
Walking speed decline	Older age[74-76] Height loss (W)[76] Greater weight (W)[76] Obesity[77] Lower physical activity[77 78] Poorer diet quality[79] Smoking (W)[76] Lower and declining cognition[62 80 81] Knee OA[82] Arthritis (W)[76] Diabetes (W)[76] Higher systolic blood pressure[83] Tooth loss[84 85] Higher inflammation (IL-6)[86 87]	Mortality[77 88] Disability[89] Cognitive decline[90] Dementia[91]
Lean mass decline	Older age[92 74] Male sex[93] Higher fat mass[94] Weight loss[95 96] Lower fitness[97] Lower dietary protein intake[98] Lower 25-hydroxyvitamin D[99] Lower serum albumin[100]	Mortality (M)[105 106]

Component	Determinants	Consequences
	Lower serum creatinine (M)[101] Higher insulin resistance (M)[102 103] Frailty[104]	
Fat mass increases	Older age[93] Male sex[93] Poorer diet quality[107 108] Higher protein intake[109] Lower physical activity[110 111]	Mortality (M)[105] Type 2 diabetes[112 113] Metabolic syndrome[114] Hypertension[114] Higher serum cholesterol (M)[115] Respiratory function decline[116] Renal function decline[117] Cognitive decline[118]
Fat mass decline	Higher physical activity[110 111]	Mortality (W)[119] Cognitive decline[118]
Bone mineral density decline	Older age[120 121] Female sex[120 122] White ethnicity[123 124] Socioeconomic disadvantage (M)[125] Lower weight[126 127 128] Weight loss[126 127 128] Lower physical activity[128 129] Poorer diet quality (W)[130] Lower calcium intake (M)[120] Higher protein intake[131 132] Smoking[120 122 133] Depressive symptoms[134-136] Lower renal function (M)[137 129 138] Hypertension (W)[139] Cardiovascular disease[140] Diabetes (W)[141 142] Higher inflammation (CRP, IL-6, TNFα)[143]	Mortality[144-147] Incident cardiovascular disease[148] Coronary artery calcification (W)[149] Fracture[150 151] Recurrent falls[152] Cognitive decline[153]

SEP: Socioeconomic position; ADL: Activities of daily living; IADL: Independent activities of daily living; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; IL-6: Interleukin-6; Il-1Ra: Interleukin-1 receptor antagonist; OA: Osteoarthritis; TNFα: Tumor necrosis factor alpha; (M): Association reported among men only; (W): Association reported among women only

1.5.2 Interrelationships between change in grip strength, gait speed, body composition and BMD

Publications exploring interrelationships between changes in grip strength, gait speed, lean mass, fat mass or BMD were identified from the epidemiological literature review. These papers had related either level or change in one of these parameters to change in another of these parameters. The publications identified had related BMD and body composition parameters to rate of grip strength and gait speed decline as well as examining body composition, gait speed and

grip strength as predictors of BMD decline. These papers are described in Sections 1.5.2.1 to 1.5.2.3. Only seven papers relating change in one parameter to change in another parameter were identified. Furthermore, no papers identified by the literature review explored changes in muscle strength, physical function and body composition (including bone) in a single cohort using three or more repeated measures.

1.5.2.1 Levels and changes in body composition parameters in relation to changes in grip strength and gait speed

Components of body composition have been identified as predictors of grip strength and gait speed decline. For example, among a cohort of 1710 Afro-Caribbean men (Mean [SD] age 54.3 [10.2] years), lower baseline and greater loss of arm lean mass were each associated with accelerated loss of grip strength[54]. Among participants of the Health ABC Study, changes in whole body DXA parameters and CT parameters relating to the abdomen and thigh were examined in relation to changes in gait speed over a 4-year follow-up[75]. Increases in thigh intermuscular fat and decreases in thigh muscle area were associated with greater decline in gait speed among men and women; the authors suggest that this could be due to an infiltration of fat into muscle, leading to reductions in lower limb mobility. Research on the association between BMD and changes in gait speed is limited but a small study of 182 women aged 70 to 84, found that changes in gait speed and forearm BMD during a 2-year follow-up were positively correlated[154].

1.5.2.2 Levels and changes in lean and fat mass in relation to changes in BMD

There is evidence that lower level and accelerated loss of lean and fat mass are associated with greater BMD decline. Among 955 postmenopausal women who participated in the Chingford Study, lower baseline DXA lean and fat mass were related to greater decline in BMD at the spine and femoral neck with larger effect sizes for lean mass[127]. Conversely, in a smaller study comprising 276 French women, aged 75 and older, lower baseline DXA fat mass and percentage fat, but not lean mass, were associated with accelerated decline in BMD at the trochanter and Ward's triangle, even after adjustment for weight change[155]. The role of lean and fat mass in the relationship between weight change and BMD change was also explored in the Concord Health and Ageing in Men Project (CHAMP): among men who lost weight, decreases in fat mass were associated with greater hip BMD loss whereas among men who gained weight, increases in lean mass were associated with greater increases in hip BMD[156].

1.5.2.3 Changes in grip strength in relation to changes in BMD

Among 662 postmenopausal women in the Finnish Osteoporosis Risk Factor and Prevention (OSTPRE) study cohort, participants were categorised into three groups ('decreased', 'maintained' and 'improved') depending on the change in their age-stratified grip strength quartile from baseline to the 10-year follow-up[157]. Those in the 'improved' group experienced reduced BMD decline at the lumbar spine and femoral neck BMD compared to those who were not.

1.5.3 Summary of epidemiological literature review

The epidemiological literature review identified common determinants for greater declines in grip strength, gait speed, lean mass and BMD and increases in fat mass, such as older age, poorer diet quality and lower physical activity. Both increases and decreases in fat mass and greater declines in the remaining parameters have been identified as risk factors for mortality. Literature examining interrelationships between changes in parameters was limited, although positive correlations between declines in lean mass, fat mass and BMD in relation to declines in grip strength and gait speed have been reported.

Strengths of this literature review include the broad range of musculoskeletal and body composition parameters considered and the systematic aspect of the searches that were performed. However, weaknesses include the restriction of searches to papers in English, potentially missing relevant papers in other languages, and the use of only one reviewer to deem articles relevant or not.

1.5.4 Limitations and critique of previous literature

Many of the articles identified from the literature review have limitations regarding the statistical techniques used. For example, of the 206 articles deemed relevant, 139 only used simple measures of change such as percentage, absolute or annual change which were based on measurements at only two time-points. The change measure was then typically used to describe average change at the population level or used as a predictor or outcome in a standard statistical modelling technique such as linear regression. Limitations of this approach are that between-individual differences in change are ignored as linear regression only models averages; change

between the two time-points is assumed to be linear when it could be non-linear; and measurement error is not accounted for. Some of the simple change measures were also grouped into quartiles before relating them to other variables which results in a loss of information.

Some publications had measured characteristics at more than two time-points and implemented more sophisticated approaches such as linear mixed effects (LME) modelling to characterise change. These models can assess change more reliably by using data from all of an individual's observations and incorporating polynomial terms to test for non-linear change; tests of whether rates of change differ according to participant characteristics can also be performed. However, although LME models allow level and rates of change to differ between individuals, they assume an overall mean rate of change for the whole sample, with individual variation around this mean. A limitation of this is that different groups of individuals may experience markedly different trajectories of change which this method would not account for.

Some publications identified in the literature also suffered from methodological limitations. For example, some publications used simplistic assessments of adiposity such as waist circumference or waist-to-hip ratio rather than using more accurate measures from DXA which partition fat, lean and bone mass. In addition, no papers identified by the review explored change in muscle strength, physical function and body composition (including bone) in a single cohort using three or more repeated measures. Therefore, a synthesis of the relationships between change in these quantities is only possible by comparison of results from several cohorts, often ascertained at different ages and in different countries, which results in less reliable comparisons.

1.6 Aims and objectives

This PhD will use novel statistical methods to describe trajectories of grip strength, gait speed, lean mass, fat mass and BMD using data from 3075 older men and women who participated in the Health ABC Study. This cohort was selected as these musculoskeletal and body composition parameters were measured at multiple time-points over a 9-year follow-up which enables a comprehensive characterisation of change. Baseline determinants and health-related consequences of lower levels and greater declines in these characteristics will be explored and interrelationships between changes in these characteristics will be examined. This work has the potential to inform the development of lifecourse intervention strategies to delay the onset and reduce the prevalence of musculoskeletal disorders in later life, such as sarcopenia and osteoporosis, and to identify groups of individuals with patterns of decline in muscle strength,

function and body composition (including bone) which place them at increased risk of poor health outcomes, such as falls, fracture, hospital admission and mortality.

1.7 Summary of thesis content

The remainder of this document comprises the following: a statistical literature review for articles which have analysed change in a quantity over time, along with a description of the techniques identified; an outline of the statistical theory for the techniques implemented in this thesis; a description of the Health ABC Study; the statistical methods and results for describing changes in musculoskeletal and body composition characteristics, investigating determinants of levels and changes in these characteristics, examining interrelationships between changes in these characteristics and examining levels and changes in these characteristics in relation to risk of adverse health outcomes; and a discussion comprising a summary of the main findings, how these findings relate to previous literature, the clinical and statistical implications of findings and an overview of strengths and weaknesses.

Chapter 2 Methods

2.1 Chapter summary

This chapter includes the following information: a review of the statistical literature relevant for this thesis; an outline of the statistical theory for the techniques implemented in this thesis; an introduction to the Health, Aging and Body Composition Study, the cohort used for analysis; and a description of the statistical methods that were implemented to address the aims and objectives of this thesis.

2.2 Statistical literature review

The range of statistical techniques applied in articles returned from the epidemiological literature search is unlikely to reflect the full range of potentially relevant statistical methods that could be useful for this PhD but which may have only previously been applied to other areas of science. To address this, a scoping literature search for publications which had used statistical techniques to examine change in a quantity over time was conducted using the Scopus database in October 2017. The advantage of using Scopus as opposed to OVID for this search is that OVID only includes articles relating to medical research whereas Scopus includes articles in other scientific fields which may also be relevant.

After the search was conducted by myself, articles deemed relevant based on the title were then carried forward and the abstracts of these articles were then screened to identify the relevant publications with the full text being examined if a decision could not be made using the abstract and title alone. Information on the number of articles returned at different stages of the literature review is presented in Table 5.

Table 5: Scopus literature search for articles examining change in a quantity over time

Stage	Search terms used	Articles returned
1	**Articles analysing change over time** TITLE (chang* OR declin* OR attenuat* OR trajector* OR "loss" OR "lost" OR "losing" OR gain*) OR ABS (change* OR declin* OR attenuat* OR trajector* OR "loss" OR "lost" OR "losing" OR gain*)	9,705,983
2	**Articles with repeated measures (same quantity measured several times)** TITLE ("repeat* measure*" OR "repeat* observation*" OR "panel data" OR "longitudinal data") OR ABS ("repeat* measure*" OR "repeat* observation*" OR "panel data" OR "longitudinal data")	89,810
3	**Articles discussing statistical techniques (articles where 'statistic' appears within five words from the others will be returned)** TITLE-ABS-KEY (method* OR model* OR technique* OR strateg* OR tool*) W/5 TITLE-ABS-KEY (statistic*)	607,929
4	**Articles relevant to Stages 1, 2 and 3** (TITLE (chang* OR declin* OR attenuat* OR trajector* OR "loss" OR "lost" OR "losing" OR gain*) OR ABS (chang* OR declin* OR attenuat* OR trajector* OR "loss" OR "lost" OR "losing" OR gain*)) **AND** (TITLE ("repeat* measure*" OR "repeat* observation*" OR "panel data" OR "longitudinal data") OR ABS ("repeat* measure*" OR "repeat* observation*" OR "panel data" OR "longitudinal data")) **AND** (TITLE-ABS-KEY (method* OR model* OR technique* OR strateg* OR tool*) W/5 TITLE-ABS-KEY (statistic*))	1,898
5	**Limit to English language and include articles, reviews and articles in press (exclude conference papers and books)** (TITLE (chang* OR declin* OR attenuat* OR trajector* OR "loss" OR "lost" OR "losing" OR gain*) OR ABS (chang* OR declin* OR attenuat* OR trajector* OR "loss" OR "lost" OR "losing" OR gain*))	1,765

Stage	Search terms used	Articles returned
	AND (TITLE ("repeat* measure*" OR "repeat* observation*" OR "panel data" OR "longitudinal data") OR ABS ("repeat* measure*" OR "repeat* observation*" OR "panel data" OR "longitudinal data")) AND (TITLE-ABS-KEY (method* OR model* OR technique* OR strateg* OR tool*) W/5 TITLE-ABS-KEY (statistic*)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re") OR LIMIT-TO (DOCTYPE , "ip")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (SRCTYPE , "j"))	
6	**Potentially relevant publications (based on the title and abstract)**	183
7	**Relevant publications (based on the title, abstract and full-text if the relevance could not be determined by the title and abstract)**	163

2.2.1 Techniques identified from the epidemiological literature review

The previous epidemiological literature search identified articles which had examined change in grip strength, gait speed, lean mass, fat mass and BMD. A total of 206 articles were identified; the number of articles that had implemented various statistical techniques is presented in Table 6.

Table 6: Number of epidemiological literature review articles implementing various techniques

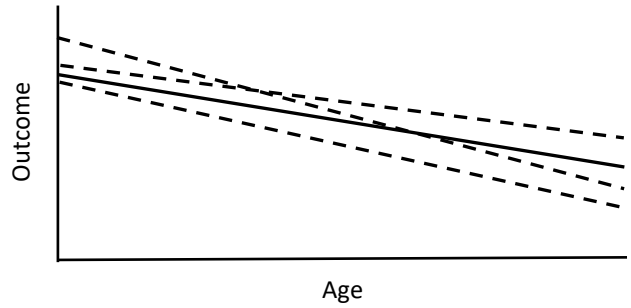
Statistical technique	Number of articles
Simple methods	139
Linear mixed effects (LME) models	49
Generalised Estimating Equations (GEE)	9
Latent growth curve (LGC) models	4
Latent class trajectory (LCT) models	2
Autoregressive cross-lagged models	3

Simple methods include deriving percentage, absolute or annual change from measurements at two time-points or using a linear regression model for the outcome at the second time-point with adjustment for the outcome at the first time-point

Linear mixed effects (LME) models were often implemented when the same quantity was measured at three or more time-points and were used in 49 of the 206 articles identified by the epidemiological literature review. This approach examines a continuous response as a function of population level (fixed) effects and individual level (random) effects, allowing intercepts and slopes, as well as the effects of predictors, to differ between individuals[158]. A simplified graphical illustration of an LME model is presented in Figure 1. Many publications exploring predictors of change included a fixed effect interaction term between the predictor and the time variable to determine whether the average rate of change was modified by the predictor. Other approaches included fitting an LME model with random intercepts and slopes to model an outcome with the time variable as the predictor; extraction of the random slopes produces person-specific estimates of the rate of change of the outcome over time[159]. Examples of extensions included the use of linear splines to account for the acceleration in the linear rate of grip strength decline after the age of 75[73] and the inclusion of a quadratic term for age to reflect the acceleration of bone loss in later life[121]. Nine articles used generalised estimating equations (GEE) which generally provide comparable results at the population level to LME models, but information regarding the variability between individuals is not provided[160]. An advantage of LME and GEE models is that they both account for the within-individual correlation of repeated measures. LME models can

also analyse unbalanced data which contain missing values or repeated measures ascertained at different times for different individuals.

Figure 1: Linear mixed effects model with random intercept and slope



The solid line represents the population average trajectory

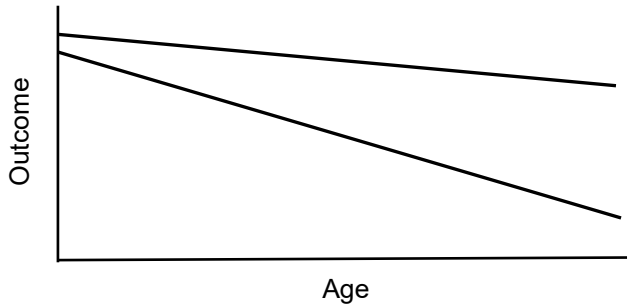
Dashed lines represent individual-specific trajectories, each having a different intercept and slope

Only four articles implemented latent growth curve (LGC) models using a structural equation modelling framework. These models derive latent factors (random effects), based on factor loadings of the original repeated measures, for the intercept and slope, representing the initial level and change in the outcome respectively[161]. For example, the intercept and slope factors for grip strength were used to: examine determinants of grip strength level and loss[49]; examine the association between grip strength level and decline in relation to mortality risk[162]; and to explore whether grip strength and reasoning ability were related in terms of their level and rate of decline[163]. Many of the properties of LGC models are similar to those of LME models, such as accounting for inter individual differences in growth parameters, and in the case of balanced designs, the models can produce identical results. Compared to LME models, LGC models are less robust when analysing unbalanced data but may have advantages when analysing more complex functions of change[164].

Only two articles implemented latent class trajectory (LCT) models[165]. This technique identifies distinct unobserved groups of individuals with similar trajectories regarding a repeated measure and computes the mean growth curve for each group. A graphical illustration of a simple LCT model is presented in Figure 2. After the optimal number and shape of the trajectories are determined using goodness-of-fit statistics, the groups derived can then be used as predictors or outcomes in conventional statistical analyses. For example, one article found that individuals with symptomatic knee osteoarthritis (OA) were at increased risk of being in the 'fast decline' gait speed group[82] and another article reported that participants in the 'fast decline' gait speed group were at the highest risk of mortality[77]. If a quantity does not exhibit individual variation around a

common growth function and has distinct trajectories which differ between groups, LCT models are more suitable than LGC and LME models. Limitations of this method are that many repeated measures are required for exploration of more complex trajectories, which often results in high levels of attrition; and an assumption is made that all individuals within a trajectory group are regarded as having the same growth parameters[166].

Figure 2: Simple latent class trajectory model



Lines represent mean trajectories for the two groups (different numbers of groups are also possible)
Individuals are assigned to the group that most closely matches their trajectory

Three articles from the literature review used autoregressive cross-lagged models to investigate temporal relationships between measures of cognition and gait speed[62 90 167]. This approach involved examining the association between cognition at time T and gait speed at time T+1 whilst accounting for gait speed at time T and vice versa. As well as exploring bidirectional associations, autoregressive cross-lagged models can prevent the detection of erroneous cross-lagged associations that are actually only due to cross-sectional correlations at earlier time-points[168]. Although these models are useful for examining temporal relationships between variables, they are less suitable for exploring the overall mathematical function governing change in a quantity over time or understanding changes occurring within an individual[168].

2.2.2 Additional techniques identified from the statistical literature review

The most common techniques identified from the statistical literature review of papers that had analysed change in a quantity over time are included in Table 7. Papers using LME models or those that derived simple measures of absolute change from two time-points were frequently identified in the epidemiological literature review and, therefore, were excluded from the statistical literature review.

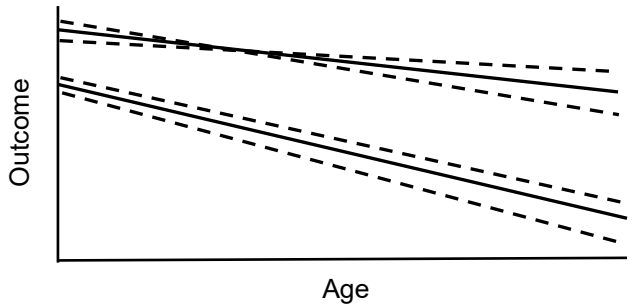
Table 7: Most common techniques used in articles from the statistical literature search

Statistical technique	Number of articles
Latent growth curve (LGC) models	30
Growth mixture models (GMM)	17
Latent class trajectory (LCT) models	13
Bayesian mixed models	12
Joint modelling (longitudinal and survival data)	8
Lagged-response models	8
Bivariate dual change score models	4

The numbers above do not contain relevant tutorial articles written for educational purposes which often included several of the techniques stated in this table. Articles which used LME models or those that derived simple measures of change from two time-points also do not feature in this table.

Many of the articles from the statistical literature review used growth mixture models (GMM) to uncover population groups with distinct trajectories and to relate membership of these groups to various outcomes and predictors[169 170]. One article in the review used this technique to derive childhood BMI trajectory groups in a cohort from South Africa and then explore whether blood pressure in late adolescence differed between these groups[170]. Growth mixture models derive separate mean trajectories for distinct groups of individuals and also allow intercepts and slopes to vary between individuals in the same group[171]. A graphical illustration of a simple GMM is presented in Figure 3. A latent class trajectory (LCT) model can be understood as a type of growth mixture model where the growth parameters for individuals in the same group are identical; similarly, an LME model can be understood as a growth mixture model where only one trajectory group is specified[171]. Advantages of growth mixture models are that they offer more flexibility than LCT models by allowing parameters to vary within each trajectory group; both these two methods allow the identification of unobserved groups with distinct trajectories[172]. However, growth mixture modelling is computationally intensive and groups which are not substantively meaningful, but which are statistically distinct from others can be obtained[172].

Figure 3: Simple growth mixture model



Solid lines represent mean trajectories of the two groups (different numbers of groups are possible)
Dashed lines represent individual-specific trajectories, each having a different intercept and slope
Individuals are assigned to the group that most closely matches their trajectory

Several articles explored change over time using Bayesian mixed models[173-175]. Like other Bayesian approaches, these models require the estimation of a posterior distribution from a prior distribution which reflects the initial beliefs about the model parameter before any information is observed, and a likelihood function, based on the observed data. These articles used Markov Chain Monte Carlo (MCMC) methods to iteratively produce samples from a distribution which is designed to converge to the posterior distribution. One article used a piecewise Bayesian linear mixed model with unknown change points, requiring estimation, to model the grip strength trajectory, based on up to 11 repeated measurements, of adults from the Fels Longitudinal Study[175]. This article also illustrated the potential of Bayesian linear mixed models to analyse unbalanced data containing uneven observation times and data missing at random; more complex extensions to handle data which are not missing at random are also available[176]. As with ordinary LME models, other advantages of Bayesian mixed models include the use of random effects to allow effects of predictors to differ between participants and account for the correlations between repeated measures relating to the same individual. Similar to the manner in which growth mixture models can be used to extend a conventional LME model, some review articles used mixture models to extend Bayesian mixed models by estimating distinct mean trajectories for groups of participants, characterised using different parameters[177 178]. However, disadvantages of Bayesian modelling in general include a lack of objectivity, due to the requirement to specify a prior distribution, and the computationally demanding convergence algorithms used to estimate the posterior distribution.

Some publications used joint models to explore the relationship between longitudinal change in a parameter and time to health-related events[179 180]. These models combine the random effects

from LME models and frailty survival models and are estimated in a single process[181], rather than a two-stage process of extracting random effects from an LME model for subsequent inclusion in a survival model. Unlike the two-stage process, joint models can account for the relationship between longitudinal change and survival data such as when the chance of dropout depends on the longitudinal information (non-random dropout)[181]. Although joint models can be applied in a frequentist (drawing conclusions from sampled data without prior beliefs of model parameters) or Bayesian framework, disadvantages include the computational time required for model fitting and the lack of software available for implementation[181].

Several papers had implemented lagged-response models, also known as dynamic models, to account for autoregressive effects (effects of previous values on current values of a repeatedly measured variable) when examining cross-sectional associations[182 183]. Basic lagged-response models examine the association between a predictor and an outcome at time T whilst accounting for the outcome at time T-1, to examine whether the predictor has an effect over and above the autoregressive effect.

A limited number of articles from the statistical literature review used bivariate dual change score models (BDCSM) to examine associations within and between two aspects of human functioning[184-186]. For example, one article suggested that increased physical activity reduced future decline in cognition[186] and another reported that better memory reduced subsequent increases in functional limitations[185]; neither study found evidence for effects in the opposite directions. These models extend latent growth curve models (simply modelling longitudinal change over time in each of the two variables), by incorporating cross-lagged associations between the variables. This is achieved by estimating: the mathematical function governing change for each variable using latent growth curve models; the effect of each variable at time T on its change between T and T+1; and the effect of each variable at time T on change in the other variable between T and T+1[186]. BDCSM can also be extended to include additional parameters reflecting the association between prior changes in each variable in relation to subsequent changes in both the same variable and the other variable[187]. For example, one publication used an extended BDCSM and found that improvements in self-esteem were associated with subsequent increases in relationship satisfaction among participants of the Panel Analysis of Intimate Relationships and Family Dynamics Study[188]. Although bivariate dual change score models allow complex hypotheses about interrelationships between variables over time to be tested, disadvantages include potentially difficult interpretations of model parameters and the treatment of cross-lagged effects as fixed and, therefore, equal for all individuals[184].

2.2.3 Techniques identified by the literature searches that will be implemented in this thesis

In this thesis, LME models are used to describe mean trajectories of characteristics over time and to obtain measures of change by the extraction of estimated random slopes. As stated in Section 2.2.1, these models are highly suitable for this as they account for the within-individual correlation of repeated measures, accommodate unbalanced data containing missing values or repeated measures ascertained at different times for different individuals, and use all of an individual's repeated measures. However, these models only assume individuals vary in level and change around a single population-average trajectory. Therefore, to examine whether there are groups of participants with markedly different mean trajectories, GMM and LCT models were applied which allow these group-specific mean trajectories to be estimated. A summary of the key properties of statistical techniques used in this document to describe trajectories of musculoskeletal and body composition parameters is presented in Table 8.

To examine temporal associations between changes in characteristics, extended BDCSM were implemented. As discussed in Section 2.2.2, these models examine prior changes in one variable in relation to subsequent changes in the other variable whilst accounting for effects of prior changes in the same variable and prior levels of both variables. Therefore, these models are suitable for addressing a key aim of this thesis: investigating interrelationships between changes in musculoskeletal and body composition characteristics.

Table 8: Aspects of statistical techniques used in this document to describe trajectories

<table>
<tr><th>Aspect</th><th>Linear mixed effects (LME) model</th><th>Latent class trajectory (LCT) model</th><th>Growth mixture model (GMM)</th></tr>
<tr><td>Purpose</td><td>To estimate the population average trajectory and parameters which reflect individual differences in level and change from this average trajectory</td><td colspan="2">To identify groups of individuals with similar trajectories and estimate average trajectories for each group</td></tr>
<tr><td>Useful output from model</td><td>Plot of the population average trajectory over time
Individual-specific parameters reflecting level and change in the modelled characteristic can be used in further analyses</td><td colspan="2">Plot of the average trajectory of each group over time
Derived groups of individuals can be used as predictors and outcomes in further analyses</td></tr>
<tr><td>Relationships between models</td><td>LME models are GMM with only one group</td><td>LCT models are GMM with the constraint that individuals within the same group are assumed to have the same trajectories</td><td>GMM are extended LME models with different average trajectories for each group
GMM are extensions of LCT models which allow different trajectories for individuals within the same group</td></tr>
<tr><td rowspan="2">Advantages</td><td rowspan="2">Straightforward to obtain measures of level and change for each individual if the mean trajectory over time is linear</td><td colspan="2">Suitable for analysing change in a quantity over time that has distinct mean trajectories for different groups of participants</td></tr>
<tr><td>Easier to fit and interpret than GMM</td><td>More flexible and make less assumptions than LME and LCT models</td></tr>
<tr><td rowspan="2">Disadvantages</td><td rowspan="2">Difficult to obtain measures of change for non-linear trajectories
Only assumes a single average trajectory for the whole population and does not allow groups in the population to have markedly different average trajectories</td><td colspan="2">Selecting the optimal number of groups and shapes of trajectories can be difficult
Derived groups may be statistically distinct but not substantively meaningful within the scientific area</td></tr>
<tr><td>Individuals within each group are assumed to have the same trajectory</td><td>Computationally intensive and algorithms to estimate parameters may not converge</td></tr>
</table>

Of the techniques stated in Table 6 and Table 7, GEE, LGC and lagged-response (dynamic) models were not implemented. GEE and LGC models are similar to LME models but have additional limitations such as the lack of information on variability between individuals (GEE) and less robustness for analysis of unbalanced designs (LGC). Lagged-response models are less relevant for this thesis as they are primarily used if it is essential to control for the previous value of the outcome when examining cross-sectional associations or if the autoregressive effect itself is of particular interest; this is not the aim for this thesis. Joint models to explore the relationship between longitudinal change and time to health-related events were not implemented. This is because an objective of this thesis is to examine the separate effects of level and change in parameters on risk of adverse outcomes and joint models which combine the derivation of change and estimation of the impact of change on risk of adverse outcomes in a single process would result in difficulty separating these effects. Bayesian hierarchical models were not implemented as the choice of an uninformative prior along with the large amount of data available to compute the likelihood function is likely to result in very similar estimates compared to frequentist equivalents of these techniques.

2.3 Statistical theory

This subsection outlines the theory for the following statistical techniques that are used in this thesis: generalised additive models for location, scale, and shape (GAMLSS); linear mixed effects (LME) modelling; latent class trajectory (LCT) modelling; growth mixture modelling (GMM); and bivariate dual change score models (BDCSM). Although GAMLSS were not identified in the literature reviews, they were used to derive age-related centile curves and standardised scores (z-scores) for musculoskeletal and body composition measures in the Health ABC Study. Centile curves provide a graphical illustration of the levels of the musculoskeletal and body composition parameters according to age. Examining changes in z-scores of a characteristic enables change in the age-adjusted ranking of participants' values of the characteristic over time to be explored. Accounting for age in the derivation of z-scores also results in linear changes in the mean z-scores for each characteristic over time which are straightforward to analyse. The other techniques were used to describe changes in musculoskeletal and body composition measures according to age. For all analysis techniques used to describe changes in these characteristics, sex-stratified analyses were conducted unless otherwise indicated. Material in this section is based on the following key resources: *Stasinopoulos MD, Rigby RA, Heller GZ, et al. Flexible Regression and Smoothing: Using GAMLSS in R. Chapman and Hall/CRC 2017*[189]*; Nagin DS. Group-based modeling*

of development. Harvard University Press 2005[190]; and *Proust-Lima C, Philipps V, Liquet B. Estimation of Extended Mixed Models Using Latent Classes and Latent Processes: The R Package lcmm. J Stat Softw 2017;78(2)*[191].

2.3.1 Generalised additive models for location, scale and shape

2.3.1.1 Background and definitions

Generalised additive models extend generalised linear models by using smooth functions to relate predictor variables to the location (mean) and scale (variance) parameters of the outcome variable as shown in Equation 1.

Equation 1: Generalised additive model for a single predictor and outcome variable

$$\boldsymbol{y} \sim \boldsymbol{\epsilon}(\boldsymbol{\mu}, \boldsymbol{\Phi})$$
$$\boldsymbol{g_1}(\boldsymbol{\mu}) = \boldsymbol{\beta_1} + \boldsymbol{\beta_2 x} + \boldsymbol{f_1}(\boldsymbol{x})$$
$$\boldsymbol{g_2}(\boldsymbol{\Phi}) = \boldsymbol{\beta_3} + \boldsymbol{\beta_4 x} + \boldsymbol{f_2}(\boldsymbol{x})$$

$\boldsymbol{y}$: *outcome variable vector of observations*; $\boldsymbol{x}$: *predictor variable vector*
$\boldsymbol{\epsilon}(\boldsymbol{\mu}, \boldsymbol{\Phi})$: *exponential family distribution with location parameter* $\boldsymbol{\mu}$ *and scale parameter* $\boldsymbol{\Phi}$
$\boldsymbol{f_1}(.), \boldsymbol{f_2}(.)$: *smooth functions for the predictor variable*
$\boldsymbol{g_1}(.), \boldsymbol{g_2}(.)$: *link functions for the parameter*

In the context of this thesis, the outcome variable is a musculoskeletal or body composition parameter such as grip strength and the predictor variable is the age at which this parameter was measured. Unlike generalised linear models, generalised additive models allow the relationship between a predictor and the scale (variance) parameter to be explored and the smooth functions ensure that the relationships between predictors and distributional parameters are not limited to a strict linear or non-linear relationship.

Generalised additive models for location, scale and shape (GAMLSS) offer even more flexibility than ordinary generalised additive models by also allowing the shape (skewness and kurtosis) parameters to be modelled in relation to predictor variables as shown in Equation 2.

Equation 2: Generalised additive model for location, scale and shape

$$\boldsymbol{y} \sim \boldsymbol{D}(\boldsymbol{\mu}, \boldsymbol{\Phi}, \boldsymbol{\nu}, \boldsymbol{\tau})$$
$$\boldsymbol{g_1}(\boldsymbol{\mu}) = \boldsymbol{\beta_0} + \boldsymbol{\beta_1 x} + \boldsymbol{f_1}(\mathbf{x})$$
$$\boldsymbol{g_2}(\boldsymbol{\Phi}) = \boldsymbol{\beta_2} + \boldsymbol{\beta_3 x} + \boldsymbol{f_2}(\mathbf{x})$$
$$\boldsymbol{g_3}(\boldsymbol{\nu}) = \boldsymbol{\beta_4} + \boldsymbol{\beta_5 x} + \boldsymbol{f_3}(\mathbf{x})$$
$$\boldsymbol{g_4}(\boldsymbol{\tau}) = \boldsymbol{\beta_6} + \boldsymbol{\beta_7 x} + \boldsymbol{f_4}(\mathbf{x})$$

$\boldsymbol{y}$: $outcome\ variable\ vector\ of\ observations$; $\boldsymbol{x}$: $predictor\ variable\ vector$
$D(\boldsymbol{\mu}, \boldsymbol{\Phi}, \boldsymbol{\nu}, \boldsymbol{\tau})$: $distribution\ with\ location\ (\boldsymbol{\mu}), scale(\boldsymbol{\Phi}), and\ shape\ parameters(\boldsymbol{\nu}, \boldsymbol{\tau})$
$\boldsymbol{f_1}(.), .., \boldsymbol{f_4}(.)$: $smooth\ functions\ for\ the\ predictor\ variable$
$\boldsymbol{g_1}(.), \ldots, \boldsymbol{g_4}(.)$: $parameter\ link\ functions$

The models listed in Equation 1 and Equation 2 can be extended by including linear terms and functions of other predictor variables. Random effects can be incorporated which can allow the intercept, linear effect of predictors and even the shape of the smoothing curves to differ between clusters of observations, for example, grip strength values from different individuals.

2.3.1.2 Parameter estimation

GAMLSS parameters are obtained using maximised penalised likelihood estimation, a type of maximum likelihood estimation where a penalty, based on the number of parameters in the model, is applied. The Rigby and Stasinopoulos (RS) algorithm can be used to maximise the penalised likelihood over each distributional parameter in turn whereas the Cole and Green (CG) algorithm uses information from the first, second and cross derivatives of the log-likelihood function with respect to each parameter to update the parameters simultaneously[189]. Although the RS algorithm may converge prematurely and run slowly for highly correlated parameters, the RS algorithm is normally faster and more stable so it is used in this thesis[189].

2.3.1.3 Checking model assumptions

Model checking is performed using the normalised (randomised) quantile residuals which have a standard normal distribution if the model is correct, regardless of the outcome variable distribution[192]. These residuals are defined in Equation 3.

Equation 3: Normalised (randomised) quantile residuals

$$\hat{u}_i = F(y_i)$$
$$\hat{r}_i = \Phi^{-1}(\hat{u}_i) = \Phi^{-1}(F(y_i))$$

$F(.)$: $cumulative\ distribution\ function\ of\ the\ outcome\ variable$
$\Phi^{-1}(.)$: $inverse\ cumulative\ distribution\ function\ of\ the\ standard\ normal\ distribution$
$\hat{r}_i$: $normalised\ (randomised)\ quantile\ residuals$

From the probability integral transform[193], it follows that $\hat{u}_i$ and $\hat{r}_i$ have standard uniform and normal distributions respectively if the model has the correct distribution for the outcome variable. Like ordinary linear models, Q-Q plots of the residuals and graphs of the residuals against the fitted values can be used to assess distributional assumptions. For GAMLSS, worm plots and Q-statistics are commonly used to assess whether the residuals are normally distributed within different ranges of the predictor variable.

2.3.1.4 Estimation of centile curves

Centile curves typically show how the distribution of an outcome changes according to age. The Box-Cox Cole and Green method to derive centile curves, more commonly known as the LMS method, assumes that the relationship between age and the outcome has a Box-Cox Cole and Green (BCCG) distribution and can be modelled using the following three parameters: Box-Cox power transformation to represent skewness (L); median (M); and coefficient of variation (S)[194]. The kurtosis of an outcome variable can be accounted for using the Box-Cox power exponential (BCPE) or the Box-Cox t (BCT) distribution[195] which includes a parameter for kurtosis along with the previous three parameters.

Suppose Y>0 is defined according to the random variable Z in Equation 4.

Equation 4: Transformations for Box-Cox distributions (Cole and Green, power exponential and t)

$$Z = \frac{1}{\sigma v}\left[\left(\frac{Y}{\mu}\right)^{v} - 1\right] \quad if\ v \neq 0$$

$$Z = \frac{1}{\sigma}\log\left(\frac{Y}{\mu}\right) \quad if\ v = 0$$

$\mu > 0, \sigma > 0\ and\ -\infty < v < \infty$
$\mu: median;\ \sigma: coefficient\ of\ variation;\ v: skewness$

Then $Y \sim BCCG$ if Z has a truncated standard normal distribution; $Y \sim BCPE$ if Z has a truncated power exponential distribution; and $Y \sim BCT$ if Z has a truncated t-distribution.

The formulation of a GAMLSS for centile estimation is stated in Equation 5.

Equation 5: Formulation of a GAMLSS for centile estimation

$$\boldsymbol{y} \sim \boldsymbol{D}(\boldsymbol{\mu}, \boldsymbol{\Phi}, \boldsymbol{\nu}, \boldsymbol{\tau})$$
$$\boldsymbol{g_1}(\boldsymbol{\mu}) = \boldsymbol{\beta_0} + \boldsymbol{\beta_1 age^{\varepsilon_1}} + \boldsymbol{f_1}(\boldsymbol{age^{\varepsilon_2}})$$
$$\boldsymbol{g_2}(\boldsymbol{\Phi}) = \boldsymbol{\beta_2} + \boldsymbol{\beta_3 age^{\varepsilon_3}} + \boldsymbol{f_2}(\boldsymbol{age^{\varepsilon_4}})$$
$$\boldsymbol{g_3}(\boldsymbol{\nu}) = \boldsymbol{\beta_4} + \boldsymbol{\beta_5 age^{\varepsilon_5}} + \boldsymbol{f_3}(\boldsymbol{age^{\varepsilon_6}})$$
$$\boldsymbol{g_4}(\boldsymbol{\tau}) = \boldsymbol{\beta_6} + \boldsymbol{\beta_7 age^{\varepsilon_7}} + \boldsymbol{f_4}(\boldsymbol{age^{\varepsilon_8}})$$

$\boldsymbol{y}: vector\ of\ observations;\ \boldsymbol{age}: vector\ containing\ the\ age\ corresponding\ to\ each\ observation$
$D(\boldsymbol{\mu}, \boldsymbol{\Phi}, \boldsymbol{\nu}, \boldsymbol{\tau}): distribution\ with\ location\ (\boldsymbol{\mu}), scale(\boldsymbol{\Phi}), and\ shape\ parameters(\boldsymbol{\nu}, \boldsymbol{\tau})$
$\boldsymbol{\tau}\ is\ absent\ when\ \boldsymbol{y} \sim BCCG$
$\boldsymbol{\varepsilon_1}, \dots, \boldsymbol{\varepsilon_8}: exponent\ parameters\ for\ age$
$\boldsymbol{f_1}(.), \dots, \boldsymbol{f_4}(.): smooth\ functions\ for\ the\ predictor\ variable$
$\boldsymbol{g_1}(.), \dots, \boldsymbol{g_4}(.): parameter\ link\ functions$

Models for centile estimation were implemented in R, a programming language and software for statistics, using the lms() function from the GAMLSS package. This function ascertains the following: exponent parameter for age; outcome variable distribution; and suitable degrees of freedom for smoothing parameters. The exponent parameter, which minimises the generalised Akaike information criterion (GAIC), is estimated for a model assuming a normally distributed outcome with constant variance. Maximum likelihood estimation is then used to estimate the optimal degrees of freedom for the smoothing parameter for the following outcome variable

distributions: BCCG, BCPE and BCT. The distribution with the smallest GAIC is selected. GAIC is based on the likelihood of the model, reflecting how well the model fits the data, along with a penalty (k) to penalise models with higher degrees of freedom which may be indicative of overfitting. As a maximum of only four degrees of freedom are permitted for each smoothing parameter in this algorithm, there was no need to increase this penalty to avoid overly complicated models. Therefore, the default penalty of k=2 was used.

Non-parametric penalised B-splines were used for smoothing which offer greater flexibility compared to parametric techniques. This method uses piecewise polynomials of order 3 for its basis with 20 equally spaced knots over the range of the predictor variable (age). For the derivation of centile curves, calibration, a default option of the lms() function was used. This shifts the centile curves to ensure that the actual proportion of individuals with values of the musculoskeletal or body composition characteristic below each centile cut-point is as expected.

2.3.2 Linear mixed effects models

2.3.2.1 Background and definitions

LME models are used for analysing clustered data with a hierarchical structure. This can occur when observations are sampled within different areas, for example, children may be recruited from different schools or countries, or, as in this thesis, when measurements relating to the same individual are repeated over time. These models are suitable for analysing change in an outcome which can be captured by a single average trajectory at the population level with between-individual variation in the initial level and magnitude of change but not in the direction of change[166]. Examples of such phenomenon would be adolescent growth or muscle strength decline in older age. Observations within the same unit are correlated and not independent. To address this, LME models extend ordinary linear models by incorporating cluster-specific random effects along with the population-level fixed effects, allowing intercepts and slopes, as well as the effects of predictors, to vary between clusters. LME models with only one level of clustering can also partition the total variance in the outcome into within-cluster and between-cluster variation to assess which source of variation is greatest.

In the context of this thesis, an LME model with a random intercept and slope for the analysis of repeated observations of an outcome such as grip strength according to a predictor variable such as age can be defined according to Equation 6.

Equation 6: Simple linear mixed effects model with a random intercept and slope

$$y_{ij} = (\beta_0 + \beta_{0i}) + (\beta_1 + \beta_{1i}) age_{ij} + \varepsilon_{ij}$$

$$\begin{pmatrix} \beta_{0i} \\ \beta_{1i} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} {\sigma_0}^2 & \sigma_{01} \\ \sigma_{01} & {\sigma_1}^2 \end{pmatrix} \right)$$

$$\varepsilon_{ij} \sim N(0, \sigma^2)$$

y_{ij}: $outcome\ variable\ observations\ from\ the\ i^{th}\ individual\ at\ the\ j^{th}\ timepoint$

age_{ij}: $age\ of\ the\ i^{th}\ individual\ at\ the\ j^{th}\ timepoint$

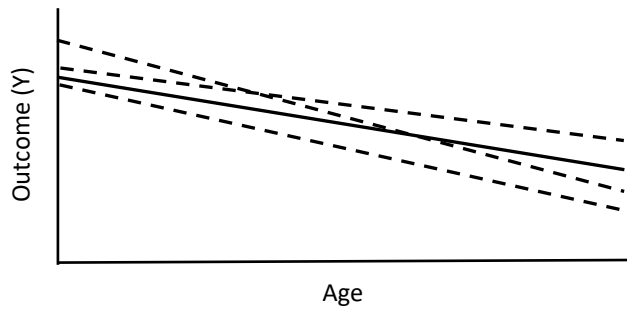
ε_{ij}: $observation\text{-}specific\ residual\ from\ the\ i^{th}\ individual\ at\ the\ j^{th}\ timepoint$

$(\beta_0 + \beta_{0i})$: $random\ intercept;\ \beta_0$: $population\text{-}level\ intercept;\ \beta_{0i}$: $person\text{-}specific\ intercept\ residual$

$(\beta_1 + \beta_{1i})$: $random\ slope;\ \beta_1$: $population\text{-}level\ slope;\ \beta_{1i}$: $person\text{-}specific\ slope\ residual$

Although Equation 6 only includes age as a linear effect, fixed effects and random effects for polynomial functions of age can also be specified. For this thesis, quadratic and cubic terms for age were used if significant for fixed effects but not as random effects as this resulted in convergence problems. The covariance matrix for the random effects is described as 'unstructured', meaning that variances and covariances are uniquely estimated. The following covariance matrices can also be specified which make stronger assumptions: independent (zero covariances); exchangeable (equal variances and identical non-zero pairwise covariances); and identity (equal variances and zero covariances). Unstructured covariance matrices will be used in this thesis as the other matrices rely on assumptions which are often unrealistic. A simplified graphical illustration of an LME model is presented in Figure 4.

Figure 4: Linear mixed effects model with random intercept and slope



The solid line represents the population average trajectory with intercept β_0 and slope β_1.

Dashed lines represent individual-specific trajectories with intercept $(\beta_0 + \beta_{0i})$ and slope $(\beta_1 + \beta_{1i})$

2.3.2.2 Parameter estimation

Parameters in LME models are usually estimated using standard maximum likelihood estimation or restricted maximum likelihood estimation. In general, maximum likelihood estimation involves determining the parameters of a statistical model that results in the highest probability of obtaining the observed data. However, the standard method estimates the variances of the random effects under the assumption that the fixed effects are correct, whereas the restricted method estimates the random effect from a function which is absent of any fixed effect parameters[196]. Although the standard method results in biased random effect estimates, this bias is small when the number of observations is large. A limitation of the restricted method is that it cannot be used to reliably compare models with different fixed effects[197]. Therefore, standard maximum likelihood estimation was used in this thesis.

2.3.2.3 Checking model assumptions

Like other statistical techniques, LME models rely on assumptions which should be checked through the use of diagnostic tests. These assumptions are identical to those of ordinary linear models: linear relationship between the predictors and outcome and that residuals are independent and normally distributed with constant variance. However, for LME models, these residual assumptions apply to the marginal ($y_{ij} - (\hat{\beta}_0 + \hat{\beta}_1 age_{ij})$) and conditional ($y_{ij} - ((\hat{\beta}_0 + \hat{\beta}_{0i}) + (\hat{\beta}_1 + \hat{\beta}_{1i}) age_{ij})$) residuals. Plots of the marginal residuals against the marginal predictions ($\hat{\beta}_0 + \hat{\beta}_1 age_{ij}$) and of the conditional residuals against the conditional predictions ($(\hat{\beta}_0 + \hat{\beta}_{0i}) + (\hat{\beta}_1 + \hat{\beta}_{1i}) age_{ij}$) can be used to assess model fit. Under the assumption of constant variance, the residuals should appear randomly scattered around the x-axis. Normality of the marginal and conditional residuals can be assessed using Q-Q plots.

2.3.3 Latent class trajectory models

2.3.3.1 Background and definitions

LCT models are used to identify unobserved groups of individuals with similar trajectories of change and to estimate distinct average trajectories for each of these groups. For example, changes in depression levels can vary between individuals in both magnitude and direction, with some individuals having consistently low or consistently high levels of depression and others having depression levels which fluctuate over time[198]. In this example, it would be more suitable

to use a LCT model to estimate the average trajectories of each group and probabilistically assign participants to each group, rather than describing change at the population level as a single average trajectory using an LME model.

A LCT model for an outcome variable such as grip strength with age as the only predictor variable can be defined using Equation 7.

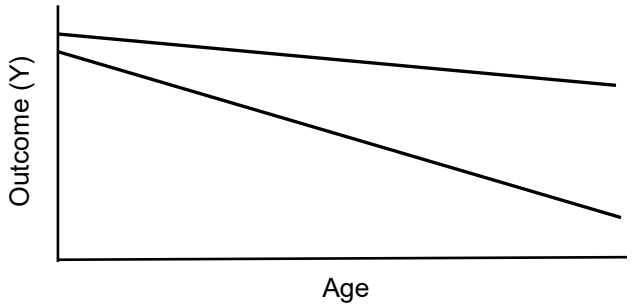
Equation 7: Simple latent class trajectory model

$$y_{ijk} = \beta_{0k} + \beta_{1k} age_{ij} + \varepsilon_{ij}$$
$$\varepsilon_{ij} \sim N(0, \sigma^2)$$

y_{ijk}: $outcome\ observation\ from\ the\ i^{th}\ individual\ at\ the\ j^{th}\ timepoint, given\ membership\ of\ group\ k$
age_{ij}: $age\ of\ the\ i^{th}\ individual\ at\ the\ j^{th}\ timepoint$
ε_{ij}: $observation\text{-}specific\ residual from\ the\ i^{th}\ individual\ at\ the\ j^{th}\ timepoint$
β_{0k}: $group\text{-}specific\ intercept;\ \beta_{1k}$: $group\text{-}specific\ slope$

Although a distinct intercept and slope is estimated for each group, there is no variation in these factors within groups, meaning that the expected trajectory for individuals in the same group is identical. A graphical illustration of a simple LCT model is presented in Figure 5.

Figure 5: Simple latent class trajectory model



Lines represent mean trajectories for the two groups (different numbers of groups are also possible)
Individuals are assigned to the group that most closely matches their trajectory

2.3.3.2 Parameter estimation

Parameters for LCT models are estimated using maximum likelihood estimation where the form of the likelihood function is as shown in Equation 8.

Equation 8: Likelihood function form for a latent class trajectory model

$$L = \prod_{i=1}^{N} L(Y_i) = \prod_{i=1}^{N} \left(\sum_{k=1}^{K} \pi_k l_k(Y_i) \right)$$

$L: overall\ form\ of\ the\ likelihood\ function$
$L(Y_i): likelihood\ function\ for\ the\ outcome\ variable\ Y\ for\ the\ i^{th}\ individual\ where\ i = \{1, 2, \dots, N\}$
$\pi_k: probability\ that\ a\ randomly\ chosen\ individual\ belongs\ to\ group\ k$
$l_k(Y_i): likelihood\ function\ for\ the\ outcome\ variable\ Y\ for\ the\ i^{th}\ individual, given\ membership\ of group\ k$
$Y_i = \{y_{i1}, y_{i2}, \dots, y_{iT}\}: set\ of\ repeated\ measures\ of\ the\ i^{th}\ individual\ over\ T\ time\text{-}points$

The formula used for the likelihood function depends on the distribution of the repeated measure outcome variable. The 'PRO TRAJ' and 'traj' packages in SPSS and Stata for implementing these models allow for the following outcome variable distributions: Bernoulli, censored normal, and Poisson. As all musculoskeletal and body composition parameters were normally distributed, a censored normal distribution with limits far outside the range of observed values was used as recommended[199].

The repeated measures within an individual are assumed to be conditionally independent, given membership of a certain group. Therefore, the individual-specific likelihood function is as presented in Equation 9. Group membership probabilities can be calculated using Equation 10 which can be extended to calculate probabilities from time-invariant predictors or as functions of predictor variables.

Equation 9: Individual-specific likelihood function for a latent class trajectory model

$$l_k(Y_i) = \prod_{j=1}^{T} p_k(y_{ij})$$

$l_k(Y_i): likelihood\ function\ of\ Y_i, given\ membership\ of\ group\ k$
$p_k(y_{ij}): probablity\ density\ function\ of\ y_{ij}, given\ membership\ of\ group\ k$
$Y_i = \{y_{i1}, y_{i2}, \dots, y_{iT}\}: set\ of\ repeated\ measures\ of\ the\ i^{th}\ individual\ over\ T\ time\text{-}points$

Equation 10: Calculation of group membership probabilities in latent class trajectory models

$$\pi_k = \frac{e^{\theta_k}}{\sum_{k=1}^{K} e^{\theta_k}}$$

π_k: $probability\ that\ a\ randomly\ chosen\ individual\ belongs\ to\ group\ k$
θ_k: $parameters\ estimated\ from\ maximum\ likelihood\ estimation\ with\ the\ constraint\ that\ \theta_1 = 0$

The posterior group membership probability is the chance that an individual belongs to a specific group, given their set of repeated measures. Individuals are then allocated to the group with the highest posterior group membership probability. After running the LCT model, the posterior group membership probability can be calculated, according to Bayes' Theorem, as shown in Equation 11.

Equation 11: Estimation of posterior group membership probability

$$\hat{p}(k|Y_i) = \frac{\pi_k \hat{l}_k(Y_i)}{\sum_{k=1}^{K} \pi_k \hat{l}_k(Y_i)}$$

$\hat{p}(k|Y_i)$: $probability\ that\ the\ i^{th} individual\ belongs\ to\ group\ k, given\ their\ set\ of\ repeated\ measures$
π_k: $probability\ that\ a\ randomly\ chosen\ individual\ belongs\ to\ group\ k$
$\hat{l}_k(Y_i)$: $maximised\ likelihood\ function\ of\ Y_i, given\ membership\ of\ group\ k$

2.3.3.3 Determining the optimum model

Once several LCT models have been fitted, each with varying numbers of groups and degrees for the polynomial functions of age, various indices can be used to determine the optimum model. The goodness-of-fit index most widely used to differentiate between these types of models is the Bayesian Information Criterion (BIC) where smaller values indicate superior fit. The formula for this fit index is presented in Equation 12.

Equation 12: Formula for Bayesian Information Criterion

$$BIC = p\ ln(n) - 2\ ln(\hat{L})$$

$\hat{L}: maximised\ likelihood\ of\ the\ LCT\ model$
$p: number\ of\ parameters$
$n: number\ of\ individuals$

Selection of models solely on the basis of goodness-of-fit indices is not recommended. Instead, researchers are recommended to use their knowledge of the scientific field, along with statistical measures of model fit, to determine the optimum model to address the question of interest[190]. For example, trajectories of decline in physical function and body composition among the very old are likely to be monotonic and have few change points. Therefore, for this thesis, the order of the polynomial age terms and the number of groups were constrained to 3 and 4 respectively. Furthermore, models were only considered if the highest order polynomial for each group was significant, as recommended in previous literature[166]. For each characteristic, the sex-specific model with the lowest BIC was selected as the optimal model.

If a secondary analysis requires the use of the derived groups as categorical variables, constraints on the minimum number of participants assigned to each group can be imposed, although this was not required for this thesis as no sparse groups (<5% of observations) were identified in models without constraints. Additional criteria which are indicative of models with a high goodness-of-fit include[200]:

- mean posterior group membership probabilities exceeding 0.7;
- odds of correct classification, derived from posterior group membership probabilities, exceeding 5;
- a high level of agreement between the proportion allocated to each group and the estimated group membership probabilities; and
- narrow confidence intervals corresponding to estimated probabilities of group membership.

All LCT models used in this thesis satisfied the goodness-of-fit criteria stated above.

2.3.4 Growth mixture models

2.3.4.1 Background and definitions

GMM extend LCT models by incorporating random effects for intercepts and slopes which can vary within groups, rather than assuming no variation in trajectories among individuals of the same group. Alternatively, GMM can be viewed as extensions of linear mixed models where fixed effects and the random effect distributions can very between the unobserved groups which are estimated, instead of only having between-individual variation around a single population-average trajectory. These models have been widely used to examine trajectories of psychological characteristics[201] and health behaviours[202 203] as both levels and changes in these characteristics can vary greatly between individuals. The mathematical definition of a simple growth mixture model is presented in Equation 13. A graphical illustration of a simple GMM is presented in Figure 6.

Equation 13: Simple growth mixture model

$$y_{ijk} = (\beta_{0k} + \beta_{0ik}) + (\beta_{1k} + \beta_{1ik}) age_{ij} + \varepsilon_{ij}$$

$$\begin{pmatrix} \beta_{0ik} \\ \beta_{1ik} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} {\sigma_{0k}}^2 & \sigma_{01k} \\ \sigma_{01k} & {\sigma_{1k}}^2 \end{pmatrix} \right)$$

$$\varepsilon_{ij} \sim N(0, \sigma^2)$$

y_{ijk}: $outcome\ observation\ from\ the\ i^{th}\ individual\ at\ the\ j^{th}\ timepoint, given\ membership\ of\ group\ k$

age_{ij}: $age\ of\ the\ i^{th}\ individual\ at\ the\ j^{th}\ timepoint$

ε_{ij}: $observation\text{-}specific\ residual\ from\ the\ i^{th}\ individual\ at\ the\ j^{th}\ timepoint$

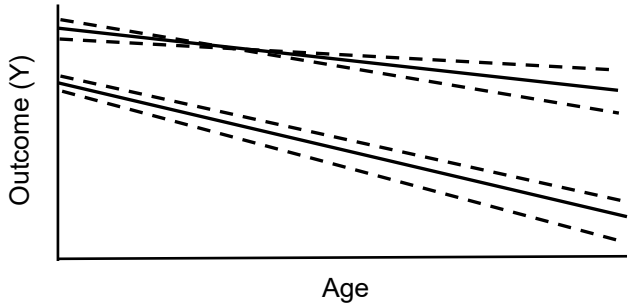
$(\beta_{0k} + \beta_{0ik})$: $random\ intercept, given\ membership\ of\ group\ k$

β_{0ik}: $person\text{-}specific\ intercept\ residual, given\ membership\ of\ group\ k$

$(\beta_{1k} + \beta_{1ik})$: $random\ slope, given\ membership\ of\ group\ k$

β_{1ik}: $person\text{-}specific\ slope\ residual, given\ membership\ of\ group\ k$

Figure 6: Simple growth mixture model



Solid lines represent mean trajectories of the two groups (different numbers of groups are possible)
Dashed lines represent individual-specific trajectories, each having a different intercept and slope
Individuals are assigned to the group that most closely matches their trajectory

GMM were implemented using the function 'hlme()' from the R package 'lcmm'. Settings and restrictions used in this thesis for GMM were similar to those used in the LME and LCT models that were implemented: unstructured variance-covariance matrix (common over latent classes); limiting the order of polynomial age terms to three for fixed effects and one for random effects; limiting the number of groups to four; and only considering models where the highest order age term is significant.

2.3.4.2 Parameter estimation

GMM parameters are estimated iteratively using maximum likelihood estimation via the Marquardt algorithm[204]. The general form of the likelihood function and the equation for calculating group membership probabilities are as defined in Equation 8 and Equation 10. Similarly, the posterior group membership probability is calculated according to Equation 11. However, $l_k(Y_i)$, the likelihood function of the outcome variable Y_i, given membership of group k, has a multivariate normal distribution (as opposed to a censored normal distribution) with a group-specific mean and variance. Other distributions are available for count and binary outcomes.

To check that the likelihood function has converged to the global maximum, the maximisation algorithm should be performed several times with different initial values. For this thesis, GMM with two or more groups were initialised from 30 random vectors of initial values; initial values resulting in the model with the highest likelihood after 15 iterations were used. This process was performed in R using the function 'gridsearch()' which is based on the Expectation Maximisation algorithm.

2.3.4.3 Assessing model fit

As in the case for LME models, marginal and conditional residuals can be derived to assess model fit. However, for models with more than one group, residuals are computed from means of the fitted values (corresponding to the group-specific marginal or conditional predictions) which are weighted according to the posterior group membership probabilities. Similarly to LME models, graphical assessments of model fit can then be performed by checking the normality of residuals using Q-Q plots and examining plots of the marginal and conditional residuals against the corresponding fitted values.

Similarly to LCT models, posterior group membership probabilities and indices such as the BIC can also be used to assess model fit and to choose between possible models with different numbers of groups. High mean posterior probabilities for each group (>0.7) and a large proportion of participants in each group with high posterior probabilities (>0.8), would suggest that participants are generally categorised with a high level of confidence, suggesting a well-fitted model.

2.3.5 Bivariate dual change score models

2.3.5.1 Background and definitions

Bivariate dual change score models (BDCSM) combine aspects of latent growth curve models and autoregressive cross-lagged models to examine temporal interrelationships between two repeatedly measured characteristics over time. These models have been used extensively in developmental psychology where establishing the temporal nature and direction of association is of primary importance[205]. Conventional BDCSM enable associations between prior levels and subsequent changes in the two characteristics being modelled to be assessed. Extended BDCSM also allow examination of prior changes in relation to subsequent changes[187] and are implemented in this thesis to explore interrelationships between changes in musculoskeletal parameters.

The set-up for applying an extended bivariate dual change score model to variables X and Y is presented in Equation 14.

Equation 14: Set-up for the bivariate dual change score model

$$X_{ij} = x_{ij} + u_{x_{ij}}; \quad Y_{ij} = y_{ij} + u_{y_{ij}}$$

$$x_{ij} = x_{i0} + \sum_{r=1}^{j} \Delta x_{ir}; \quad y_{ij} = y_{i0} + \sum_{r=1}^{j} \Delta y_{ir}$$

$$\Delta x_{ir} \coloneqq x_{ir} - x_{ir-1}; \quad \Delta y_{ir} \coloneqq y_{ir} - y_{ir-1}$$

$$\begin{pmatrix} x_{i0} \\ y_{i0} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{x_0} \\ \mu_{y_0} \end{pmatrix}, \begin{pmatrix} {\sigma_{x_0}}^2 & \sigma_{x_0 y_0} \\ \sigma_{x_0 y_0} & {\sigma_{y_0}}^2 \end{pmatrix} \right)$$

$$\begin{pmatrix} u_{x_{ij}} \\ u_{y_{ij}} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} {\sigma_{u_x}}^2 & \sigma_{u_x u_y} \\ \sigma_{u_x u_y} & {\sigma_{u_y}}^2 \end{pmatrix} \right)$$

X_{ij}, Y_{ij}: *observed values for variables X and Y from the* i^{th} *individual at the* j^{th} *timepoint*

x_{ij}, y_{ij}: *latent true scores for X and Y from the* i^{th} *individual at the* j^{th} *timepoint*

$u_{x_{ij}}, u_{y_{ij}}$: *residuals for observed values corresponding to variables X and Y*

In this set-up, the observed values for variables X and Y comprise underlying latent true scores and residuals. Latent true scores can be decomposed into the latent true scores at the first time-point (x_{i0} and y_{i0}) and the sum of the previous changes in these scores between the previous successive time-points. Successive changes in X and Y can then be modelled using the bivariate dual change score model described mathematically in Equation 15.

Equation 15: Extended bivariate dual change score model for variables X and Y

$$\Delta x_{ij} = s_{x_i} + \beta_x x_{ij-1} + \gamma_{yx} y_{ij-1} + \phi_x \Delta x_{ij-1} + \varepsilon_{xy} \Delta y_{ij-1}$$

$$\Delta y_{ij} = s_{y_i} + \beta_y y_{ij-1} + \gamma_{xy} x_{ij-1} + \phi_y \Delta y_{ij-1} + \varepsilon_{yx} \Delta x_{ij-1}$$

$$\begin{pmatrix} s_{x_i} \\ s_{y_i} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{s_x} \\ \mu_{s_y} \end{pmatrix}, \begin{pmatrix} {\sigma_{s_x}}^2 & \sigma_{s_x s_y} \\ \sigma_{s_x s_y} & {\sigma_{s_y}}^2 \end{pmatrix} \right)$$

s_{x_i}, s_{y_i}: *constant change components for the* i^{th} *individual*

β_x, β_y: *effects of prior levels of the same variable on subsequent changes*

γ_{yx}, γ_{xy}: *effects of prior levels of the other variable on subsequent changes*

ϕ_x, ϕ_y: *effects of prior changes in the same variable on subsequent changes*

$\varepsilon_{xy}, \varepsilon_{yx}$: *effects of prior changes in the other variable on subsequent changes*

2.3.5.2 Parameter estimation

Maximum likelihood estimation is normally used for parameter estimation under the assumption that the joint distribution of the two variables being modelled is multivariate normal[205]. Conventional standard error estimates of parameters may be impacted by minor violations in this assumption; Huber-White robust standard errors can be used in light of this. Full information maximum likelihood (FIML) using all available data can be implemented for parameter estimation under the assumption that data is either missing at random (conditional on observed data) or missing completely at random. Other estimation methods, such as unweighted least squares which involves minimising the sum of squared residuals, can also be used.

Improper solutions, such as non-positive definite covariance matrices of estimated parameters and negative variances and convergence problems are not uncommon for these models. Possible reasons for this include the high number of parameters that require estimation and the requirement to estimate or restrict variance parameters which are close to zero[205]. Methods to address these problems include the selection of different initial values for parameters; the use of different estimators; and restriction, rather than free estimation, of certain parameter values.

2.3.5.3 Assessing model fit

Many goodness-of-fit metrics are available for these models. These metrics may: assess the difference between the assumed and observed covariance matrix such as the standardized root mean squared error (SRMSE) or root mean squared error of approximation (RMSEA); compare the extent to which the model is an improvement on a null model assuming no associations between variables such as the comparative fit index (CFI) or Tucker–Lewis index (TLI); or examine deviation from a saturated model which fits perfectly such as the chi-square goodness-of-fit test[205].

2.4 The Health ABC Study

All analysis in this thesis uses data from the Health, Aging and Body Composition (Health ABC) Study. This subsection outlines: the purpose of this study; the methods and criteria for the selection of participants for this study; and participant information that was collected.

2.4.1 Purpose of the study

The original objectives of the Health ABC Study were to: understand factors influencing body composition changes and functional decline in older age among community-dwelling older people; investigate interrelationships between these factors; and understand and address differences in age-related decline and life expectancy between individuals and between ethnicities. It was hypothesised that health conditions and behavioural factors are related to declines in function partly due to body composition changes. A further aim was to enable a characterisation of multimorbidity according to functional status and health care use[206].

This population-based prospective cohort study was established by the Laboratory of Epidemiology and Population Sciences (part of Intramural Research Program (IRP) in the National Institute on Aging (NIA)). The study was conducted through research contracts with the Coordinating Unit at the University of California, San Francisco and the field centres, University of Pittsburgh, and University of Tennessee Health Science Center, Memphis[206].

2.4.2 The Health ABC study sample

The Health ABC study comprises a racially diverse sample of 3075 men and women (aged 70-79 years at baseline) who were recruited in 1997-1998. A random sample of white people and all age-eligible black people, from designated ZIP code areas surrounding Pittsburgh and Memphis, who were entitled to Medicare, were recruited. Only individuals who reported no difficulty in climbing 10 stairs without resting and no difficulty walking one quarter of a mile were eligible to participate. Individuals with the following characteristics were excluded: inability to communicate with the interviewer; clear cognitive impairment; having a life-threatening illness[207] or difficulties with activities of daily living (ADL); having an intention of moving outside the area within three years, or currently enrolled in a lifestyle intervention trial. Written, informed consent was provided by all participants and the study was approved by the institutional review boards at both fieldwork sites[208].

Clinical assessments on body composition, muscle strength and function were conducted annually for six years and at Years 8, 10 and 16. Information on participants' function and health was collected every six months through phone interviews. Adverse health events such as hospital admission, deaths, falls, fractures, cardiovascular events, cancers and illness such as dementia and diabetes were recorded during follow-up. Key diseases and deaths were recorded and biannual phone interviews were conducted until Year 16[206].

2.4.3 Baseline participant characteristics

This subsection outlines the baseline participant characteristics which were used in this thesis, normally as adjustments in statistical analyses. At baseline (Year 1), height and weight were measured using a Harpenden Stadiometer (Holtain Ltd, Crosswell, UK) and a standard balance beam scale respectively. BMI was calculated by dividing weight (kg) by height (m) squared. Height and weight were highly correlated ($r=0.45$, $p<0.001$ for men; $r=0.31$, $p<0.001$ for women); to avoid multi-collinearity in models, a sex-specific standardised residual of weight-adjusted-for-height was derived.

Sex, race, socioeconomic status (educational attainment and housing tenure), and health behaviours such as smoking status, alcohol consumption and physical activity were ascertained by nurse-administered questionnaires. Educational attainment was categorised as: 'below high school' (less than 12 years of schooling or did not finish high school or receive their General Educational Development Certificate); 'high school graduate'; or 'post-secondary' (having any college education)[209]. To ascertain housing tenure, participants were asked whether or not they or their partner owned a house or apartment and the land immediately surrounding it.

For physical activity assessment, the time spent performing the following activities over the previous 7 days, along with the intensity level, was recorded: paid work, volunteering or caregiving activities; aerobics, weight or circuit training, high-intensity exercises, moderate-intensity exercises; gardening, heavy chores, light housework, grocery shopping, laundry, climbing stairs; and walking (for exercise and for other purposes). Time spent on each activity was multiplied by the corresponding metabolic equivalent unit (MET) value[210] and used to estimate energy expenditure in kilocalories per kg of body weight per week (kcal/kg/wk). To calculate total physical activity (kcal/wk), these estimates for all activities were summed and then multiplied by body weight (kg) as in previously published analyses[211 212].

For the medication inventory, participants were asked to bring all over-the-counter and prescription medicines used in the previous two weeks to their Year 1 clinic visit[213]. The following details were recorded for each medication: drug name; frequency and dose; route of administration; and the Iowa Drug Information System ingredient code. It was assumed that the 10 participants with no recorded medication inventory were not taking any medications. Number of systems medicated (out of gastrointestinal, endocrine, respiratory, musculoskeletal, cancers, mental health and cardiovascular) was calculated and used as a marker of overall comorbidity.

At Year 2, dietary intake over the previous year was assessed using a nurse-administered food frequency questionnaire (FFQ) comprising 108 items. The questionnaire, designed by Block Dietary Data Systems (Berkeley, California), was based on food intakes of participants of the third National Health and Nutrition Examination Survey who were aged over 65 years and who lived in the Northeast and South. To assess the extent to which Health ABC participants' diets conformed to recommendations of the Dietary Guidelines for Americans of 1995 and the Food Guide Pyramid of 1992, a healthy eating index (HEI) was calculated for each participant; higher scores reflected healthier diets[214]. More information on the components of this HEI has been published previously[215].

Detailed information on anthropometry, body composition, physical and cognitive function, muscle strength, and socio-demographic, lifestyle and clinical characteristics was ascertained at multiple time-points in the Health ABC Study as illustrated in Table 9.

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Table 9: Time-points at which information was ascertained in the Health ABC Study

Measure	Year															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Grip strength	■	■		■		■		■		■						■
Walking speed		■	■	■	■	■		■		■						■
Whole body DXA	■	■	■	■	■	■		■		■						
Hip DXA	■		■		■			■		■						
Height	■			■		■		■		■						■
Weight	■	■	■	■	■	■		■		■						■
Smoking status	■		■		■			■	■	■	■	■	■	■		
Alcohol consumption	■										■					
Food frequency questionnaire		■														
Self-reported physical activity*	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Education	■															
Finances*	■				■											
Health insurance*	■				■	■		■	■	■	■	■	■	■		
Marital status	■			■		■		■	■	■	■	■	■	■		
2 minute / 400m walk	■	■		■		■		■		■						
Balance walks	■			■		■				■						■
Standing balance	■			■		■		■		■	■					■
Chair stands	■			■		■		■		■	■					■
Quadriceps strength	■	■		■		■		■		■						■
Digital symbol substitution test	■				■			■		■	■					
Teng Mini-Mental State exam	■		■		■					■	■					
Self-reported general health	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
ADLs/IADLs*	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Knee pain	■	■	■	■	■	■										
Back pain	■	■				■										
Prescribed medications	■	■	■		■	■		■		■	■					
Non-prescribed medications	■	■	■		■	■				■						
Depression	■			■		■		■	■	■	■					
Anxiety	■		■			■										
Happiness/social support	■	■	■	■	■	■										
Sleep	■		■		■											
Arthritis	■	■	■	■	■											
Cancer	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Heart attack/angina	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Hypertension	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Diabetes	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Osteoporosis	■															
Pulmonary conditions	■				■	■		■	■	■	■	■	■	■		
Hospital admissions	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Falls	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Fractures	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Mortality	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

ADL: Activities of daily living; IADL: Independent activities of daily living
*Different questions were asked at different time-points
Year 1 is the baseline year of first contact

2.4.4 Musculoskeletal and body composition characteristics

Customary gait speed in metres per second (m/s) was ascertained at Years 2-6, 8, 10 and 16 by asking participants to walk at their normal speed down a 20m corridor. The use of assistive devices such as walking sticks was permitted[77].

Grip strength was measured two times for each hand at Years 1, 2, 4, 6, 8, 10 and 16 using a Jamar handgrip dynamometer (JAMAR Technologies, Inc., Hatfield, PA)[216]. Maximum grip strength at each year was calculated and used for all subsequent analyses. If participants had experienced upper limb surgery such as arthroplasty, tendon repair or synovectomy in the past three months, their grip strength on the corresponding hand was not assessed.

Whole body dual-energy X-ray absorptiometry scans (Hologic QDR 4500A; Hologic, Bedford, MA) were performed at Years 1-6, 8 and 10 and used to ascertain whole body fat mass[96]. Appendicular lean mass was calculated by summing lean mass of the arms and legs. Total hip BMD and femoral neck BMD was measured using the same device at Years 1, 3, 5, 8 and 10.

Relatively few participants had data available at Year 16 so this time-point was not used for analyses in this thesis.

2.4.5 Adverse health outcomes

Deaths from baseline until 30th September 2014 were determined from death certificates, hospital records and interviews with next of kin[217]. All deaths and their causes were adjudicated by a central committee. Participants were requested to report any hospital admissions during follow-up and were asked specific questions about their previous admissions every 6 months[218]. Medical records for each reported admission were collected containing information on admission and discharge dates and the main reason for admission. Information on diagnoses and length of stay were checked by local review. Previous fractures were ascertained by self-report every six months and confirmed by radiology reports. For this thesis, fracture events were limited to fragility fractures, defined as 'spontaneous or with modest trauma, such as a fall from a standing height' [219]. Adjudication for admissions and fractures was complete until 14th August 2012; events occurring after this date were not used for analysis in this thesis. At every year of follow-up, up to and including Year 14, participants were asked if they had fallen over and landed on the floor or the ground during the last 12 months.

2.5 Data checking and validation

All Health ABC data used in this thesis were checked by myself to ensure that unfeasible values were removed prior to analyses. For variables ascertained at only one time-point, this involved using: histograms to identify extreme values; scatterplots to check relationships between variables which were expected to be related, such as height and weight; and cross-tabulations to check logical consistency, for example, that no cigarettes were smoked by non-smokers. Sections 2.5.1 - 2.5.3 describe the more complex data cleaning procedures that were conducted for variables measured at multiple time-points. Relative to the size of the dataset and the number of repeated measurements available, only a tiny proportion of values for each variable (<1%) were set to missing.

2.5.1 Grip strength

At Years 1 and 2, pain or arthritis that had recently become worse was an exclusion criterion, whereas at Years 4, 6, 8 and 10, participants with pain or arthritis had their grip strength assessed, provided that they were willing. To ensure consistency with Years 1 and 2, grip strength values recorded in later years from participants who said that pain or arthritis would prevent them from squeezing as hard as they could were set to missing.

At each time-point, grip strength was assessed two times for each hand. Scatterplots were used to visually assess the agreement between the four values at each assessment; extreme outliers that were unfeasible based on visual inspection, when compared to the other grip strength values of the participant, were set to missing so they would not feature in any analysis. Maximum grip strength at each assessment was then calculated and used for all subsequent analyses.

2.5.2 Body composition measurements from DXA scans

Checks were performed to ensure that BMD was correctly calculated and that body composition components, such as total mass, fat mass, lean mass and BMC, were correlated in the expected manner. Appendicular lean mass (ALM) was calculated from the lean mass variables for the arms and legs; missing values for a person's limb were replaced with non-missing values for the other corresponding limb if available. At each age, separate scatterplots for the ALM and fat mass parameters, relating to different compartments of the body, were examined; unfeasible values, based on visual inspection, were set to missing.

2.5.3 Other longitudinal data cleaning

Repeated measures of the following characteristics were checked by separately plotting the longitudinal trajectories for every individual:

- Height
- Weight
- BMI
- Grip strength
- Gait speed
- Whole body fat mass
- Appendicular lean mass (ALM)
- Total hip BMD

Extreme values which were unlikely, when taking into account other values in the individual's trajectory, were set to missing. In uncertain situations, a consensus decision was reached between myself and one of my PhD supervisors regarding whether to retain a data value.

2.6 Statistical methods

2.6.1 Subsection summary

Section 2.6 outlines the statistical analyses conducted for this thesis, categorised according to the following types of analyses: describing longitudinal changes in musculoskeletal and body composition characteristics; examining baseline determinants of level and change in these characteristics; examining interrelationships between changes in these characteristics; and examining level and change in these characteristics in relation to risk of adverse health outcomes. Further details of the statistical theory are provided in Section 2.3.

Unless otherwise indicated, all analyses described in Section 2.6 were stratified by sex, based on all available data to maximise the sample size and conducted using Stata, release 15 (StataCorp, College Station, TX, USA).

2.6.2 Longitudinal changes in characteristics

2.6.2.1 Derivation of change measures

Simple measures of annual change (absolute and percentage) from baseline to Year 10 were derived for characteristics (grip strength, gait speed, ALM, fat mass and hip BMD) using the following calculations:

Annual absolute change = $\frac{Y_{10}-Y_1}{FUP}$

Annual percentage change = $\frac{100\times\frac{Y_{10}-Y_1}{Y_1}}{FUP}$

where Y_1 and Y_{10} represent the value of the characteristic at Year 1 (baseline) and Year 10 respectively and FUP represents the individual's follow-up time; negative values of change are indicative of declines. Gait speed was not measured at Year 1 so values from Year 2 were used for this characteristic.

To calculate percentage change using data from all time-points, percentage change since baseline was calculated at each time-point and then person-specific regression lines were fitted to predict percentage change since baseline, from the age at each time-point; each participant's estimated annual percentage change is given by the regression coefficient for age, estimated even when data at some time-points were missing. As percentage change has limitations for comparing changes between characteristics with different coefficients of variation, additional measures of change from baseline to Year 10 were derived by standardising characteristics at Year 10 using the mean and SD values at baseline. Conditional change measures (independent of baseline level) were characterised by residuals obtained after estimating sex-specific linear regression models for characteristics at follow-up (Year 10) from characteristics at baseline with adjustment for individual follow-up duration[220]. These simplistic approaches are limited but important as they allow comparison with the results obtained from previous studies with the results of the more sophisticated analyses implemented in this thesis.

Results corresponding to these methods are included in Section 3.2.2.

2.6.2.2 Calculation of descriptive statistics and centile curves

Participant characteristics at baseline and measures of annual change in these characteristics were described among men and women separately using means and standard deviations (SDs).

Sex-differences in means were assessed using t-tests. Means and 95% confidence intervals for the key characteristics were plotted at each year they were ascertained. Centile curves for the key characteristics were derived using generalised additive models for location, scale and shape and implemented using the GAMLSS package in R, as described in Section 2.3.1.

Results corresponding to these methods are included in Sections 3.2.2 and 3.2.3.

2.6.2.3 Comparison of changes between characteristics

Box plots were used to visualise the distributions of the annual percentage change variables (derived from person-specific regression models) and t-tests were used to compare the means of these variables between men and women. The F-test for the homogeneity of variances, also known as the Variance Ratio Test, was used to compare the variance of the percentage change measures between characteristics.

As percentage change has limitations for comparing changes between characteristics with different coefficients of variation, boxplots of change measures from baseline to Year 10 that were derived by standardising characteristics at Year 10 using the mean and SD values at baseline were also presented.

Change analysis using the person-specific regression lines was restricted to 2917 participants with data on at least one change measure; each change measure required values of the characteristic at baseline and at least one other time-point. Analysis using the standardised change measures was restricted to 1599 participants with data on at least one characteristic at both baseline and Year 10. Results corresponding to these methods are included in Section 3.2.4.

2.6.2.4 Variance at follow-up explained by change since baseline

To estimate the proportion of variance in each characteristic at Year 10 that was explained by the baseline level and conditional change from baseline to Year 10, R-squared values were calculated from sex-specific linear regression models with the characteristic at Year 10 as the outcome and the baseline characteristic and the conditional change measure as each predictor in turn.

This analysis was restricted to 1599 participants with data on at least one conditional change measure; each conditional change measure requires values of the characteristic at baseline and Year 10. Results corresponding to these methods are included in Section 3.2.5.

2.6.2.5 Estimation of longitudinal mean trajectories

To examine the shape of the mean trajectories of the characteristics over time, sex-specific LME models with random intercepts and slopes, which included age as a linear term, were fitted for each characteristic. Quadratic and cubic age terms were included if they were significant ($p<0.05$). The mean trajectories were then plotted, together with their 95% confidence bands.

GMM (fitted using the 'lcmm' R package[191]) and LCT models were implemented to assess whether there were distinct groups of individuals following markedly different trajectories regarding each characteristic. For each technique, the model with the lowest BIC was chosen as the optimum model under the following restrictions; limiting the order of polynomial age terms to three for fixed effects (one for random effects for GMM); limiting the number of possible groups to four; and only considering models where the highest order age term for each group was significant.

All trajectory analysis was based on the sample of 2917 participants with data on at least one of the characteristics (grip strength, gait speed, ALM, whole-body fat mass and hip BMD) at two or more time-points. Results corresponding to these methods are included in Sections 3.2.6 and 3.2.7.

2.6.2.6 Sensitivity analyses

Sensitivity analyses included stratification by race within each sex. Furthermore, mean trajectories from participants with observations at all time-points were compared with trajectories from participants with observations at a minimum of two time-points to determine whether results were influenced by sample attrition.

Results corresponding to these sensitivity analyses are included in Section 3.2.8.

2.6.3 Determinants of level and change in characteristics

2.6.3.1 Potential baseline determinants considered

Potential determinants, ascertained at baseline (Year 1) included: age, height, weight-for-height residual, smoking status, alcohol consumption, physical activity, healthy eating index (ascertained at Year 2), educational attainment; housing tenure and number of systems medicated. These

were selected based on the determinants of changes in musculoskeletal and body composition characteristics identified in the epidemiological literature review (Section 1.5) and on the availability of data in the Health ABC Study (Section 2.4.3). All analyses were adjusted for a four-level sex-race categorical variable indicating the four possible combinations of sex and race. Sex-specific z-scores were derived for all continuous exposures and outcomes to enable the comparison of effect sizes.

2.6.3.2 Derivation of change measures for musculoskeletal and body composition characteristics

The following process was used to obtain change measures for each characteristic: model the relationship between age and the median, variance, skewness and kurtosis of the characteristic using sex-specific GAMLSS; extract z-scores, known as normalised (randomised) quantile residuals, for each observation which indicate how high or low they are from what would be expected, given sex and age; apply sex-specific LME models with random intercepts and slopes to the z-scores with time from baseline as the only fixed effect; extract the random slopes for each participant as the measure of change. This process used all available data for each characteristic over Years 1-10.

2.6.3.3 Potential baseline determinants in relation to level and change in musculoskeletal parameters

The relationship between each potential determinant and both baseline level and longitudinal change in each characteristic was examined using linear regression models adjusted for age and for a sex-race variable indicating the four possible combinations of sex and race. Statistically significant ($p<0.05$) correlates were then included in mutually adjusted models. Sex-specific weight-for-height residuals were strongly correlated with sex-specific z-scores for appendicular lean mass ($r=0.71$, $p<0.001$) and fat mass ($r=0.91$, $p<0.001$); to avoid multi-collinearity in models, weight-for-height residual was not included in models for these outcomes.

For each musculoskeletal or body composition characteristic, participants with data on baseline level and change, over at least two time points, were included in the analyses; 2917 participants had such data on at least one of the characteristics and comprised the analytical sample for the determinants analysis. Results corresponding to these methods are included in Section 3.3.

2.6.3.4 Sensitivity analyses

Sensitivity analyses involved including interaction terms between each potential determinant and the sex-race variable, to assess the effect size and significance of these terms, and stratifying analyses by sex.

Results corresponding to these sensitivity analyses are included in Section 3.3.8.

2.6.4 Interrelationships between changes in characteristics

2.6.4.1 Derivation of change measures

The process used to obtain change measures for the musculoskeletal and body composition characteristics was the same as described in Section 2.6.3.2 which involved applying sex-specific LME models to z-scores obtained from sex-specific GAMLSS models. However, to ascertain change measures over different parts of the study follow-up, this process was implemented for each characteristic over the following periods: Years 1-10, Years 1-6 and Years 6-10. These intervals were selected to ensure that change measures were based on data available at multiple time-points.

Conditional change measures, based on data at Year 1 (baseline) and Year 10, were also derived as outlined in Section 2.6.2.1 to check that results were similar when using change measures that were completely independent of baseline levels.

2.6.4.2 Correlations between changes in characteristics

Pearson correlations between change measures were examined within the following years of follow-up: Years 1-6, Years 6-10 and Years 1-10. A correlation matrix of partial Pearson correlations between change measures over Years 1-10 was also produced to examine mutually-adjusted associations. Pearson correlations between conditional change measures, derived using data at Years 1 and 10, were also examined as a sensitivity analysis.

To explore temporal associations between changes in characteristics, Pearson correlations between changes in characteristics over Years 1-6 in relation to subsequent changes in characteristics over Years 6-10 were explored. Correlations of interest were examined graphically by examining mean changes in characteristics over Years 6-10 according to tertiles of change over Years 1-6. Correlations of interest were also examined using linear regression after adjustment for

the four-level sex-race variable, age and diet quality. These adjustments comprised the set of baseline characteristics that were associated with changes in two or more of the musculoskeletal and body composition characteristics in the determinants analysis, as shown in Section 3.3.9 and Table 18).

Change measures based on z-scores from GAMLSS required measurements of the musculoskeletal or body composition characteristic at two or more time-points; conditional change measures required measurements at Years 1 and 10. As the number of participants that featured in each correlation analysis differed depending on the follow-up window and the measure of change used, this number is stated in the footnotes of each table of correlations presented in Section 3.4.2 and 3.4.3. Results for examining correlations between change measures within Years 1-6, Years 6-10 and Years 1-10 are included in Section 3.4.2 and results for temporal associations between changes in characteristics are presented in Section 3.4.3.

2.6.4.3 Use of principal component analysis to explore changes

A principal component analysis of the variables for changes in characteristics (derived by applying LME models to z-scores obtained from GAMLSS) over Years 1-10 was conducted to investigate whether there were interpretable components that explain a substantial proportion of variation in these changes. This method derives variables (components) that are independent linear combinations of the change variables that explain the most variation in the data[221]. This analysis was based on the covariance matrix, as opposed to the correlation matrix, as all measures were on the same scale (sex-specific z-scores). Principal components may represent the extent to which participants experience an overall decline in all characteristics or a contrast between participants with a greater decline in some characteristics and a smaller decline in others.

As principal component analysis requires complete data, the analysis sample comprised the 2574 participants with data on all change measures; each change measure requires values of the characteristic at two or more time-points over Years 1-10. Results corresponding to these methods are included in Section 3.4.4.

2.6.4.4 Use of bivariate dual change score models to examine interrelationships

Extended bivariate dual change score models were implemented for each pair of characteristics out of grip strength, gait speed, ALM, fat mass and hip BMD. Extended models were used as they enable the relationships between prior changes and subsequent changes in the two variables

examined to be explored. As these models require the measurement of characteristics at the same time-points, data at Years 2, 4, 6, 8 and 10 were used for all characteristics apart from hip BMD where data at Years 1, 3, 5, 8 and 10 were used for an approximation. These models were implemented among the pooled sample of men and women as well as among sex-specific samples. To assess consistency of results, combinations of different samples (pooled and sex-specific), units for analyses (original units, LMS z-scores and z-scores derived from baseline mean and variance values) and estimation methods (maximum likelihood and unweighted least squares) were used.

These models were applied to all available data to maximise the sample size. Results corresponding to these methods are included in Section 3.4.5 and 3.4.6.

2.6.5 Level and change in musculoskeletal and body composition characteristics in relation to risk of adverse health outcomes

2.6.5.1 Derivations of change measures

The process used to obtain change measures for the musculoskeletal and body composition characteristics was the same as described in Section 2.6.3.2 which involved applying sex-specific LME models to z-scores obtained from sex-specific GAMLSS models. However, for each characteristic, only data from Years 1-6 were used; outcomes included adverse events (deaths, fragility fractures, hospital admissions and falls) occurring after a participant's latest measurement of the characteristic. This approach was implemented to reduce the possibility of reverse causation by ensuring that the adverse health outcome was ascertained after the exposure and to ensure change measures for characteristics were based on a sufficient number of repeated measures.

2.6.5.2 Availability of dates for adverse health events

Dates were available for deaths, hospital admissions and fragility fractures but not for falls. To allow a time-to-event analysis for falls, participants reporting a fall in the previous 12 months were regarded as having fallen 6 months before the date this information was ascertained.

Information on the ascertainment of adverse health events in the Health ABC Study is outlined in Section 2.4.5.

2.6.5.3 Cox models relating level and change in musculoskeletal and body composition characteristics to risk of adverse outcomes

For each characteristic, baseline level (calculated as the mean of the values from Years 1-6) and longitudinal change were examined in relation to each adverse event using time-to-first-event Cox proportional hazards models with death as a censoring event for the other adverse events. Sex-specific z-scores were derived for all continuous exposures to enable the comparison of effect sizes. Time-at-risk started from a participant's latest measurement of the characteristic and, for those who did not experience the adverse event or leave the study early, ended on 30th September 2014 for deaths and 14th August 2012 for hospital admissions and fragility fractures as stated in Section 2.4.5. For participants who did not fall, the censoring date was the latest date at which they had experienced no falls during the time at risk and had complete data for all previous responses regarding falls.

For each characteristic, participants with data on baseline level and change, over at least two time points from Years 1-6, were included in the analyses. This resulted in an analysis sample of 2904 participants with both these measures available for at least one of the musculoskeletal and body composition characteristics.

2.6.5.4 Use of competing risk models to validate results from Cox models

Due to the high number of deaths occurring during follow-up among individuals of this age group, a competing risk analysis for hospital admission and fragility fracture, with death as a competing event, was also performed using the Fine-Gray subdistribution hazards model[222]. To incorporate the effect a predictor has on the events of interest and the competing event, this technique models the effect of predictors on the cumulative incidence function of the event of interest. The cumulative incidence function reflects the probability that the event occurs before a given time. Deaths occurring outside the time-at-risk of the primary event were not considered as competing events. For the falls analyses, a competing risk analysis was not possible as competing events (deaths occurring before an individual's first fall) would only occur after the censoring date (latest date at which they had experienced no falls and had complete data for previous fall questions).

2.6.5.5 Adjustment for previous adverse events in Cox and competing risk models

Previous fragility fractures, admissions and falls occurring before the time at risk were associated ($p<0.01$) with increased risk of the corresponding event during follow-up; this has been reported in previous studies[223-225]. However, the predictors characterising previous admission and falls violated the proportional hazards assumption; to address this, Cox models stratified on whether or not participants had a previous event were implemented for fragility fractures, admissions and falls. Stratified competing risk models could not be implemented with the available software so models were adjusted for previous events.

2.6.5.6 Adjustment for potential baseline confounders identified in the analysis of determinants of level and change

All models were adjusted for age when first regarded as being at risk and for the four-level sex-race variable. When exploring how the level of the musculoskeletal or body composition characteristic (grip strength, gait speed, ALM, fat mass and hip BMD) related to the risk of adverse outcomes, models were also adjusted for the set of baseline characteristics that were associated with the levels of two or more of these musculoskeletal and body composition characteristics in mutually-adjusted analysis; an analogous approach was used when the predictor was change in the characteristic. Therefore, based on the results for baseline determinants of level and change (Section 3.3.9 and Table 18), survival analysis models for level were additionally adjusted for height, weight-for-height residual (excluded for ALM and fat mass due to collinearity), physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were only additionally adjusted for diet quality.

2.6.5.7 Treatment of missing values for adverse events

Participants with missing responses during the time at risk and before their first fall were not included in the survival analyses for falls as their time-to-first failure could not reliably be determined. Similarly, participants with possible fragility fractures (categorised as 'possible' and not 'definite' and fracture types that were unknown/missing) occurring either before their first definite fragility fracture or at any time during follow-up among those who did not experience a fragility fracture were not included in the survival analysis for this outcome.

Results corresponding to these methods outlined in Sections 2.6.5.1 - 2.6.5.7 are included in Sections 3.5.3 - 3.5.7.

2.6.5.8 Baseline participant characteristics in relation to risk of adverse events

For completeness, and to determine the adjustments to include in models to improve precision in sensitivity analyses, the same set of potential baseline determinants of level and change in musculoskeletal and body composition parameters were examined in relation to risk of the adverse events. As stated in Section 2.6.3.1, these baseline characteristics included age, height, weight-for-height residual, smoking status, alcohol consumption, physical activity, healthy eating index, educational attainment; housing tenure and number of systems medicated. Univariate models for each baseline characteristic in relation to each adverse event included age and the sex-race variable; characteristics associated ($p<0.05$) with the adverse event were then included in mutually-adjusted models. Both Cox and competing risk models were used with the baseline clinic as the start of the time at risk.

Results corresponding to these methods are included in Section 3.5.8.1.

2.6.5.9 Sensitivity analyses

Several sensitivity analyses were performed. First, interaction terms between the sex-race variable and the measures of level and change were included in models and both their effect size and statistical significance was assessed to ensure associations were similar among each of the four combinations of sex and race. Second, models including level and change measures simultaneously were used to ensure associations between change measures and the risk of adverse outcomes were not driven by the measure for level and vice versa. Third, models were additionally adjusted for the baseline characteristics (listed in Section 2.6.5.8) that were significant predictors of at least two of the adverse outcomes in mutually-adjusted models. Therefore, as well as the adjustments stated in Section 2.6.5.6, survival analysis models in this sensitivity analysis for level in relation to adverse events were additionally adjusted for smoking status and housing tenure; survival models for change in relation to adverse events were additionally adjusted for weight-for-height residual, smoking status, physical activity, education, housing tenure and number of systems medicated. Fourth, survival models were restricted to participants with complete data on the corresponding musculoskeletal or body composition parameter at Years 1-6. Finally, evidence of non-linear relationships between level and change exposures and risk of adverse outcomes was examined by assessing the statistical significance and effect size of quadratic terms for these exposures.

Results corresponding to these sensitivity analyses are included in Section 3.5.8.2.

2.6.5.10 Associations between previous changes in characteristics and adverse outcomes after accounting for current measures

Of clinical interest is whether previous measurements of musculoskeletal and body composition characteristics improve the prediction of adverse health outcomes, over and above current measures. To investigate this, conditional change measures from Year 4 to 6 and from Year 2 to 4 were characterised by residuals obtained from sex-specific linear regression models predicting characteristics at Year 4 from characteristics at Year 6 and from models predicting characteristics at Year 2 from characteristics at Years 4 and 6, respectively; both conditional change measures and the Year 6 levels were independent. For each characteristic, mutually-adjusted Cox models were used to examine levels at Year 6 and the two conditional change variables in relation to risk of each adverse outcome with the same sets of adjustments as used in the main survival analysis (Section 2.6.5.6); only adverse outcomes occurring after Year 6 were included. As hip BMD was ascertained at Years 1, 3 and 5 as opposed to at Years 2, 4 and 6, data on these earlier time-points were used for this characteristic.

For each characteristic, participants with residual change over the two time periods and data on measurements at Year 6 (Year 5 for hip BMD) were included in this analysis. This resulted in an analysis sample of 2346 participants with this information available for at least one of the musculoskeletal and body composition characteristics. Results corresponding to these methods are included in Section 3.5.9.

2.6.5.11 Combined impact of grip strength and hip BMD in relation to adverse outcomes

One question of interest is whether participants with low levels or high declines in both grip strength and hip BMD have significantly greater risks of adverse outcomes than participants with low levels or high declines in only one of these characteristics. Another area of interest is whether the effects of grip strength and hip BMD on risk of adverse outcomes are independent of each other or whether there are interaction effects such that the impact of low (or declining) grip strength on risk of outcomes is greater in the presence of low (or declining) hip BMD.

To investigate this, a 4-level categorical variable was derived for levels of grip strength and hip BMD: low grip strength and hip BMD; low grip strength only; low hip BMD only; and neither low grip strength or low hip BMD (low values were characterised as those in the lowest sex-specific

third of the distribution). An analogous variable was derived for changes in LMS z-scores for grip strength and hip BMD: high decline in grip strength and hip BMD; high decline in grip strength only; high decline in hip BMD only; and neither high decline in grip strength or hip BMD (high declines were characterised as those in the highest sex-specific third of the distribution). These categorical variables were then examined separately in relation to each adverse outcome. Furthermore, the statistical significance of interaction effects between the continuous variables for grip strength and hip BMD were examined. Analyses were adjusted for the sex-race variable and age and then for additional characteristics as stated in Section 2.6.5.6, depending on whether the 4-level categorical variable represented levels or changes in grip strength and hip BMD.

The sample for this part of the analysis comprised the 2603 participants with data on levels and changes in both grip strength and hip BMD. Results corresponding to these methods are included in Sections 3.5.10 and 3.5.11.

Chapter 3 Results

3.1 Chapter summary

This chapter presents the results and a summary of findings for the following four sets of analyses: description of longitudinal changes in musculoskeletal and body composition characteristics; investigation of baseline determinants of level and change in these characteristics; an examination of interrelationships between changes in characteristics; and an examination of level and change in characteristics in relation to risk of adverse health outcomes.

3.2 Longitudinal changes in characteristics

3.2.1 Subsection summary

Section 3.2 describes longitudinal changes in musculoskeletal and body composition characteristics over a 9-year follow-up period. A summary of these findings is included in Section 3.2.9. The methods corresponding to these results are included in Section 2.6.2.

3.2.2 Descriptive statistics

Baseline anthropometric, musculoskeletal and body composition parameters among the sample of 2917 Health ABC participants with data on at least one of the characteristics (grip strength, gait speed, ALM, whole body fat mass, and hip BMD) at two or more time-points are presented in Table 10. Mean and standard deviation (SD) for age was 74.1 (2.9) years. Women had higher fat mass but all other measures were greater among men ($p<0.001$ for all associations). Although both black men and women had slower gait speed compared to their white counterparts and black men had lower fat mass, the remaining measures were greater among black participants.

Compared to the 158 Health ABC participants who were not included in this sample, mean baseline grip strength was higher among men ($p=0.003$) but there were no significant differences in the remaining musculoskeletal and body composition parameters among men or women.

Annual changes (absolute and percentage) in participant characteristics from baseline to Year 10 are shown in Table 11. All characteristics declined from baseline to follow-up on average,

regardless of whether absolute or percentage change was used. Annual absolute declines were greater for women than men for fat mass ($p<0.001$); men experienced greater absolute declines in grip strength, ALM and hip BMD. Results were similar for most characteristics when percentage change was used instead of absolute change, characteristics with the greatest mean percentage decline were gait speed (1.7% per year) and grip strength (1.7% among men and 1.3% among women); mean percentage declines regarding all other characteristics were less than 0.7%.

The methods corresponding to these results are included in Section 2.6.2.1.

Table 10: Baseline participant characteristics according to sex and race

Characteristic [Mean (SD) or N (%)]	Men			Women		
	White (n=907)	Black (n=511)	All (n=1418)	White (n=823)	Black (n=676)	All (n=1499)
Age (years)	74.4 (2.9)	74.0 (2.7)	74.2 (2.8)*†	74.1 (2.8)	73.8 (2.9)	74.0 (2.9)*†
Height (m)	1.74 (0.06)	1.73 (0.07)	1.73 (0.07)*	1.59 (0.06)	1.60 (0.06)	1.60 (0.06)*
Weight (kg)	81.4 (12.4)	81.3 (14.3)	81.4 (13.1)*	66.1 (12.1)	75.7 (15.8)	70.4 (14.6)*†
BMI (kg/m^2)	27.0 (3.7)	27.1 (4.3)	27.0 (3.9)*	26.0 (4.5)	29.7 (5.9)	27.6 (5.5)*†
Grip strength (kg)	39.7 (7.7)	42.8 (8.7)	40.8 (8.2)*†	23.6 (5.1)	26.6 (6.2)	25.0 (5.8)*†
Gait speed (m/s)	1.23 (0.19)	1.10 (0.20)	1.19 (0.21)*†	1.16 (0.19)	1.01 (0.20)	1.09 (0.21)*†
ALM (kg)	23.3 (3.2)	25.0 (3.9)	23.9 (3.6)*†	15.3 (2.4)	18.2 (3.2)	16.6 (3.1)*†
Fat mass (kg)	24.7 (6.9)	23.2 (7.4)	24.2 (7.1)*†	27.0 (7.9)	31.6 (10.2)	29.1 (9.3)*†
Hip BMD (g/cm^2)	0.94 (0.14)	1.02 (0.15)	0.97 (0.15)*†	0.77 (0.13)	0.86 (0.15)	0.81 (0.15)*†

SD: Standard deviation; ALM: Appendicular lean mass; BMD: Bone mineral density

*Statistically significant sex differences ($p<0.05$); †Statistically significant racial differences within sex ($p<0.05$)

Table 11: Annual absolute and percentage change in participant characteristics from baseline to Year 10 among men and women

Characteristic (Mean (SD))	Annual absolute change			Annual percentage change			Obs
	Men	Women	P-value	Men	Women	P-value	
Height (m)	-0.003 (0.002)	-0.003 (0.002)	0.061	-0.16 (0.10)	-0.18 (0.10)	<0.001	1449
Weight (kg)	-0.31 (0.75)	-0.36 (0.75)	0.141	-0.36 (0.88)	-0.49 (1.01)	0.007	1600
BMI (kg/m^2)	-0.02 (0.25)	-0.05 (0.30)	0.023	-0.05 (0.89)	-0.14 (1.03)	0.064	1600
Grip strength (kg)	-0.74 (0.65)	-0.36 (0.49)	<0.001	-1.69 (1.54)	-1.25 (1.95)	<0.001	1537
Gait speed (m/s)	-0.022 (0.023)	-0.020 (0.022)	0.129	-1.72 (1.93)	-1.71 (2.00)	0.924	1364
ALM (kg)	-0.16 (0.19)	-0.08 (0.14)	<0.001	-0.66 (0.76)	-0.46 (0.81)	<0.001	1482
Fat mass (kg)	-0.04 (0.48)	-0.20 (0.52)	<0.001	-0.08 (2.00)	-0.63 (1.78)	<0.001	1481
Hip BMD (g/cm^2)	-0.005 (0.006)	-0.004 (0.006)	0.001	-0.50 (0.67)	-0.47 (0.79)	0.348	1468

BMI: Body mass index; ALM: Appendicular lean mass; BMD: Bone mineral density

Obs: Number of non-missing observations

Change measures were calculated by subtracting measurements at baseline from Year 10 measurements and dividing by individual follow-up duration. Negative values indicate average decline from baseline to the Year 10 follow-up

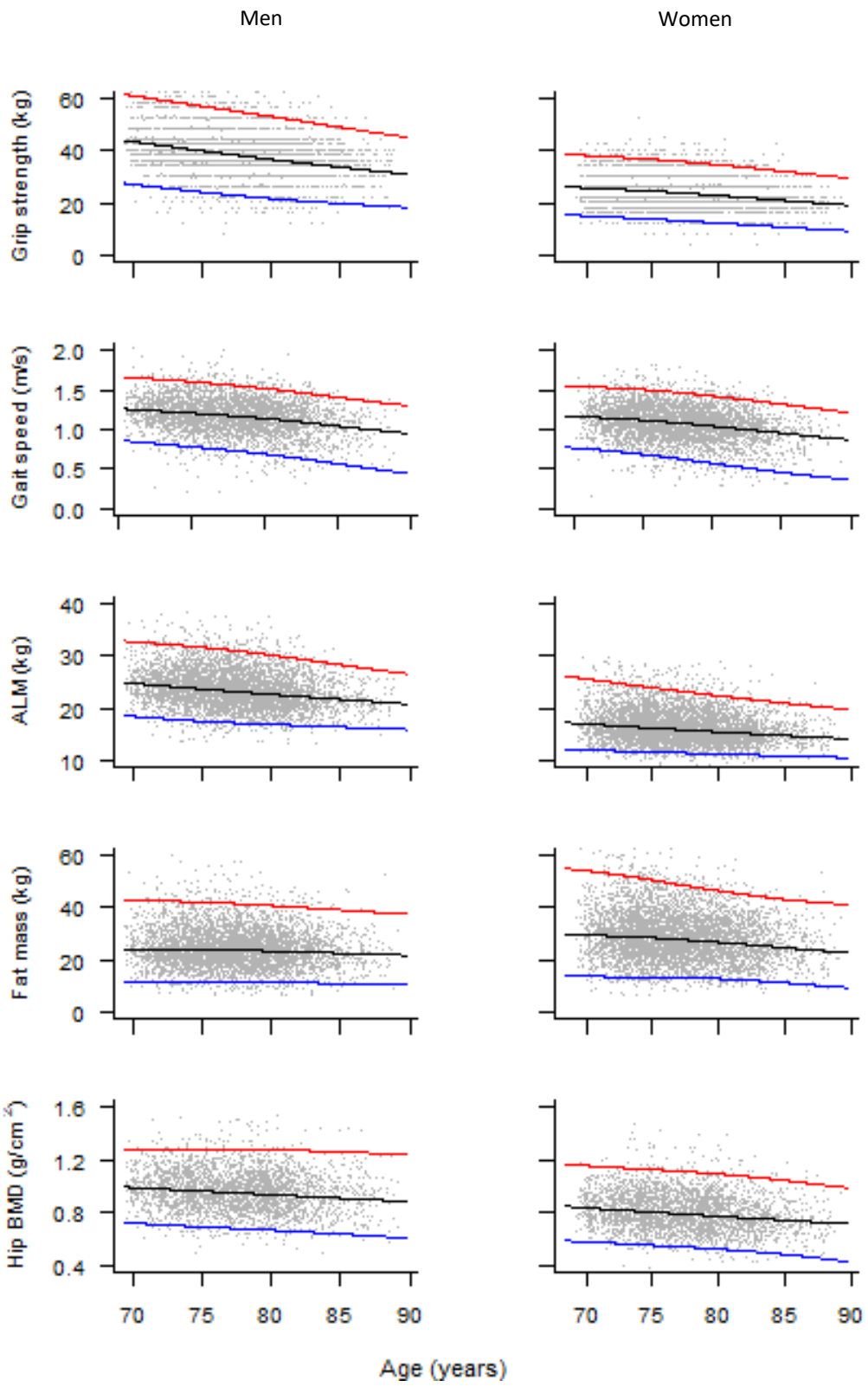
Baseline gait speed was ascertained at Year 2; other baseline characteristics were ascertained at Year 1

3.2.3 Centile curves for characteristics

The individual data points for each of the characteristics with the centile curves (derived by the LMS method) overlaid are illustrated in Figure 7; all repeated measurements are included. For all characteristics, there was substantial variation in values at all ages and median values declined with older age.

The methods corresponding to these results are included in Section 2.6.2.2.

Figure 7: Individual data points for musculoskeletal and body composition characteristics with centile curves overlaid



ALM: Appendicular lean mass; BMD: Bone mineral density

Centile curves (2.5th, 50th and 97.5th) were derived using the Box-Cox Cole and Green (BCCG) distribution (also known as the LMS method); top and bottom centile curves enclose 95% of the distribution

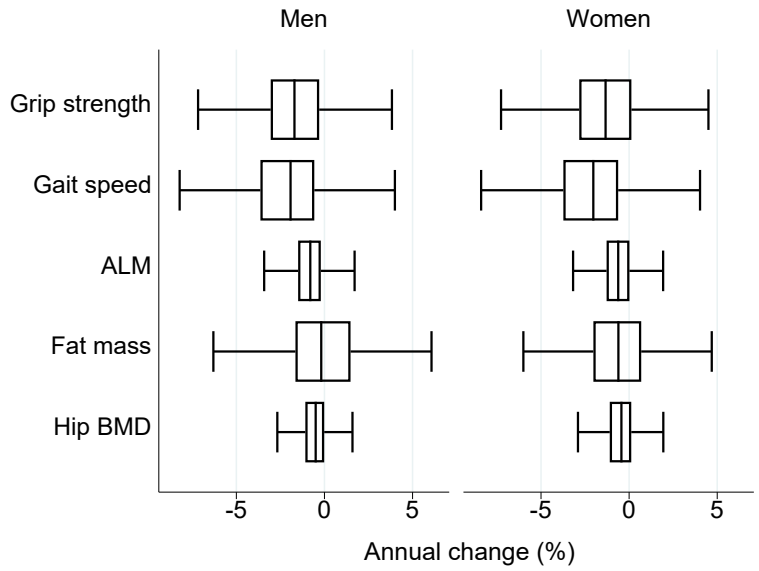
3.2.4 Boxplots of changes in characteristics

Boxplots of estimated annual percentage change in each characteristic are shown in Figure 8. Among both men and women, mean percentage decline in grip strength and gait speed was greater compared with each of the other characteristics ($p<0.02$ for all comparisons). Variation in percentage decline in grip strength, gait speed and fat mass was greater compared with each of the other characteristics ($p<0.001$ for all comparisons).

Boxplots of the standardised characteristics at Year 10 (using the baseline mean and standard deviation) are illustrated in Figure 9. Although the variation of the change measures is normalised using this method, decline in grip strength and gait speed was greater compared to the other characteristics, as in the case when percentage changes were examined.

The methods corresponding to these results are included in Section 2.6.2.3.

Figure 8: Boxplots of estimated annual percentage change in characteristics among men and women



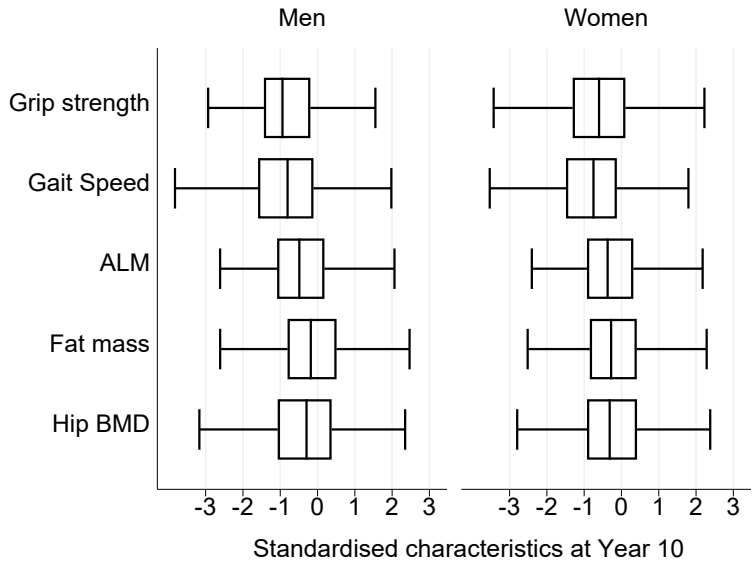
ALM: Appendicular lean mass; BMD: Bone mineral density

The three vertical lines in the box represent the lower quartile (Q1), median and upper quartile (Q3). The lower whisker is the smallest value that is greater than Q1 − 1.5 × IQR and the upper quartile is the largest value which is less than Q3 + 1.5 × IQR, where IQR = Q3-Q1.

Estimates of mean percentage change for each participant were derived using person-specific regression models for percentage change since baseline calculated at each time-point with age at each time-point as the only predictor. Estimated mean percentage change is given by the regression coefficient for age.

Analysis was restricted to 1418 men and 1499 women with data on at least one change measure; each change measure requires values of the characteristic at baseline and at least one other time-point.

Figure 9: Standardised characteristics at Year 10 using baseline mean and standard deviation



ALM: Appendicular lean mass; BMD: Bone mineral density

Characteristics at Year 10 were standardised using the mean and SD values at baseline

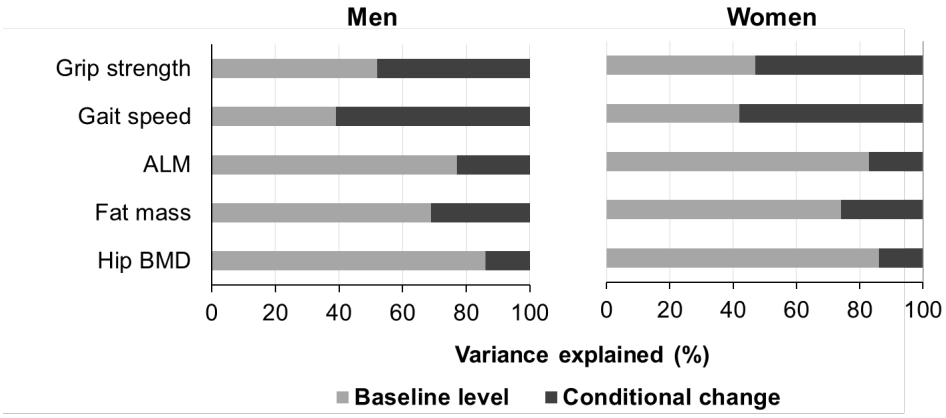
Analysis was restricted to 1599 participants with data on at least one characteristic at both baseline and Year 10

3.2.5 Proportion of variation in characteristics at follow-up explained by baseline level and conditional change

The proportion of variation in each characteristic at follow-up (Year 10) which was explained by baseline level and conditional change (change since baseline that was independent of baseline level) is illustrated in Figure 10. Among men and women, a large proportion of the variation (48-61%) in grip strength and gait speed at Year 10 was explained by conditional change since baseline, whereas for the other characteristics, this figure was only 14-31%.

The methods corresponding to these results are included in Section 2.6.2.4.

Figure 10: Proportion of variance at Year 10 explained by baseline level and conditional change since baseline



ALM: Appendicular lean mass; BMD: Bone mineral density

Measures of conditional change were derived using a residual change method and were independent of baseline level

Pearson correlations between baseline and follow-up measures: grip strength (men: 0.72, women: 0.69); gait speed (men: 0.62, women: 0.65); ALM (men: 0.88, women: 0.91); Fat mass (men: 0.83, women: 0.86); Hip BMD (men: 0.93, women: 0.93)

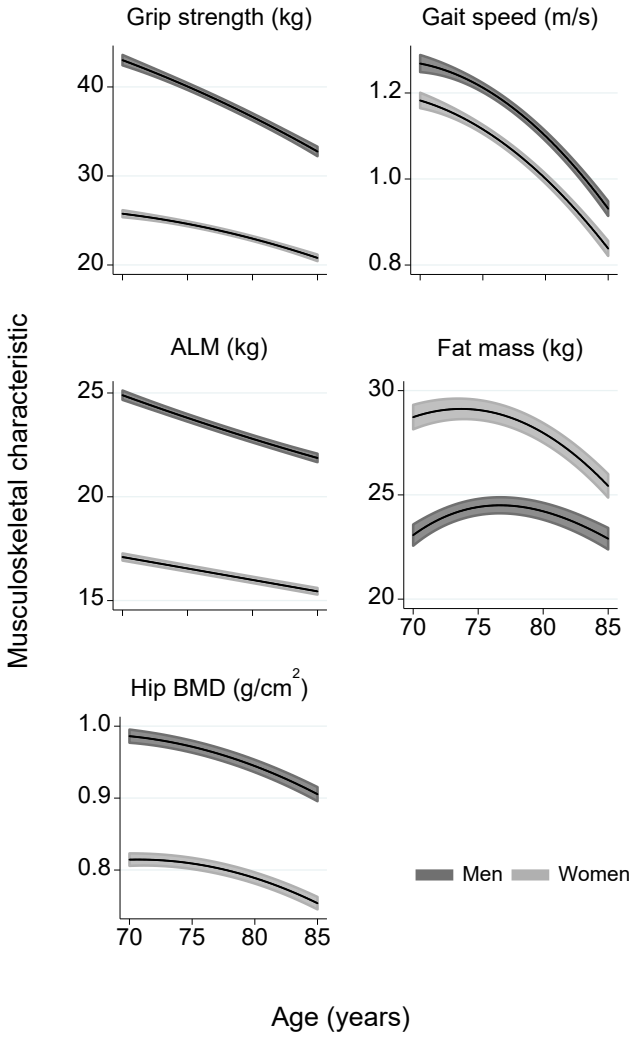
Analyses restricted to 735 men and 864 women with data on at least one conditional change measure; each conditional change measure requires values of the characteristic at baseline and Year 10

3.2.6 Mean trajectories of characteristics

Figure 11 shows the mean trajectories of the characteristics for men and women, together with their 95% confidence bands. Decline in grip strength, gait speed and hip BMD accelerated over time as indicated by their quadratic relationship with age; a linear decline in ALM was observed. Fat mass increased, remained level and then decreased among men with a smaller period of initial increase among women.

The methods corresponding to these results are included in Section 2.6.2.5.

Figure 11: Mean (95% CI) trajectories of characteristics among men and women



ALM: Appendicular lean mass; BMD: Bone mineral density

Mean trajectories were derived using linear mixed effects models with random intercepts and slopes. Quadratic and cubic age terms were included as fixed effects if significant ($p<0.05$)

For each characteristic, trajectories from participants with at least two observations were included

3.2.7 Identification of unobserved groups with different mean trajectories for the characteristics

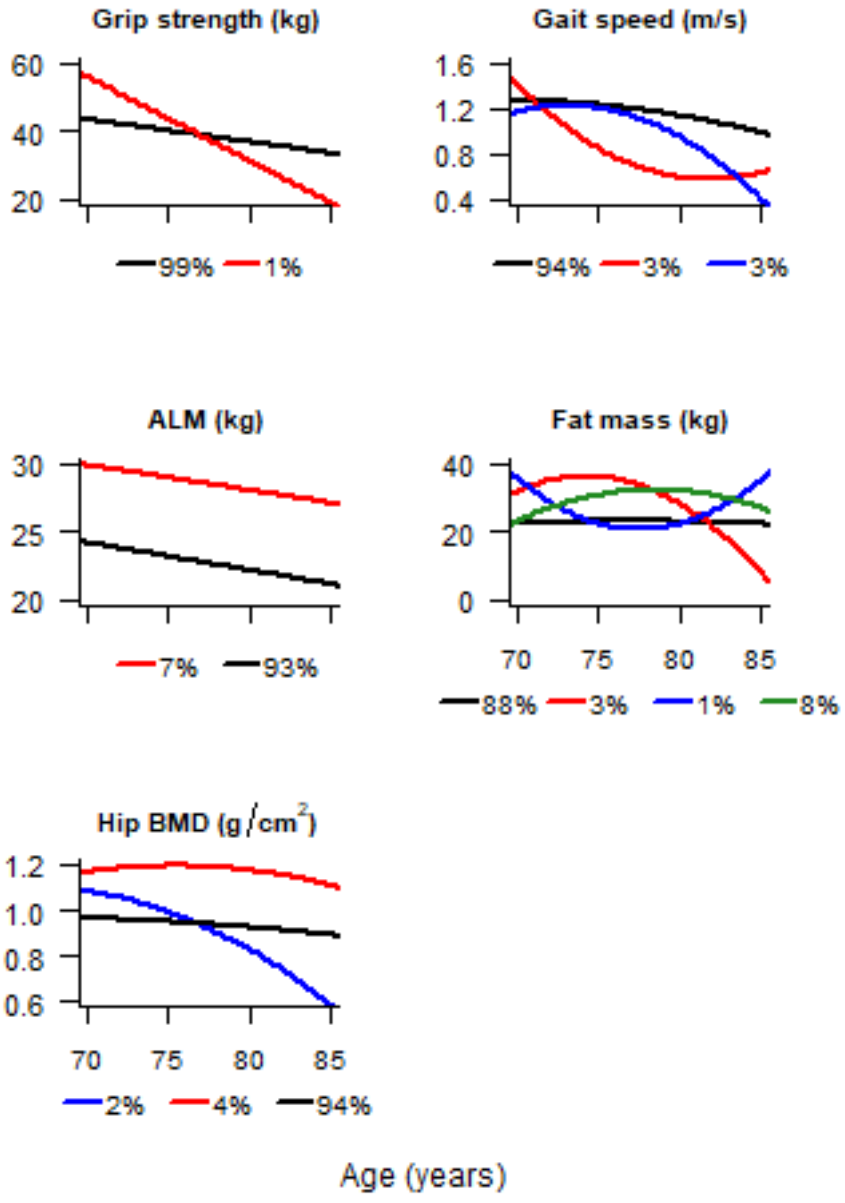
Mean trajectories of unobserved groups among men and women, obtained from GMM are illustrated in Figure 12 and Figure 13. All models contained a dominant group comprising at least 85% of the sex-specific sample with sparse numbers of participants in other groups. This suggests that a LME model with a single population average trajectory is sufficient for describing changes

in these characteristics among this age group and duration of follow-up. Mean trajectories of groups ascertained from the LCT model had much larger differences in levels of the characteristics rather than in rates of loss (Figure 14, Figure 15). However, there was a more even spread regarding the number of participants in each group.

As stated in Section 2.6.2.5, the model with the lowest BIC was chosen as the optimum model under the following restrictions; limiting the order of polynomial age terms to three for fixed effects (one for random effects for GMM); limiting the number of possible groups to four; and only considering models where the highest order age term for each group was significant. However, the patterns outlined above for GMM and LCT models were similar for the sub-optimal models that were fitted.

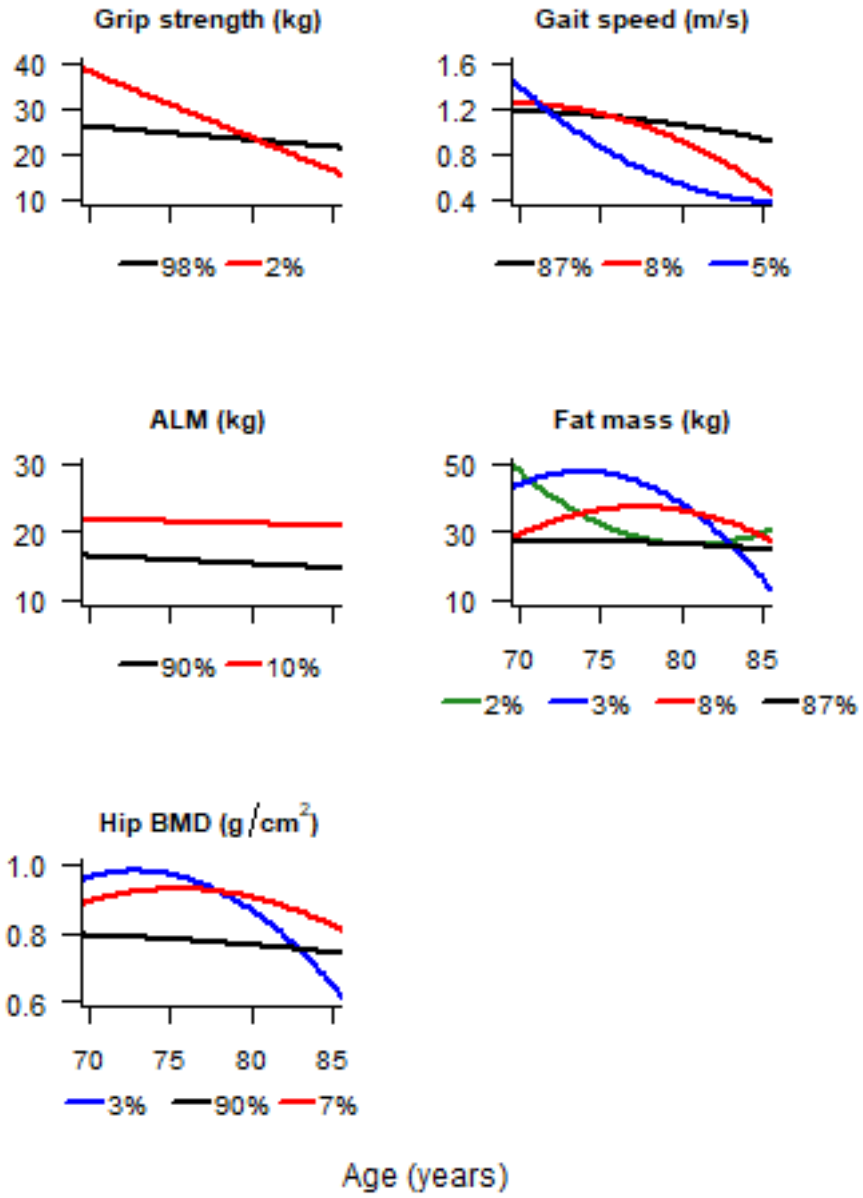
The methods corresponding to these results are included in Section 2.6.2.5.

Figure 12: Mean trajectories of groups among men from growth mixture models



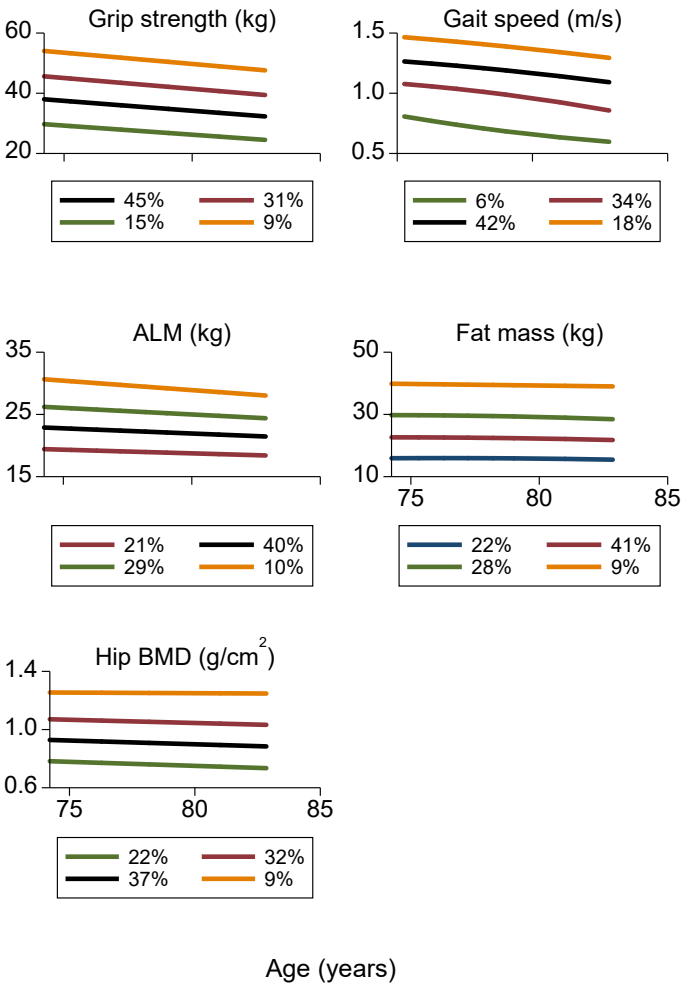
The proportion of men in each group is stated below the graph

Figure 13: Mean trajectories of groups among women from growth mixture models



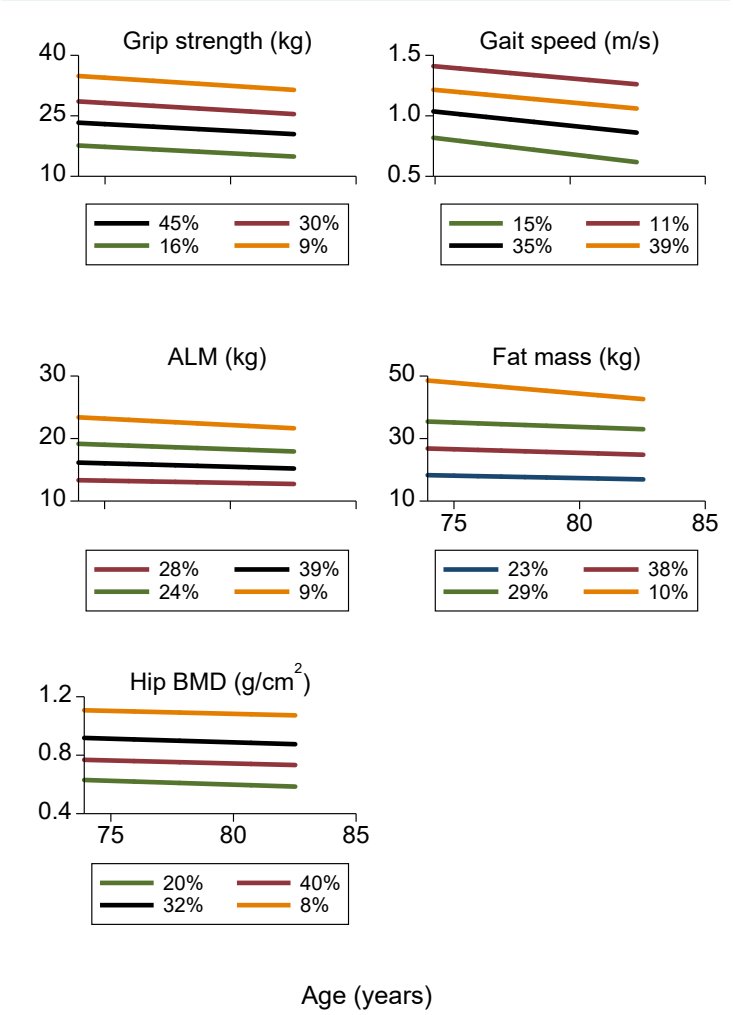
The proportion of women in each group is stated below the graph

Figure 14: Mean trajectories of groups among men from latent class trajectory models



The proportion of men in each group is stated below the graph

Figure 15: Mean trajectories of groups among women from latent class trajectory models



The proportion of women in each group is stated below the graph

3.2.8 Sensitivity analyses

After stratification by race within each sex, results were broadly similar between races (Appendix 1 – Appendix 3). Differences in mean trajectories between races were greater regarding levels of the characteristics rather than in rates of change.

In comparison with participants with data at two or more time-points, those with complete data had mean trajectories with slightly higher initial levels and/or lower rates of decline regarding some of the musculoskeletal parameters (Appendix 4), probably due to survivor bias. However, age-related changes in the characteristics were broadly similar between both groups. Mean trajectories from GMM and LCT models among participants with complete data were similar to those from participants with data at two or more time-points; GMM contained a dominant group

comprising a large proportion of the sample and mean trajectories from LCT models had much larger differences in levels of the characteristics rather than in rates of loss (Appendix 5 – Appendix 8).

The methods corresponding to the results from these sensitivity analyses are included in Section 2.6.2.6.

3.2.9 Summary of findings

This part of the thesis (Section 3.2) has described 9-year changes in musculoskeletal and body composition parameters among participants of the Health ABC Study. Declines in grip strength, gait speed and hip BMD accelerated with advancing age whereas declines in ALM were linear; fat mass increased, plateaued, and then decreased. Declines were greater, and the proportion of variance at follow-up explained by baseline level was lower, for gait speed and grip strength (39-52%) compared to the other characteristics (69-86%). Insights about longitudinal changes in characteristics from GMM and LCT models were limited with mean trajectories from GMM containing a dominant group comprising at least 85% of the sex-specific sample and those from LCT models differing considerably more with regard to level than change.

3.3 Determinants of level and change in characteristics

3.3.1 Subsection summary

Section 3.3 presents results relating to the following objective of this thesis: to examine baseline determinants of level and change in musculoskeletal and body composition characteristics. This section also includes a summary of these findings (Section 3.3.9). As stated in Section 2.6.3.1, the potential determinants considered included: age, height, weight-for-height residual, smoking status, alcohol consumption, physical activity, healthy eating index (ascertained at Year 2), educational attainment; housing tenure and number of systems medicated. All univariate and mutually-adjusted models accounted for age, sex and race.

The methods corresponding to the results in Section 3.3 are included in Section 2.6.3.

3.3.2 Descriptive statistics of baseline characteristics

Baseline characteristics of the 2917 Health ABC participants with data on at least one of the characteristics (grip strength, gait speed, ALM, whole body fat mass, and hip BMD) at two or more time-points are described in Table 12. On average, men were taller than women ($p<0.001$) and adiposity levels, indicated by greater weight-for-height residuals, were higher among black compared to white women ($p<0.001$). Although physical activity was higher among men ($p<0.001$), they had poorer diet quality, higher alcohol consumption and were more likely to have ever smoked compared to women ($p<0.001$ for all associations). Among both sexes, alcohol consumption was lower among black participants ($p<0.001$) but diet quality was poorer ($p<0.001$). Levels of educational attainment and home ownership were higher among men than women and among white participants compared to black participants ($p\leq0.005$ for all associations). Number of systems medicated was higher among women than men and among white participants compared to black participants ($p<0.05$ for all associations).

Compared to the 158 participants who were not included in the analysis sample, both men and women in the analysis sample were more likely to be white and have post-secondary education ($p<0.004$).

Table 12: Baseline participant characteristics according to sex and race

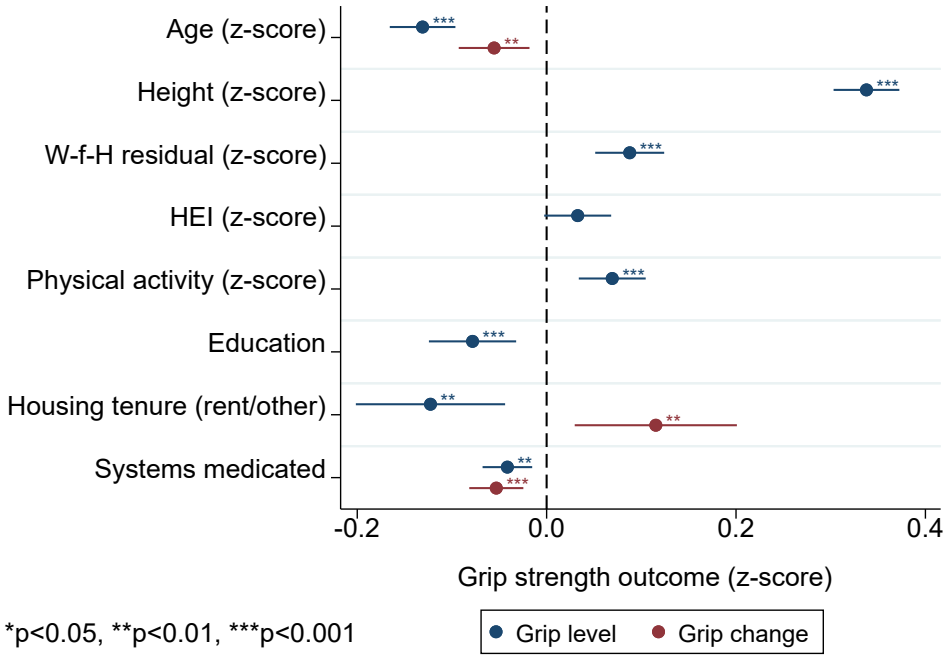
Characteristic [Mean (SD) or N(%)]	Men			Women		
	White (n=907)	Black (n=511)	All (n=1418)	White (n= 823)	Black (n=676)	All (n=1499)
Age (years)	74.4 (2.9)	74.0 (2.7)	74.2 (2.8)*†	74.1 (2.8)	73.8 (2.9)	74.0 (2.9)*†
Height (m)	1.74 (0.06)	1.73 (0.07)	1.73 (0.07)*	1.59 (0.06)	1.60 (0.06)	1.60 (0.06)*
Weight-for-height residual (SD score)	0.00 (0.92)	0.00 (1.10)	0.00 (0.99)	-0.30 (0.87)	0.35 (1.03)	-0.01 (1.00)†
Ever smoked	639 (70.6%)	353 (69.1%)	992 (70.1%)*	337 (40.9%)	297 (44.1%)	634 (42.4%)*
Alcohol consumption: None	320 (35.5%)	274 (54.0%)	594 (42.2%)*†	390 (47.4%)	471 (69.8%)	861 (57.5%)*†
<1 per week	174 (19.3%)	99 (19.5%)	273 (19.4%)*†	186 (22.6%)	139 (20.6%)	325 (21.7%)*†
1-7 times per week	291 (32.3%)	89 (17.6%)	380 (27.0%)*†	205 (24.9%)	54 (8.0%)	259 (17.3%)*†
>1 per day	117 (13.0%)	45 (8.9%)	162 (11.5%)*†	41 (5.0%)	11 (1.6%)	52 (3.5%)*†
Physical activity (kcal/week)	6861 (5536)	6760 (6658)	6824 (5962)*	5616 (4195)	6159 (5948)	5860 (5065)*
Healthy Eating Index	70.6 (11.4)	63.3 (12.0)	68.1 (12.1)*†	72.4 (11.8)	68.5 (11.8)	70.7 (12.0)*†
Education: Below high school	122 (13.5%)	254 (49.8%)	376 (26.6%)*†	83 (10.1%)	257 (38.2%)	340 (22.8%)*†
High school graduate	238 (26.3%)	122 (23.9%)	360 (25.4%)*†	344 (41.8%)	234 (34.8%)	578 (38.7%)*†
Post secondary	546 (60.3%)	134 (26.3%)	680 (48.0%)*†	395 (48.1%)	181 (26.9%)	576 (38.6%)*†
Housing tenure (rent/other)	166 (18.7%)	127 (25.0%)	293 (21.0%)*†	218 (27.1%)	248 (37.2%)	466 (31.7%)*†
Number of systems medicated**	3.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)*†	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)*†

*Statistically significant sex differences ($p<0.05$); †Statistically significant racial differences within sex ($p<0.05$); **Median (lower quartile, upper quartile)
Number of systems medicated included the gastrointestinal, endocrine, respiratory, musculoskeletal and cardiovascular systems, and also cancers, and mental health

3.3.3 Determinants of level and change in grip strength

Associations between baseline characteristics and grip strength level and change are presented in Figure 16 and Table 13. In univariate analyses, correlates of lower baseline grip strength included older age, shorter height, lower adiposity (weight-for-height residual), lower physical activity, poorer diet quality, higher educational attainment; not owner-occupying one's home and greater comorbidity (more systems medicated); only the association regarding diet quality was not robust in mutually-adjusted analysis. In univariate and mutually-adjusted models, older age, owner-occupying one's home and greater comorbidity were associated with greater loss of grip strength.

Figure 16: Mutually-adjusted associations between participant characteristics and grip strength level and change with adjustment for sex and race



W-f-H: Weight for height residual; HEI: Healthy eating index

This figure presents the estimates in the mutually-adjusted models in Table 13

Estimates per higher band of educational attainment and for renting/other as opposed to owning one's home; remaining estimates are per unit increase in the characteristic

Change measures derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for grip change illustrates that an increase/presence of the predictor was associated with reduced loss of grip strength over time and a negative coefficient reflects accelerated loss

A four-level sex-race variable was included in all models to account for these characteristics

Table 13: Associations between baseline participant characteristics and grip strength level and change

Participant characteristic	Grip strength level at baseline (z-score)				Grip strength change during follow-up (z-score)†			
	Adjusted for sex and race		Mutually-adjusted		Adjusted for sex and race		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Age (z-score)*	**-0.18 (-0.21,-0.14)**	**<0.001**	**-0.13 (-0.17,-0.10)**	**<0.001**	**-0.05 (-0.09,-0.02)**	**0.004**	**-0.06 (-0.09,-0.02)**	**0.004**
Height (z-score)*	**0.34 (0.31,0.38)**	**<0.001**	**0.34 (0.30,0.37)**	**<0.001**	-0.03 (-0.07,0.01)	0.102		
Weight-for-height residual (z-score)*	**0.10 (0.06,0.13)**	**<0.001**	**0.09 (0.05,0.12)**	**<0.001**	-0.00 (-0.04,0.04)	0.952		
Ever smoked	0.05 (-0.02,0.12)	0.186			0.01 (-0.06,0.09)	0.723		
Alcohol consumption**	-0.02 (-0.06,0.02)	0.298			-0.02 (-0.06,0.02)	0.307		
Physical activity (z-score)*	**0.12 (0.09,0.16)**	**<0.001**	**0.07 (0.03,0.10)**	**<0.001**	0.01 (-0.02,0.05)	0.495		
Healthy Eating Index (z-score)*	**0.04 (0.00,0.08)**	**0.041**	0.03 (-0.00,0.07)	0.069	-0.02 (-0.06,0.02)	0.244		
Education**	**-0.06 (-0.11,-0.01)**	**0.012**	**-0.08 (-0.12,-0.03)**	**0.001**	-0.00 (-0.05,0.05)	0.970		
Housing tenure (rent/other)	**-0.15 (-0.23,-0.07)**	**<0.001**	**-0.12 (-0.20,-0.04)**	**0.002**	**0.11 (0.03,0.20)**	**0.009**	**0.12 (0.03,0.20)**	**0.008**
Number of systems medicated*	**-0.04 (-0.07,-0.01)**	**0.005**	**-0.04 (-0.07,-0.02)**	**0.002**	**-0.05 (-0.08,-0.03)**	**<0.001**	**-0.05 (-0.08,-0.02)**	**<0.001**

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; Other estimates are for the presence versus absence of the characteristic

†Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for grip strength change illustrates that an increase/presence of the predictor was associated with reduced loss of grip strength over time and a negative coefficient reflects accelerated loss of grip strength

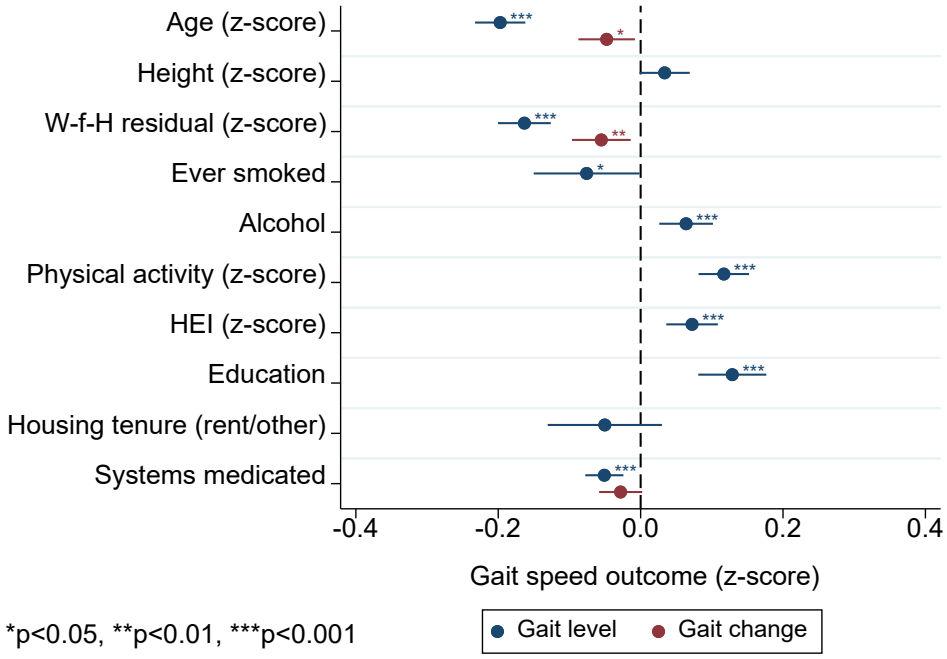
A four-level sex-race variable was included in all models to account for these characteristics

Significant associations ($p<0.05$) are highlighted in bold and red

3.3.4 Determinants of level and change in gait speed

Relationships between participant characteristics and gait speed level and change are presented in Table 14 and Figure 17. Correlates of slower gait speed included older age, shorter height, higher adiposity, ever smoking, lower alcohol consumption, lower physical activity, poorer diet quality, lower educational attainment, not owner occupying one's home and greater comorbidity; in mutually-adjusted analysis, only associations regarding height and housing tenure were not robust. Older age, higher adiposity and greater comorbidity were associated with accelerated decline in gait speed in univariate analyses; associations for comorbidity were not robust in the mutually-adjusted model.

Figure 17: Mutually-adjusted associations between participant characteristics and gait speed level and change with adjustment for sex and race



W-f-H: Weight for height residual; HEI: Healthy eating index

This figure presents the estimates in the mutually-adjusted models in Table 14

Estimates per higher band of alcohol consumption and educational attainment; for ever smoking vs not and for renting/other vs owning one's home; remaining estimates are per unit increase in the characteristic

Change measures derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for gait speed change illustrates that an increase/presence of the predictor was associated with reduced loss of gait speed over time and a negative coefficient reflects accelerated loss

A four-level sex-race variable was included in all models to account for these characteristics

Table 14: Associations between baseline participant characteristics and gait speed level and change

Participant characteristic	Gait speed level at baseline (z-score)				Gait speed change during follow-up (z-score)†			
	Adjusted for sex and race		Mutually-adjusted		Adjusted for sex and race		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Age (z-score)*	**-0.19 (-0.23,-0.16)**	**<0.001**	**-0.20 (-0.23,-0.16)**	**<0.001**	**-0.04 (-0.08,-0.00)**	**0.038**	**-0.05 (-0.09,-0.01)**	**0.018**
Height (z-score)*	**0.04 (0.01,0.08)**	**0.018**	0.03 (-0.00,0.07)	0.06	-0.02 (-0.06,0.02)	0.260		
Weight-for-height residual (z-score)*	**-0.16 (-0.20,-0.13)**	**<0.001**	**-0.16 (-0.20,-0.13)**	**<0.001**	**-0.06 (-0.10,-0.02)**	**0.005**	**-0.06 (-0.10,-0.01)**	**0.009**
Ever smoked	**-0.09 (-0.17,-0.02)**	**0.012**	**-0.08 (-0.15,-0.00)**	**0.045**	-0.02 (-0.10,0.07)	0.708		
Alcohol consumption**	**0.09 (0.06,0.13)**	**<0.001**	**0.06 (0.03,0.10)**	**0.001**	0.01 (-0.03,0.05)	0.631		
Physical activity (z-score)*	**0.11 (0.08,0.15)**	**<0.001**	**0.12 (0.08,0.15)**	**<0.001**	-0.01 (-0.05,0.03)	0.735		
Healthy Eating Index (z-score)*	**0.09 (0.06,0.13)**	**<0.001**	**0.07 (0.04,0.11)**	**<0.001**	-0.02 (-0.06,0.02)	0.302		
Education**	**0.19 (0.14,0.23)**	**<0.001**	**0.13 (0.08,0.18)**	**<0.001**	0.01 (-0.05,0.06)	0.809		
Housing tenure (rent/other)	**-0.11 (-0.19,-0.02)**	**0.012**	-0.05 (-0.13,0.03)	0.219	-0.02 (-0.11,0.07)	0.708		
Number of systems medicated*	**-0.06 (-0.09,-0.03)**	**<0.001**	**-0.05 (-0.08,-0.02)**	**<0.001**	**-0.03 (-0.06,-0.00)**	**0.042**	-0.03 (-0.06,0.00)	0.069

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; Other estimates are for the presence versus absence of the characteristic

†Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for gait speed change illustrates that an increase/presence of the predictor was associated with reduced loss of gait speed over time and a negative coefficient reflects accelerated loss of gait speed

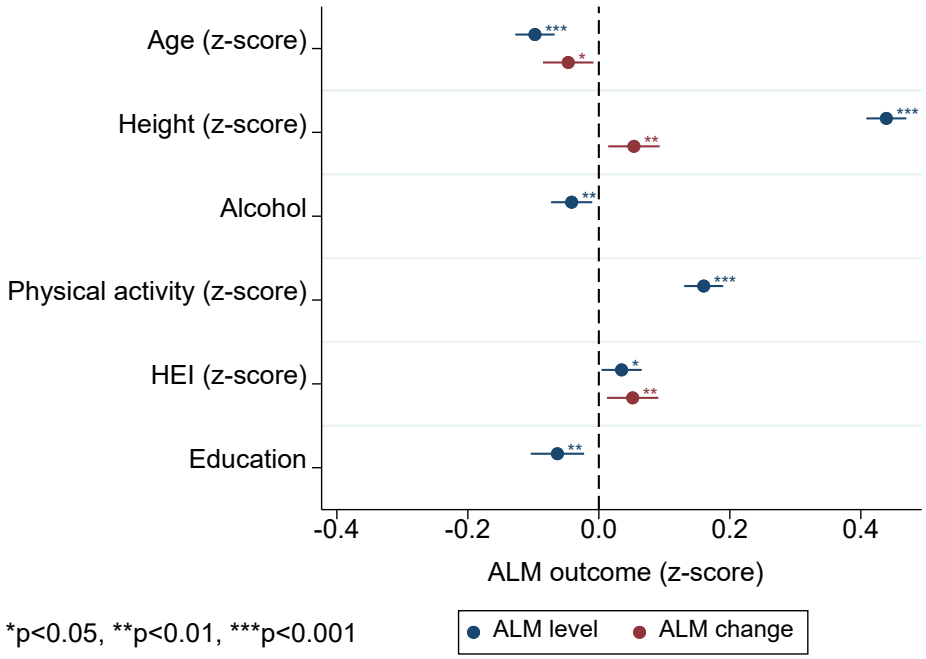
A four-level sex-race variable was included in all models to account for these characteristics

Significant associations (p<0.05) are highlighted in bold and red

3.3.5 Determinants of level and change in ALM

Table 15 and Figure 18 present associations between participant characteristics and level and change in ALM. In univariate and mutually-adjusted models, older age, shorter height, higher alcohol consumption, lower physical activity, poorer diet quality and higher educational attainment were associated with lower ALM. Older age, shorter height and poorer diet quality were also associated with greater decline in ALM in univariate and mutually-adjusted analyses.

Figure 18: Mutually-adjusted associations between participant characteristics and appendicular lean mass level and change with adjustment for sex and race



HEI: Healthy eating index

This figure presents the estimates in the mutually-adjusted models in Table 15

Estimates per higher band of alcohol consumption and educational attainment; remaining estimates are per unit increase in the characteristic

Change measures derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for ALM change illustrates that an increase/presence of the predictor was associated with reduced loss of ALM over time and a negative coefficient reflects accelerated loss

A four-level sex-race variable was included in all models to account for these characteristics

Table 15: Association between baseline participant characteristics and appendicular lean mass level and change

Participant characteristic	ALM level at baseline (z-score)				ALM change during follow-up (z-score)†			
	Adjusted for sex and race		Mutually-adjusted		Adjusted for sex and race		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Age (z-score)*	**-0.15 (-0.18,-0.12)**	**<0.001**	**-0.10 (-0.13,-0.07)**	**<0.001**	**-0.05 (-0.09,-0.01)**	**0.009**	**-0.05 (-0.09,-0.01)**	**0.017**
Height (z-score)*	**0.45 (0.42,0.48)**	**<0.001**	**0.44 (0.41,0.47)**	**<0.001**	**0.06 (0.02,0.10)**	**0.002**	**0.05 (0.01,0.09)**	**0.008**
Ever smoked	-0.03 (-0.10,0.04)	0.346			-0.05 (-0.13,0.02)	0.179		
Alcohol consumption**	**-0.05 (-0.08,-0.01)**	**0.006**	**-0.04 (-0.07,-0.01)**	**0.010**	0.02 (-0.02,0.06)	0.330		
Physical activity (z-score)*	**0.20 (0.16,0.23)**	**<0.001**	**0.16 (0.13,0.19)**	**<0.001**	-0.02 (-0.06,0.02)	0.269		
Healthy Eating Index (z-score)*	**0.05 (0.01,0.08)**	**0.007**	**0.03 (0.00,0.07)**	**0.026**	**0.05 (0.01,0.09)**	**0.008**	**0.05 (0.01,0.09)**	**0.010**
Education**	**-0.06 (-0.10,-0.01)**	**0.011**	**-0.06 (-0.10,-0.02)**	**0.002**	0.03 (-0.02,0.07)	0.317		
Housing tenure (rent/other)	-0.04 (-0.12,0.04)	0.290			0.00 (-0.08,0.09)	0.953		
Number of systems medicated*	0.02 (-0.00,0.05)	0.069			-0.03 (-0.05,0.00)	0.062		

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; Other estimates are for the presence versus absence of the characteristic

†Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for ALM change illustrates that an increase/presence of the predictor was associated with reduced loss of ALM over time and a negative coefficient reflects accelerated loss of ALM

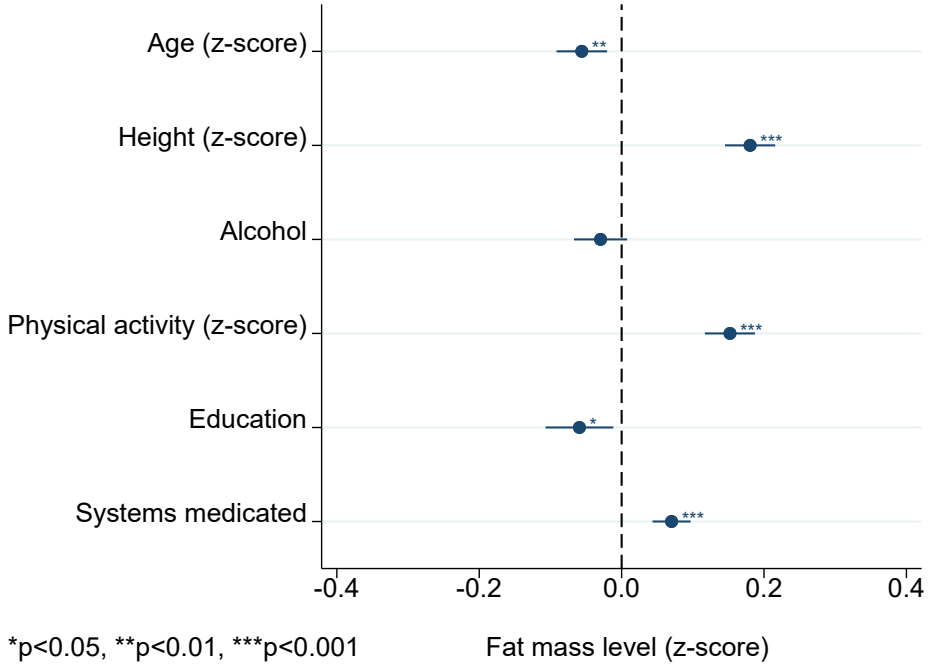
A four-level sex-race variable was included in all models to account for these characteristics

Significant associations ($p<0.05$) are highlighted in bold and red

3.3.6 Determinants of level and change in fat mass

Associations between characteristics and both level and change in fat mass are shown in Table 16 and Figure 19. In univariate analyses, correlates of lower fat mass level included: older age, shorter height, higher alcohol consumption, lower physical activity, higher educational attainment, owner occupying one's home and lower comorbidity; only associations for alcohol consumption were not robust to adjustment in mutually adjusted analyses. No baseline characteristics were associated with changes in fat mass.

Figure 19: Mutually-adjusted associations between participant characteristics and fat mass level with adjustment for sex and race



Estimates per higher band of alcohol consumption and educational attainment; remaining estimates are per unit increase in the characteristic

This figure presents the estimates in the mutually-adjusted models in Table 16

A four-level sex-race variable was included in all models to account for these characteristics

Change measures derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for fat mass change illustrates that an increase/presence of the predictor was associated with reduced loss of fat mass over time and a negative coefficient reflects accelerated loss

A four-level sex-race variable was included in all models to account for these characteristic

Table 16: Associations between baseline characteristics and fat mass level and change

Participant characteristic	Fat mass level at baseline (z-score)				Fat mass change during follow-up (z-score)†			
	Adjusted for sex and race		Mutually-adjusted		Adjusted for sex and race		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Age (z-score)*	**-0.09 (-0.12,-0.05)**	**<0.001**	**-0.06 (-0.09,-0.02)**	**0.002**	-0.04 (-0.07,0.00)	0.051		
Height (z-score)*	**0.19 (0.16,0.23)**	**<0.001**	**0.18 (0.15,0.22)**	**<0.001**	0.01 (-0.03,0.04)	0.744		
Ever smoked	0.03 (-0.04,0.11)	0.419			0.01 (-0.07,0.09)	0.780		
Alcohol consumption**	**-0.04 (-0.08,-0.00)**	**0.032**	-0.03 (-0.07,0.01)	0.119	-0.01 (-0.05,0.02)	0.465		
Physical activity (z-score)*	**0.15 (0.12,0.19)**	**<0.001**	**0.15 (0.12,0.19)**	**<0.001**	-0.03 (-0.07,0.01)	0.125		
Healthy Eating Index (z-score)*	0.02 (-0.02,0.06)	0.319			0.04 (-0.00,0.08)	0.053		
Education**	**-0.06 (-0.11,-0.01)**	**0.015**	**-0.06 (-0.11,-0.01)**	**0.015**	0.03 (-0.02,0.08)	0.231		
Housing tenure (rent/other)	**0.08 (0.00,0.17)**	**0.044**	**0.11 (0.03,0.19)**	**0.007**	-0.02 (-0.10,0.07)	0.708		
Number of systems medicated*	**0.06 (0.03,0.09)**	**<0.001**	**0.07 (0.04,0.10)**	**<0.001**	0.00 (-0.02,0.03)	0.762		

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; Other estimates are for the presence versus absence of the characteristic

†Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for fat mass change illustrates that an increase/presence of the predictor was associated with reduced loss of fat mass over time and a negative coefficient reflects accelerated loss of fat mass

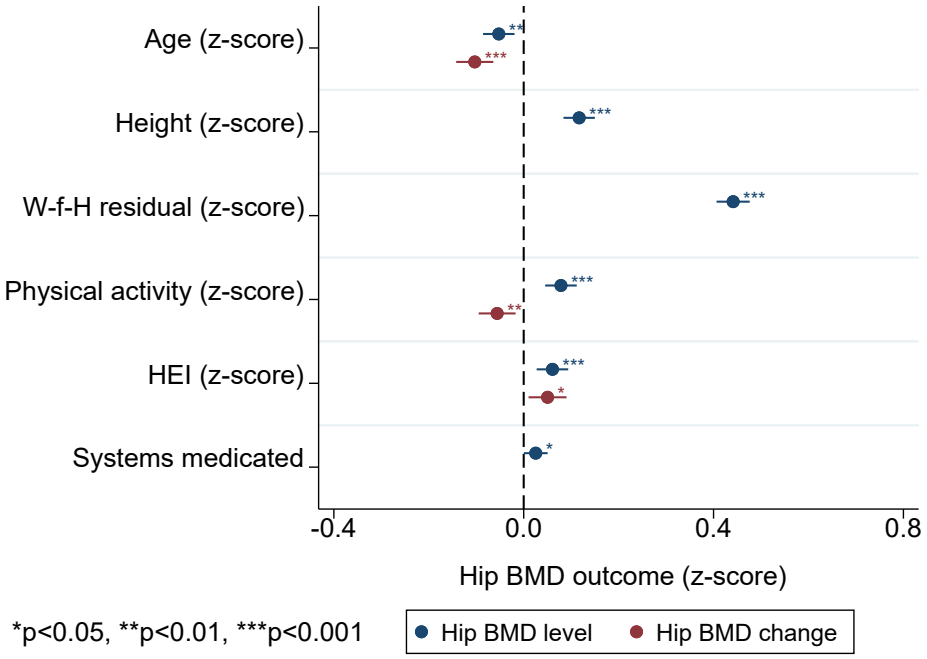
A four-level sex-race variable was included in all models to account for these characteristics

Significant associations ($p<0.05$) are highlighted in bold and red

3.3.7 Determinants of level and change in hip BMD

Relationships between participant characteristics and level and change in hip BMD are illustrated in Table 17 and Figure 20. Older age, shorter height, lower adiposity, lower physical activity, poorer diet quality and less comorbidity were associated with lower hip BMD in univariate and mutually-adjusted analyses. In univariate analyses, correlates of accelerated decline in hip BMD included older age, higher physical activity, poorer diet quality and lower educational attainment; only educational attainment was not associated with hip BMD change in the mutually-adjusted model.

Figure 20: Mutually-adjusted associations between participant characteristics and hip BMD level and change with adjustment for sex and race



W-f-H: Weight for height residual; HEI: Healthy eating index

This figure presents the estimates in the mutually-adjusted models in Table 17

Estimates are per unit increase in the characteristic

Change measures derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for hip BMD change illustrates that an increase/presence of the predictor was associated with reduced loss of hip BMD over time and a negative coefficient reflects accelerated loss

A four-level sex-race variable was included in all models to account for these characteristics

Table 17: Associations between baseline characteristics and hip BMD level and change

Participant characteristic	Hip BMD level at baseline (z-score)				Hip BMD change during follow-up (z-score)†			
	Adjusted for sex and race		Mutually-adjusted		Adjusted for sex and race		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Age (z-score)*	**-0.11 (-0.15,-0.08)**	**<0.001**	**-0.05 (-0.09,-0.02)**	**0.002**	**-0.09 (-0.13,-0.05)**	**<0.001**	**-0.10 (-0.14,-0.06)**	**<0.001**
Height (z-score)*	**0.11 (0.08,0.15)**	**<0.001**	**0.12 (0.08,0.15)**	**<0.001**	-0.03 (-0.07,0.01)	0.113		
Weight-for-height residual (z-score)*	**0.46 (0.43,0.49)**	**<0.001**	**0.44 (0.41,0.48)**	**<0.001**	-0.01 (-0.05,0.03)	0.670		
Ever smoked	-0.06 (-0.13,0.02)	0.143			0.07 (-0.00,0.15)	0.064		
Alcohol consumption**	0.03 (-0.00,0.07)	0.083			0.02 (-0.02,0.06)	0.263		
Physical activity (z-score)*	**0.16 (0.12,0.20)**	**<0.001**	**0.08 (0.05,0.11)**	**<0.001**	**-0.05 (-0.08,-0.01)**	**0.018**	**-0.06 (-0.09,-0.02)**	**0.005**
Healthy Eating Index (z-score)*	**0.08 (0.05,0.12)**	**<0.001**	**0.06 (0.03,0.09)**	**<0.001**	**0.05 (0.01,0.09)**	**0.008**	**0.05 (0.01,0.09)**	**0.014**
Education**	0.02 (-0.03,0.07)	0.442			**0.05 (0.00,0.10)**	**0.041**	0.04 (-0.01,0.10)	0.105
Housing tenure (rent/other)	-0.05 (-0.14,0.03)	0.210			0.08 (-0.00,0.17)	0.061		
Number of systems medicated*	**0.06 (0.03,0.09)**	**<0.001**	**0.03 (0.00,0.05)**	**0.047**	-0.01 (-0.04,0.02)	0.399		

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; Other estimates are for the presence versus absence of the characteristic

†Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for hip BMD change illustrates that an increase/presence of the predictor was associated with reduced loss of hip BMD over time and a negative coefficient reflects accelerated loss of hip BMD

A four-level sex-race variable was included in all models to account for these characteristics

Significant associations ($p<0.05$) are highlighted in bold and red

3.3.8 Sensitivity analyses

Some relationships between baseline characteristics and level and change in musculoskeletal and body composition characteristics differed between the main sex-pooled analysis and the sex-stratified sensitivity analysis. For example, lower educational attainment was related to slower gait speed and, counterintuitively, higher levels of grip strength and ALM in the pooled analysis. However, these latter two associations were only significant among women in sex-stratified analysis (Appendix 9 and Appendix 13). Therefore, it would appear that some of these counterintuitive associations among women were driving the counterintuitive associations observed in the pooled analyses.

Other sensitivity analyses involved examining evidence of interaction effects between baseline characteristics and the four-level sex-race variable. Although there were some significant ($p<0.05$) interactions, the vast majority of these interaction effects differed in magnitude and not direction of effect. Furthermore, a substantial number of interactions were investigated; a number of significant interactions are to be expected by chance and also due to the large number of observations in the analysis sample which possibly gives power to detect interactions statistically, even if they are not biologically convincing.

Overall, associations between baseline participant characteristics and both level and change in musculoskeletal and body composition outcomes were broadly similar between the sex-pooled and sex-stratified analyses.

The methods corresponding to results from these sensitivity analyses are included in Section 2.6.3.4.

3.3.9 Summary of findings

3.3.9.1 Age and anthropometry

Significant ($p<0.05$) mutually-adjusted associations between baseline participant characteristics and both level and change in musculoskeletal and body composition outcomes are summarised in Table 18. Older age was related to both lower level and accelerated decline in all outcomes apart from fat mass where it was only related to lower level. Shorter height was associated with lower levels of grip strength, ALM, fat mass and hip BMD; shorter height was also associated with greater decline in ALM but this was the case among women only in sex-stratified analysis

(Appendix 14). Lower adiposity, indicated by lower weight-for-height residuals, was a risk factor for lower grip strength and hip BMD; higher adiposity was a risk factor for both lower level and accelerated loss of gait speed.

3.3.9.2 Health behaviours

Health behaviours were related to level and change in outcomes. Ever smoking was associated with lower gait speed, and higher alcohol consumption was associated with both higher gait speed and lower ALM. Lower physical activity was related to lower levels of all outcomes and, surprisingly, reduced decline in hip BMD. However, the relationship between physical activity and hip BMD decline was observed among women only in sex-stratified analysis (Appendix 18). Poorer diet quality, indicated by lower HEI scores, was associated with low gait speed and both low level and greater decline in ALM and hip BMD.

3.3.9.3 Socio-economic position and comorbidity

Level and change in outcomes were also correlated with markers of socioeconomic position and levels of comorbidity. For example, lower educational attainment was related to slower gait speed and, counterintuitively, higher levels of grip strength and ALM. However, these latter two associations were only significant among women in sex-stratified analysis (Appendix 9 and Appendix 13). Not owner occupying one's home was associated with lower grip strength and higher fat mass but reduced decline in grip strength; in sex-stratified analyses, relationships regarding grip strength declines and fat mass were only robust among women (Appendix 10 and Appendix 15). Greater comorbidity was related to lower levels and greater declines in grip strength, slower gait speed and higher levels of fat mass and hip BMD.

3.3.9.4 Implications for adjustments to include in analysis of level and change in musculoskeletal and body composition characteristics in relation to risk of adverse outcomes

As stated in Section 2.6.5.6, baseline characteristics that were associated with the levels of two or more of the musculoskeletal and body composition parameters in mutually-adjusted analysis were included as adjustments in survival models for level of musculoskeletal and body composition parameters in relation to risk of adverse health outcomes; an analogous approach was used when the predictor was change in the characteristic. Therefore, based on the results for baseline determinants of level and change, survival analysis models for level were, additionally to sex, race and age, adjusted for height, weight-for-height residual (excluded for ALM and fat mass due to collinearity), physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were only adjusted for diet quality in addition to age, sex and race. The four level sex-race variable and age were included as adjustments in all survival analysis models.

Table 18: Significant mutually-adjusted associations between baseline participant characteristics and level and change in outcomes

Baseline characteristic	Grip strength		Gait speed		ALM		Fat mass		Hip BMD	
	Lower level	Greater decline	Lower level	Greater decline	Lower level	Greater decline	Lower level	Greater decline	Lower level	Greater decline
Age	Older age	Older age	Older age	Older age	Older age	Older age	Older age		Older age	Older age
Height	Shorter height				Shorter height	Shorter height	Shorter height		Shorter height	
Weight-for-height residual	Lower adiposity		Higher adiposity	Higher adiposity					Lower adiposity	
Ever smoked			Ever smoked							
Alcohol consumption			Less alcohol		More alcohol					
Physical activity	Lower activity		Lower activity		Lower activity		Lower activity		Lower activity	Higher activity
Healthy Eating Index			Poorer diet		Poorer diet	Poorer diet			Poorer diet	Poorer diet
Educational attainment	Higher education		Lower education		Higher education		Higher education			
Housing tenure	Not own	Owner occupy					Owner occupy			
Number of systems medicated	Greater comorbidity	Greater comorbidity	Greater comorbidity				Lower comorbidity		Lower comorbidity	

ALM: Appendicular lean mass; w-f-h: Weight-for-height

3.4 Interrelationships between changes in characteristics

3.4.1 Subsection summary

Section 3.4 presents results in relation to the following objective of this thesis: to examine interrelationships between changes in musculoskeletal and body composition characteristics. A summary of these findings is included in Section 3.4.7.

3.4.2 Correlations between changes in characteristics

Pearson correlations between changes in LMS z-scores for characteristics over Years 1-10 are presented in Table 19. A high number of correlations were both significant ($p<0.05$) and positive, suggesting that declines in these characteristics co-occur; the strongest correlations were between changes in body composition parameters (ALM, fat mass and hip BMD) where correlation coefficients ranged from 0.34 to 0.44 ($p<0.001$ for all correlations). Moderate correlations between changes in grip strength and changes in ALM ($r=0.21$, $p<0.001$) and hip BMD ($r=0.20$, $p<0.001$) were also observed. Similar findings were observed when correlations were stratified by both sex and race (Appendix 19 - Appendix 22). Results were also similar for correlations between changes in these LMS z-scores over Years 1-6 (Table 20) and Years 6-10 (Table 21).

Correlations over Years 1-10 were also similar for partial Pearson correlations between change measures (Table 22) and for simple Pearson correlations between conditional change measures that were independent of baseline levels (Table 23).

The methods corresponding to these results are included in Section 2.6.4.2.

Table 19: Pearson correlations between changes in characteristics over Years 1-10

	Grip strength	Gait speed	ALM	Fat mass
Gait speed	**0.12**			
P-value	***<0.001***			
ALM	**0.21**	**0.07**		
P-value	***<0.001***	***<0.001***		
Fat mass	**0.10**	0.03	**0.44**	
P-value	***<0.001***	*0.112*	***<0.001***	
Hip BMD	**0.20**	**0.15**	**0.36**	**0.34**
P-value	***<0.001***	***<0.001***	***<0.001***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Changes in gait speed were ascertained from Years 2-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

Participants with at least two change measures (n=2885) were included; each change measure requires values of the characteristic at two or more time-points from Years 1-10

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Table 20: Pearson correlations between changes in characteristics over Years 1-6

	Grip strength	Gait speed	ALM	Fat mass
Gait speed	**0.06**			
P-value	***0.002***			
ALM	**0.13**	**0.07**		
P-value	***<0.001***	***<0.001***		
Fat mass	**0.08**	0.02	**0.41**	
P-value	***<0.001***	*0.203*	***<0.001***	
Hip BMD	**0.15**	**0.08**	**0.27**	**0.27**
P-value	***<0.001***	***<0.001***	***<0.001***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Changes in gait speed and hip BMD were ascertained from Years 2-6 and Years 1-5 respectively

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

Participants with at least two change measures (n=2878) were included; each change measure requires values of the characteristic at two or more time-points from Years 1-6

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Table 21: Pearson correlations between changes in characteristics over Years 6-10

	Grip strength	Gait speed	ALM	Fat mass
Gait speed	**0.10**			
P-value	***<0.001***			
ALM	**0.18**	0.03		
P-value	***<0.001***	*0.159*		
Fat mass	**0.12**	0.03	**0.34**	
P-value	***<0.001***	*0.251*	***<0.001***	
Hip BMD	**0.11**	**0.12**	**0.21**	**0.28**
P-value	***<0.001***	***<0.001***	***<0.001***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Changes in hip BMD were ascertained from Years 5 to 10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

Participants with at least two change measures (n=1769) were included; each change measure requires values of the characteristic at two or more time-points from Years 6-10

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Table 22: Partial Pearson correlations between changes in characteristics over Years 1-10

	Grip strength	Gait speed	ALM	Fat mass
Gait speed	**0.09**			
P-value	***<0.001***			
ALM	**0.16**	0.01		
P-value	***<0.001***	*0.483*		
Fat mass	-0.02	-0.03	**0.37**	
P-value	*0.354*	*0.130*	***<0.001***	
Hip BMD	**0.12**	**0.13**	**0.21**	**0.22**
P-value	***<0.001***	***<0.001***	***<0.001***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Changes in gait speed were ascertained from Years 2-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

Participants with complete data on all change measures (n= 2574) were included; each change measure requires values of the characteristic at two or more time-points from Years 1-10

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Table 23: Pearson correlations between conditional change measures over Years 1-10

	Grip strength	Gait speed	ALM	Fat mass
Gait speed	**0.14**			
P-value	***<0.001***			
ALM	**0.29**	0.07		
P-value	***<0.001***	*0.072*		
Fat mass	**0.09**	0.05	**0.45**	
P-value	***0.020***	*0.234*	***<0.001***	
Hip BMD	**0.27**	**0.24**	**0.36**	**0.29**
P-value	***<0.001***	***<0.001***	***<0.001***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Participants with at least two conditional change measures (n=1512) were included; each conditional change measure requires values of the characteristic at baseline and Year 10

Change measures were derived using a residual change method and are independent of baseline level

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

3.4.3 Temporal correlations between changes in characteristics

Pearson correlations between changes in characteristics over Years 1-6 in relation to subsequent changes in characteristics over Years 6-10 are presented in Table 24. Greater grip strength and gait speed decline over Years 1-6 were each associated with less decline in the same quantity over Years 6-10, suggesting an effect of regression to the mean; these relationships are presented graphically in Figure 21. Declines in all characteristics over Years 1-6 were associated with greater declines in hip BMD over Years 6-10 with stronger associations observed for ALM and fat mass; graphical illustrations of these relationships are presented in Figure 22. Results were similar when these temporal correlations were stratified according to both sex and race (Appendix 23 - Appendix 26). These associations described above were robust to adjustment for sex, race, age and diet quality (Table 25). Declines in ALM over Years 1-6 were correlated with declines in grip strength and gait speed over Years 6-10 and declines in grip strength over Years 1-6 were correlated with declines in gait speed over Years 6-10 (Table 24); however these correlations were weak ($r<0.11$).

The methods corresponding to these results are included in Section 2.6.4.2.

Table 24: Pearson correlations between changes in LMS z-scores over Years 1-6 in relation to changes in LMS z-scores over Years 6-10

Changes in LMS z-scores over Years 6-10	Changes in LMS z-scores over Years 1-6				
	Grip strength	**Gait speed**	**ALM**	**Fat mass**	**Hip BMD**
Grip strength	**-0.33**	0.02	**0.10**	**0.05**	0.01
P-value	***<0.001***	*0.372*	***<0.001***	***0.030***	*0.596*
Gait speed	**0.09**	**-0.19**	**0.06**	0.04	**0.09**
P-value	***<0.001***	***<0.001***	***0.009***	*0.145*	***<0.001***
ALM	0.01	-0.03	0.01	**0.08**	0.01
P-value	*0.572*	*0.180*	*0.832*	***<0.001***	*0.791*
Fat mass	-0.04	0.00	0.04	0.03	**0.06**
P-value	*0.119*	*0.931*	*0.072*	*0.172*	***0.012***
Hip BMD	**0.08**	**0.08**	**0.18**	**0.16**	**0.12**
P-value	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Change in gait speed was derived over Years 2-6 and Years 6-10; change in hip BMD was derived over Years 1-5 and Years 5-10

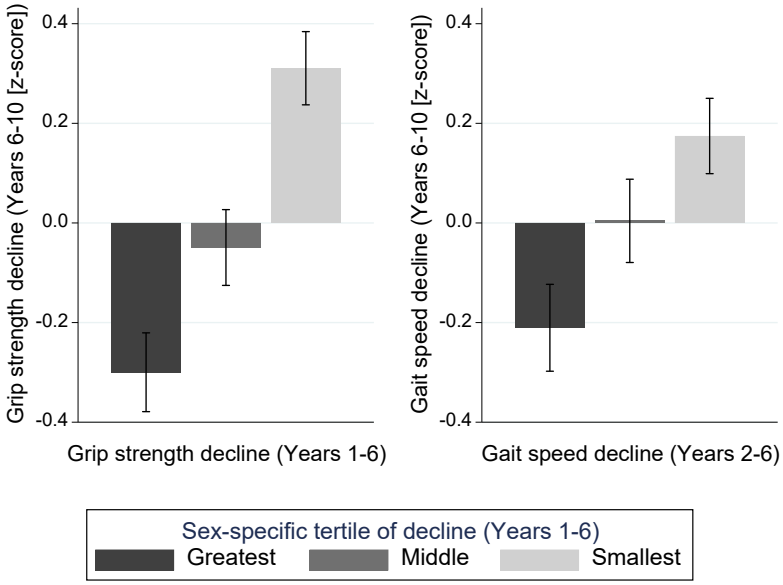
Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

Participants with at least one change measure from both Years 1-6 and Years 6-10 were included (n=1766); each change measure requires values of the characteristic at two or more time-points over the interval of assessment

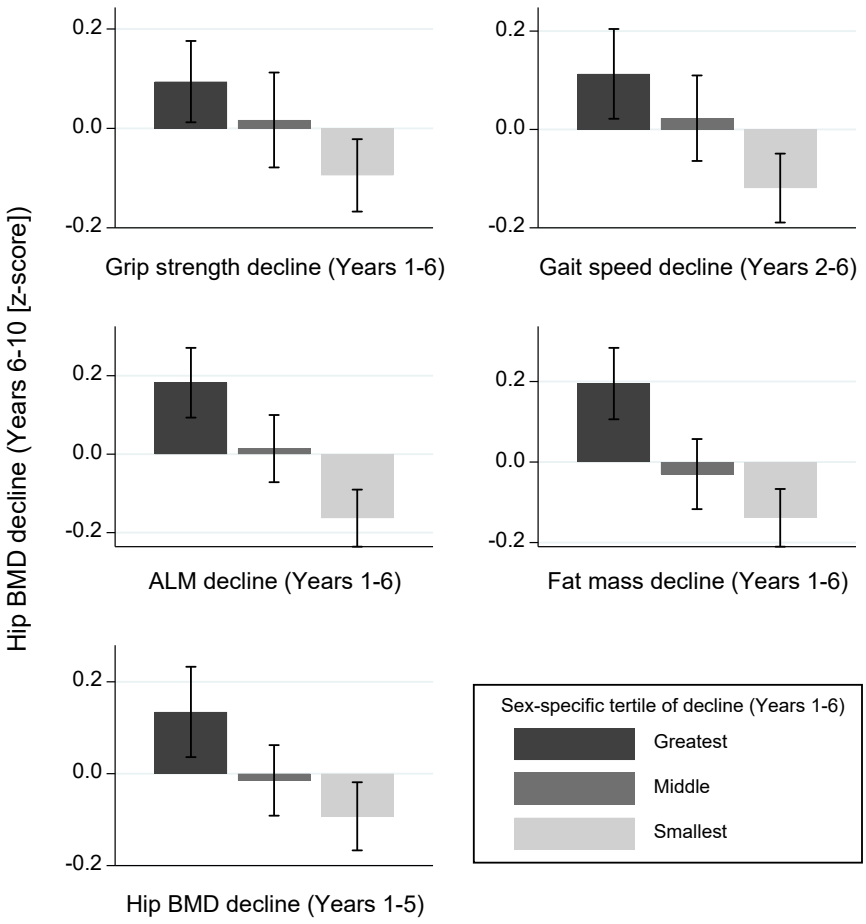
Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Figure 21: SD difference in grip strength and gait speed change over Years 6-10 according to tertile of decline in each characteristic over Years 1-6



Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Figure 22: SD difference in hip BMD over Years 6-10 according to tertile of decline in each characteristic over Years 1-6



Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Table 25: Changes in LMS z-scores from Years 1-6 in relation to changes in LMS z-scores from Years 6-10

Predictor (change from Years 1-6)	Outcome (change from Years 6-10)	Adjustments			
		None		Four-level sex-race variable, age and diet quality	
		Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Grip strength	Grip strength	-0.31 (-0.35,-0.27)	<0.001	-0.31 (-0.36,-0.27)	<0.001
Gait speed	Gait speed	-0.19 (-0.23,-0.14)	<0.001	-0.18 (-0.23,-0.14)	<0.001
Grip strength	Hip BMD	0.08 (0.04,0.13)	0.001	0.08 (0.03,0.12)	0.001
Gait speed	Hip BMD	0.08 (0.03,0.13)	0.001	0.09 (0.04,0.14)	<0.001
ALM	Hip BMD	0.18 (0.13,0.22)	<0.001	0.19 (0.15,0.24)	<0.001
Fat mass	Hip BMD	0.17 (0.12,0.22)	<0.001	0.17 (0.11,0.22)	<0.001
Hip BMD	Hip BMD	0.13 (0.08,0.18)	<0.001	0.11 (0.06,0.16)	<0.001

BMD: Bone mineral density; ALM: Appendicular lean mass

Change in gait speed was derived over Years 2-6 and Years 6-10; change in hip BMD was derived over Years 1-5 and Years 5-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

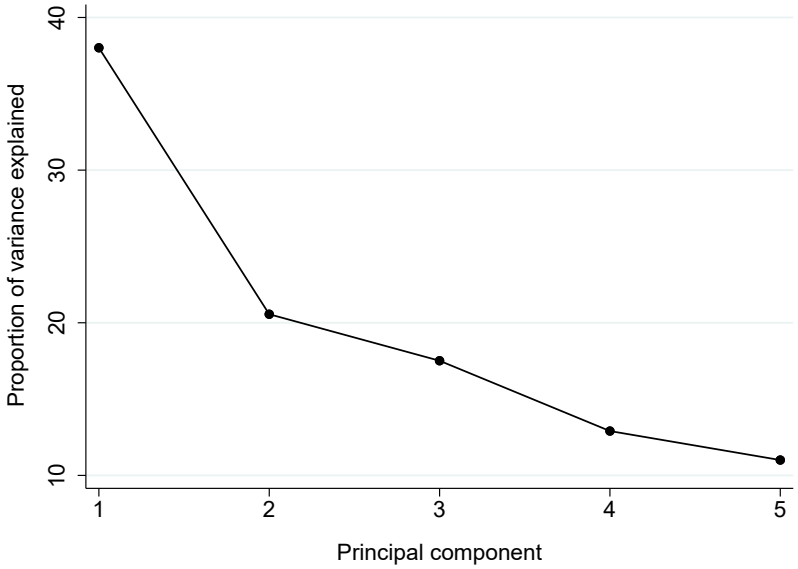
Estimates represent SD difference in outcomes per SD increase in predictor (sex-specific z-scores used for change measures)

3.4.4 Principal component analysis of changes in characteristics

To explore whether changes in characteristics occurred together or with some characteristics declining more than others, a principal component analysis of the change measures over Years 1-10 was implemented. The methods corresponding to these results are included in Section 2.6.4.3.

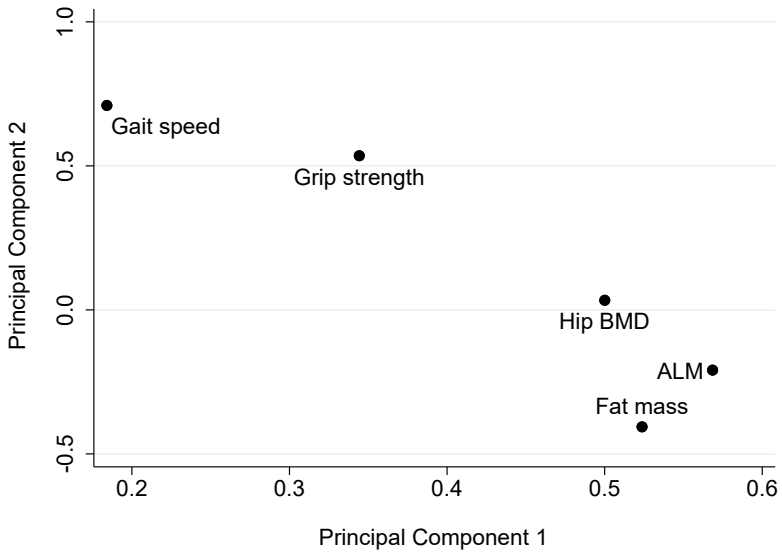
The first and second principal components explained 38% and 21% of the total variance respectively (Figure 23). The loadings of each characteristic for these two principal components are presented in Figure 24. The first component reflects the extent to which participants experienced overall declines regarding the set of characteristics with the highest loadings for declines in body composition parameters and the lowest loading for gait speed decline. The second component reflects a contrast in the rates of decline in ALM and fat mass in comparison to the rates of decline in grip strength and gait speed.

Figure 23: Proportion of variance explained by each principal component



The principal component analysis was restricted to participants with complete data on all change measures (n= 2574); each change measure requires values of the characteristic at two or more time-points from Years 1-10

Figure 24: Principal component loadings for each characteristic



The principal component analysis was restricted to participants with complete data on all change measures (n= 2574); each change measure requires values of the characteristic at two or more time-points from Years 1-10

3.4.5 Convergence problems using bivariate dual change score models

Bivariate dual change score models were implemented for each pair of characteristics (10 pairs in total) out of grip strength, gait speed, ALM, fat mass and hip BMD. However, despite the use of different samples (pooled and sex-specific), units for analyses (original units, LMS z-scores and z-scores derived from baseline mean and variance values) and estimation methods (maximum likelihood and unweighted least squares), at least 50% of the models failed to converge in all scenarios (Table 26). Problems included local, rather than global, solutions to maximum likelihood estimates of parameters and estimation of non-symmetric hessian matrices and non-positive definite covariance matrices for latent variables and the set of estimated parameters. The high number of models with convergence problems could be due to a lack of variation within or between individuals for some of the characteristics examined, resulting in estimation of variance parameters close to zero. This is suggested by the fact that the majority of models that failed to converge contained hip BMD, the characteristic with the lowest within- and between-individual variation in longitudinal change.

The methods corresponding to these results are included in Section 2.6.4.4.

Table 26: Number of bivariate dual change score models that failed to converge (out of 10) depending on the sample, units for analysis and estimation method

Sample	Units for analysis	Estimation method	
		Maximum likelihood	Unweighted least squares
Pooled sample (men and women)	LMS z-scores	10	7
	Original units	7	10
	Z-scores*	5	6
Men	LMS z-scores	10	9
	Original units	7	10
	Z-scores*	8	8
Women	LMS z-scores	7	8
	Original units	8	10
	Z-scores*	6	10

LMS z-scores were derived from generalised additive models for location, scale and shape

*Derived at each time-point using the sex-specific mean and standard deviation at Year 2 (Year 1 for hip BMD)

3.4.6 Interpretation of bivariate dual change score models which converged

The proportion of models that converged was highest (50%) when models were applied to the entire sample of men and women with sex-specific z-scores (calculated using the mean and standard deviation at baseline) as the units of analysis and maximum likelihood as the estimation method (Table 26). For completeness, the parameter estimates from the five models which converged in this scenario are presented in Appendix 42-Appendix 46. Changes in grip strength were positively correlated with subsequent changes in gait speed and fat mass but not vice versa. There were no temporal correlations between changes in grip strength and ALM. Changes in ALM were positively correlated with subsequent changes in gait speed but not vice versa. Changes in ALM were positively correlated with future changes in fat mass and changes in fat mass were also positively correlated with changes in ALM ($p<0.001$ for all associations listed above).

The methods corresponding to these results are included in Section 2.6.4.4.

3.4.7 Summary of findings

Significant and positive correlations between most change measures suggest that declines in these characteristics occur together. This is also supported by findings from the principal component analysis of the change measures where the first component reflected the extent to which participants experienced overall declines in the characteristics examined. However, the second component reflected a contrast between the extent of declines in body composition parameters versus declines in muscle strength and function. The strongest correlations were observed between changes in ALM, fat mass and hip BMD.

Regarding the temporal correlations between changes in LMS z-scores, declines in ALM preceded declines in grip strength and gait speed; declines in grip strength preceded declines in gait speed; and declines in all characteristics preceded declines in hip BMD. However, the magnitude of these temporal correlations were weak ($0.06<r<0.18$). Some of these associations differed compared to the temporal correlations estimated from bivariate dual change score models. For example, according to these models, there were no temporal correlations between changes in grip strength and ALM and greater declines in grip strength were related to greater subsequent declines in fat mass. One possible reason for these differences is the use of different units of analysis: z-scores standardised using the baseline mean and SD for the bivariate dual change score models as opposed to using LMS z-scores. Another possible reason is that the bivariate dual change score models only detect temporal correlations between changes in characteristics that are

independent of associations between prior levels and subsequent changes in characteristics and independent of associations between prior changes and subsequent changes in the same characteristic.

3.5 Level and change in characteristics and risk of adverse health outcomes

3.5.1 Subsection summary

Section 3.5 presents results in relation to the following objective of this thesis: to examine level and change in musculoskeletal and body composition characteristics in relation to risk of adverse health outcomes. The main results directly relating to this objective are included in Section 3.5.3 - 3.5.7; additional results on the impact of changes in characteristics on risk of outcomes after accounting for current measures and on the combined impact of levels and changes in characteristics on risk of outcomes are outlined in Sections 3.5.9 - 3.5.11. This section ends with a summary of these findings (Section 3.5.12).

All models were adjusted for the sex-race variable and age. As explained in Section 2.6.5.6, survival analysis models for level were additionally adjusted for height, weight-for-height residual (except for ALM and fat mass due to collinearity), physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were only additionally adjusted for diet quality.

3.5.2 Descriptive statistics for adverse health outcomes

Descriptive statistics for the survival analysis of adverse health outcomes with grip strength level and change as indicative exposures are presented in Table 27. These descriptive statistics differed slightly depending on the musculoskeletal or body characteristic used for the survival analysis as the time-points the characteristic was ascertained and occurrence of missing values for the characteristic would affect the start of the follow-up time for each participant in the analysis. However, as shown in Appendix 27 - Appendix 30, these descriptive statistics were similar for survival analyses where the exposure was level and change in participant characteristics other than grip strength.

Median age at the start of follow-up was 78.1 years. Median follow-up time (number of years to the first event or until participants were censored by end of follow-up) was greater for death (9.0) and fragility fracture (7.7) compared to hospital admission (2.5) or falls (2.1).

Compared to women, a significantly ($p<0.05$) higher proportion of men died (70.3% vs 57.2%) or had a hospital admission (84.8% vs 82.0%); a higher proportion of women had fragility fractures (19.9% vs 9.8%) and falls (74.9% vs 62.4%). Compared to white participants, a higher proportion of black participants died ($p<0.05$) but a lower proportion experienced fragility fractures ($p<0.001$) and falls ($p<0.001$), whilst proportions admitted to hospital were similar; this was the case among men and women. Death was a competing event for fragility fracture considerably more often than for hospital admission due to both the lower prevalence of fragility fractures compared to hospital admissions and the rarity of dying without having had any hospital admissions. Before the start of follow-up (when participants were regarded as not being at risk of adverse events in the survival analysis), the prevalence of fragility fractures was much lower than that for hospital admissions and falls.

Table 27: Descriptive statistics for the survival analysis of adverse health outcomes with grip strength level and change as indicative exposures

Characteristic [N(%) or median (lower quartile, upper quartile)]	All (n=2861)	White men (n=897)	Black men (n=498)	Men (n=1395)	White women (n=813)	Black women (n=653)	Women (n=1466)
Age at start of follow-up	78.1 (76.0, 80.6)	78.6 (76.2, 80.9)	77.8 (75.5, 80.2)*	78.3 (76.0, 80.7)	78.3 (76.1, 80.7)	77.5 (75.8, 80.1)*	78.0 (76.0, 80.5)
Follow-up time							
Death	9.0 (4.4, 11.6)	8.4 (3.9, 11.5)	6.5 (2.2, 11.3)*	7.7 (3.3, 11.5)	10.5 (6.4, 11.7)	9.3 (4.8, 11.6)*	10.1 (5.7, 11.7)
Fragility fracture	7.7 (3.2, 9.7)	7.6 (3.2, 9.6)	6.2 (2.2, 9.6)*	7.2 (2.8, 9.6)	8.1 (3.5, 9.7)	8.2 (3.9, 9.8)	8.2 (3.8, 9.7)
Hospital admission	2.5 (1.0, 5.9)	2.3 (0.9, 5.3)	1.9 (0.8, 4.3)	2.1 (0.8, 5.0)	3.2 (1.3, 7.1)	2.9 (1.1, 6.4)	3.0 (1.2, 6.9)
Fall	2.1 (0.7, 4.9)	2.2 (0.8, 5.0)	2.1 (1.0, 5.2)	2.1 (0.9, 5.0)	1.8 (0.6, 4.7)	2.3 (0.7, 5.0)	2.0 (0.6, 4.8)
Occurrence during follow-up							
Death	1818 (63.5%)	609 (67.9%)	371 (74.5%)*	980 (70.3%)	446 (54.9%)	392 (60.0%)*	838 (57.2%)
Fragility fracture	416 (14.9%)	110 (12.6%)	25 (5.0%)*	135 (9.8%)	212 (27.2%)	69 (10.9%)*	281 (19.9%)
Hospital admission	2385 (83.4%)	768 (85.6%)	415 (83.3%)	1183 (84.8%)	668 (82.2%)	534 (81.8%)	1202 (82.0%)
Fall	1737 (69.0%)	538 (67.4%)	204 (52.0%)*	742 (62.4%)	600 (79.7%)	395 (68.6%)*	995 (74.9%)
Competing risk variable (fragility fracture)							
No fracture or death	1097 (39.3%)	338 (38.6%)	160 (32.2%)*	498 (36.3%)	316 (40.5%)	283 (44.6%)*	599 (42.3%)
Death and no fracture**	1275 (45.7%)	428 (48.9%)	312 (62.8%)*	740 (53.9%)	252 (32.3%)	283 (44.6%)*	535 (37.8%)
Fracture	416 (14.9%)	110 (12.6%)	25 (5.0%)*	135 (9.8%)	212 (27.2%)	69 (10.9%)*	281 (19.9%)
Competing risk variable (hospital admission)							
No admission or death	322 (11.3%)	77 (8.6%)	41 (8.2%)	118 (8.5%)	114 (14.0%)	90 (13.8%)	204 (13.9%)
Death and no admission**	154 (5.4%)	52 (5.8%)	42 (8.4%)	94 (6.7%)	31 (3.8%)	29 (4.4%)	60 (4.1%)
Admission	2385 (83.4%)	768 (85.6%)	415 (83.3%)	1183 (84.8%)	668 (82.2%)	534 (81.8%)	1202 (82.0%)
Prevalence before follow-up[†]							
Fragility fracture	134 (4.8%)	26 (3.0%)	6 (1.2%)*	32 (2.3%)	73 (9.4%)	29 (4.6%)*	102 (7.2%)
Hospital admission	1302 (45.5%)	453 (50.5%)	234 (47.0%)	687 (49.2%)	319 (39.2%)	296 (45.3%)*	615 (42.0%)
Fall	1551 (61.6%)	482 (60.4%)	177 (45.2%)*	659 (55.4%)	540 (71.7%)	352 (61.1%)*	892 (67.1%)

N(%) relate to the number and proportion of participants experiencing the corresponding event

There were statistically significant sex differences ($p<0.05$) between all characteristics apart from age at the start of follow-up

*Statistically significant racial differences within sex ($p<0.05$)

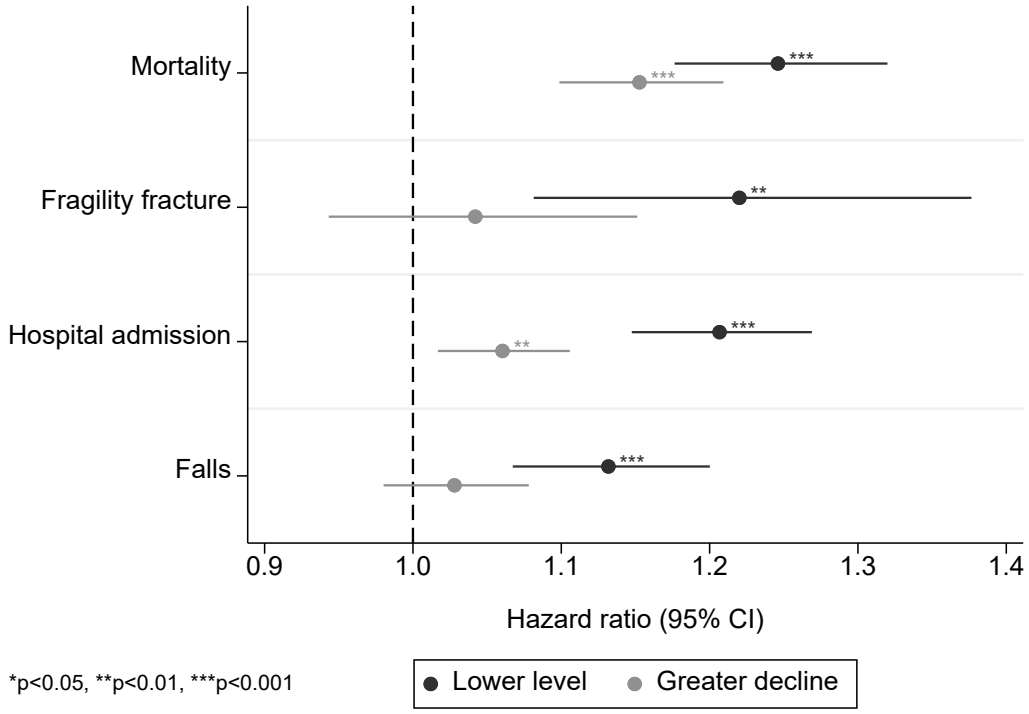
**Represent competing events as death prevents the failure event of interest from occurring
[†]Events occurring before participants were regarded as being at risk of adverse events in the survival analyses
274 (65.9%) of those who had a fracture during follow-up also died during follow-up; figures for hospital admission and falls were 1613 (67.6%) and 1012 (58.3%)

3.5.3 Grip strength level and change in relation to adverse outcomes

Associations between grip strength level and change in relation to risk of mortality, fragility fracture, hospital admission and falls are presented in Figure 25 and Table 28. In Cox models, lower grip strength was associated with increased risk of all adverse events; greater grip strength decline was related to higher risk of mortality and hospital admission. Associations from Cox and competing risk models were similar.

The methods corresponding to results in Sections 3.5.3 - 3.5.7 are included in Sections 2.6.5.1 - 2.6.5.7.

Figure 25: Risk of adverse outcome per SD decrease in grip strength level and per SD increase in grip strength decline



Mean level and change were calculated using data from Years 1, 2, 4 and 6

Change measure was ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Models for level were adjusted for sex, race, age, height, weight-for-height residual, alcohol consumption, physical activity, diet quality, education and number of systems medicated; models for change were adjusted for sex, race, age and diet quality

For fragility fractures, hospital admissions and falls, an indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models

Table 28: Risk of adverse outcomes per SD decrease in grip strength level and per SD increase in grip strength decline

Outcome	Model	Mean grip strength level over Years 1-6 (z-score)*				Grip strength decline over Years 1-6 (z-score)**			
		Stratified Cox model		Competing risk model		Stratified Cox model		Competing risk model	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Death	1	**1.22 (1.16,1.28)**	**<0.001**			**1.16 (1.11,1.22)**	**<0.001**		
	2	**1.25 (1.18,1.32)**	**<0.001**			**1.15 (1.10,1.21)**	**<0.001**		
Fragility fracture	1	**1.20 (1.08,1.34)**	**0.001**	**1.12 (1.01,1.24)**	**0.029**	1.04 (0.95,1.15)	0.386	0.99 (0.90,1.09)	0.867
	2	**1.22 (1.08,1.38)**	**0.001**	**1.13 (1.01,1.27)**	**0.040**	1.04 (0.94,1.15)	0.418	0.99 (0.90,1.10)	0.883
Hospital admission	1	**1.17 (1.12,1.23)**	**<0.001**	**1.14 (1.09,1.19)**	**<0.001**	**1.07 (1.02,1.11)**	**0.002**	**1.05 (1.00,1.09)**	**0.030**
	2	**1.21 (1.15,1.27)**	**<0.001**	**1.18 (1.12,1.24)**	**<0.001**	**1.06 (1.02,1.11)**	**0.006**	**1.04 (1.00,1.09)**	**0.044**
Fall†	1	**1.13 (1.07,1.19)**	**<0.001**			1.04 (0.99,1.08)	0.137		
	2	**1.13 (1.07,1.20)**	**<0.001**			1.03 (0.98,1.08)	0.256		

HR: Hazard ratio SD: Standard deviation *Calculated from all available data from Years 1, 2, 4 and 6

**Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls and as an adjustment in competing risk models for fragility fracture and hospital admission

Model 1: Adjusted for the four-level sex-race variable and age

Model 2: Models for level were additionally adjusted for height, weight-for-height residual, physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were additionally adjusted for diet quality

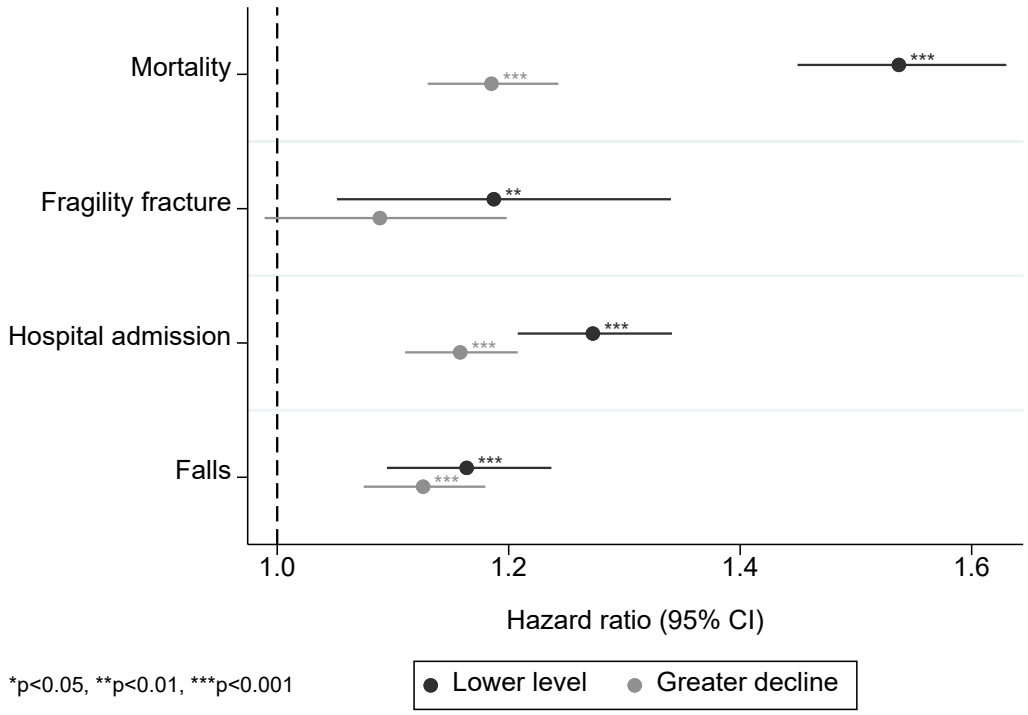
†Competing risk analysis for falls was not possible as competing events (deaths occurring before an individual's first fall) would only occur after the censoring date (latest date at which they had experienced no falls and had complete data for previous fall questions).

Significant associations ($p<0.05$) are highlighted in bold and red

3.5.4 Gait speed level and change in relation to adverse outcomes

Relationships between gait speed level and change and risk of adverse health outcomes are shown in Figure 26 and Table 29. Apart from the non-significant association between gait speed decline and risk of fragility fracture, lower level and greater loss of gait speed were each associated with increased risk of all outcomes in Cox models. The relationship between gait speed level and risk of fragility fracture was not robust in the competing risk model.

Figure 26: Risk of adverse outcome per SD decrease in gait speed level and per SD increase in gait speed decline



Mean level and change were calculated using data from Years 2, 3, 4, 5 and 6

Change measure was ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Models for level were adjusted for sex, race, age, height, weight-for-height residual, physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were adjusted for sex, race, age and diet quality

For fragility fractures, hospital admissions and falls, an indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models

Table 29: Risk of adverse outcomes per SD decrease in gait speed level and per SD increase in gait speed decline

Outcome	Model	Mean gait speed level over Years 1-6 (z-score)*				Gait speed decline over Years 1-6 (z-score)**			
		Stratified Cox model		Competing risk model		Stratified Cox model		Competing risk model	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Death	1	**1.50 (1.42,1.59)**	**<0.001**			**1.19 (1.14,1.25)**	**<0.001**		
	2	**1.54 (1.45,1.63)**	**<0.001**			**1.19 (1.13,1.24)**	**<0.001**		
Fragility fracture	1	**1.14 (1.02,1.28)**	**0.021**	1.02 (0.91,1.14)	0.728	1.09 (0.99,1.20)	0.076	1.02 (0.93,1.13)	0.608
	2	**1.19 (1.05,1.34)**	**0.006**	1.04 (0.93,1.17)	0.514	1.09 (0.99,1.20)	0.082	1.03 (0.93,1.13)	0.604
Hospital admission	1	**1.26 (1.20,1.33)**	**<0.001**	**1.23 (1.17,1.29)**	**<0.001**	**1.17 (1.12,1.22)**	**<0.001**	**1.15 (1.10,1.20)**	**<0.001**
	2	**1.27 (1.21,1.34)**	**<0.001**	**1.24 (1.17,1.31)**	**<0.001**	**1.16 (1.11,1.21)**	**<0.001**	**1.14 (1.09,1.19)**	**<0.001**
Fall	1	**1.17 (1.11,1.24)**	**<0.001**			**1.13 (1.08,1.18)**	**<0.001**		
	2	**1.16 (1.09,1.24)**	**<0.001**			**1.13 (1.07,1.18)**	**<0.001**		

HR: Hazard ratio SD: Standard deviation

*Calculated from all available data from Years 2, 3, 4, 5 and 6

**Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls and as an adjustment in competing risk models for fragility fracture and hospital admission

Model 1: Adjusted for the four-level sex-race variable and age

Model 2: Models for level were additionally adjusted for height, weight-for-height residual, physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were additionally adjusted for diet quality

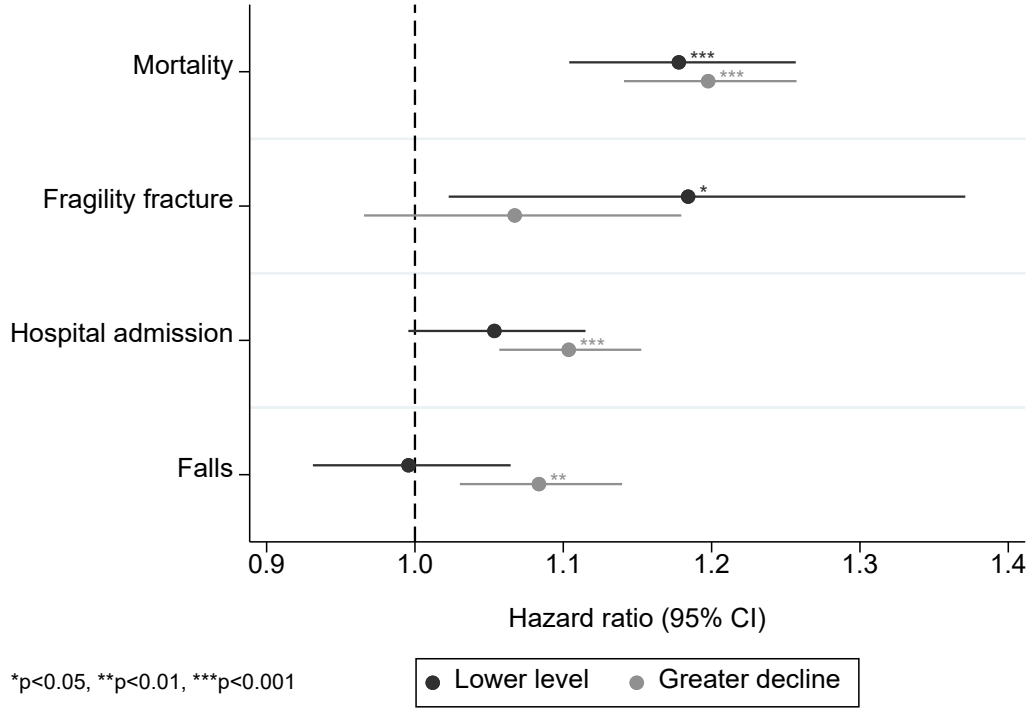
[†]Competing risk analysis for falls was not possible as competing events (deaths occurring before an individual's first fall) would only occur after the censoring date (latest date at which they had experienced no falls and had complete data for previous fall questions).

Significant associations ($p<0.05$) are highlighted in bold and red

3.5.5 ALM level and change in relation to adverse outcomes

Figure 27 and Table 30 present associations between level and change in ALM and risk of subsequent adverse events. In Cox models, lower ALM was related to higher risk of mortality and fragility fracture whereas greater decline in ALM was related to increased risk of mortality, hospital admission and falls. The association between ALM level and fragility fracture was not significant in competing risk models.

Figure 27: Risk of adverse outcome per SD decrease in ALM level and per SD increase in ALM decline



Mean level and change were calculated using data from Years 1, 2, 3, 4, 5 and 6

Change measure was ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Models for level were adjusted for sex, race, age, height, physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were adjusted for sex, race, age and diet quality

For fragility fractures, hospital admissions and falls, an indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models

Table 30: Risk of adverse outcomes per SD decrease in ALM level and per SD increase in ALM decline

Outcome	Model	Mean ALM level over Years 1-6 (z-score)*				ALM decline over Years 1-6 (z-score)**			
		Stratified Cox model		Competing risk model		Stratified Cox model		Competing risk model	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Death	1	**1.13 (1.08,1.19)**	**<0.001**			**1.20 (1.15,1.26)**	**<0.001**		
	2	**1.18 (1.10,1.26)**	**<0.001**			**1.20 (1.14,1.26)**	**<0.001**		
Fragility fracture	1	**1.16 (1.03,1.31)**	**0.016**	1.10 (0.97,1.24)	0.128	1.06 (0.96,1.17)	0.244	0.99 (0.91,1.09)	0.869
	2	**1.18 (1.02,1.37)**	**0.024**	1.11 (0.96,1.29)	0.149	1.07 (0.97,1.18)	0.202	1.00 (0.91,1.10)	0.994
Hospital admission	1	1.03 (0.98,1.07)	0.288	1.02 (0.97,1.06)	0.48	**1.11 (1.06,1.16)**	**<0.001**	**1.10 (1.05,1.14)**	**<0.001**
	2	1.05 (1.00,1.11)	0.071	1.05 (0.99,1.11)	0.097	**1.10 (1.06,1.15)**	**<0.001**	**1.09 (1.04,1.14)**	**<0.001**
Fall	1	1.00 (0.95,1.06)	0.875			**1.08 (1.03,1.14)**	**0.001**		
	2	1.00 (0.93,1.06)	0.898			**1.08 (1.03,1.14)**	**0.002**		

HR: Hazard ratio SD: Standard deviation

*Calculated from all available data from Years 1, 2, 3, 4, 5 and 6

**Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls and as an adjustment in competing risk models for fragility fracture and hospital admission

Model 1: Adjusted for the four-level sex-race variable and age

Model 2: Models for level were additionally adjusted for height, physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were additionally adjusted for diet quality

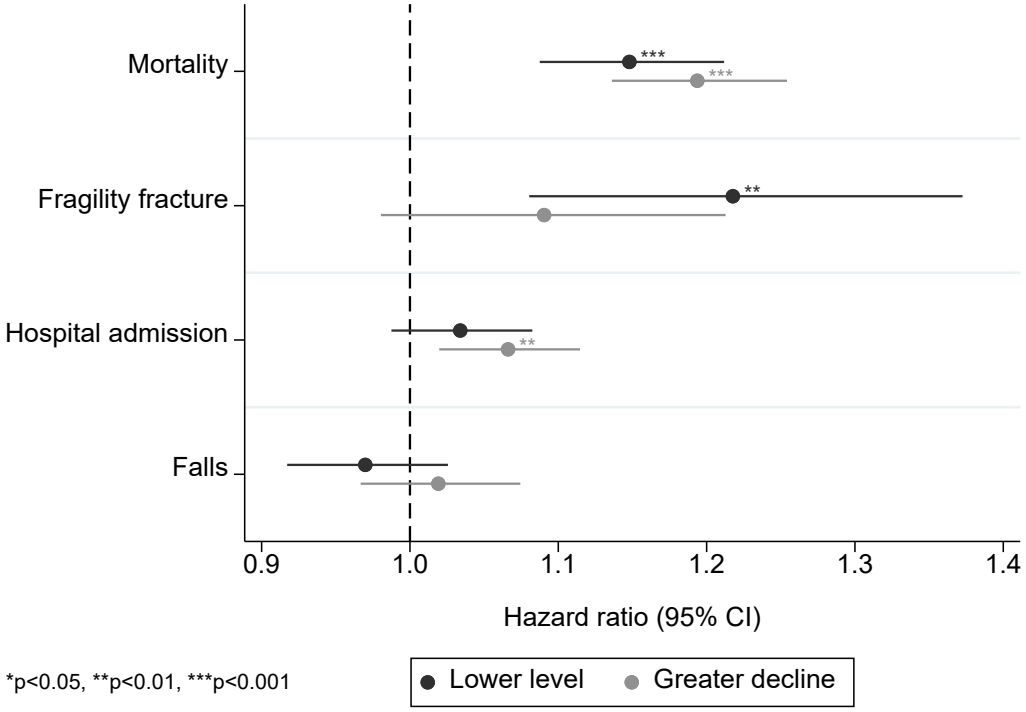
[†]Competing risk analysis for falls was not possible as competing events (deaths occurring before an individual's first fall) would only occur after the censoring date (latest date at which they had experienced no falls and had complete data for previous fall questions).

Significant associations ($p<0.05$) are highlighted in bold and red

3.5.6 Fat mass level and change in relation to adverse outcomes

Relationships between fat mass level and change and risk of adverse outcomes are shown in Figure 28 and Table 31. As was the case for ALM, lower levels were related to increased risk of mortality and fragility fracture and greater declines were associated with increased risk of mortality and hospital admission in Cox models. Relationships were similar in both Cox and competing risk models.

Figure 28: Risk of adverse outcome per SD decrease in fat mass level and per SD increase in fat mass decline



Mean level and change were calculated using data from Years 1, 2, 3, 4, 5 and 6

Change measure was ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Models for level were adjusted for sex, race, age, height, physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were adjusted for sex, race, age and diet quality

For fragility fractures, hospital admissions and falls, an indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models

Table 31: Risk of adverse outcomes per SD decrease in fat mass level and per SD increase in fat mass decline

Outcome	Model	Mean fat mass level over Years 1-6 (z-score)*				Fat mass decline over Years 1-6 (z-score)**			
		Stratified Cox model		Competing risk model		Stratified Cox model		Competing risk model	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Death	1	**1.14 (1.08,1.19)**	**<0.001**			**1.20 (1.14,1.26)**	**<0.001**		
	2	**1.15 (1.09,1.21)**	**<0.001**			**1.19 (1.14,1.25)**	**<0.001**		
Fragility fracture	1	**1.22 (1.09,1.36)**	**<0.001**	**1.16 (1.04,1.30)**	**0.009**	1.10 (1.00,1.22)	0.061	1.02 (0.93,1.12)	0.680
	2	**1.22 (1.08,1.37)**	**0.001**	**1.16 (1.03,1.31)**	**0.014**	1.09 (0.98,1.21)	0.111	1.01 (0.91,1.11)	0.866
Hospital admission	1	1.02 (0.98,1.07)	0.291	1.01 (0.97,1.05)	0.728	**1.08 (1.04,1.13)**	**<0.001**	**1.08 (1.03,1.12)**	**0.001**
	2	1.03 (0.99,1.08)	0.155	1.02 (0.97,1.07)	0.403	**1.07 (1.02,1.11)**	**0.005**	**1.06 (1.01,1.11)**	**0.011**
Fall	1	0.97 (0.92,1.02)	0.243			1.03 (0.98,1.08)	0.257		
	2	0.97 (0.92,1.03)	0.283			1.02 (0.97,1.07)	0.481		

HR: Hazard ratio SD: Standard deviation

*Calculated from all available data from Years 1, 2, 3, 4, 5 and 6

**Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls and as an adjustment in competing risk models for fragility fracture and hospital admission

Model 1: Adjusted for the four-level sex-race variable and age

Model 2: Models for level were additionally adjusted for height, physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were additionally adjusted for diet quality

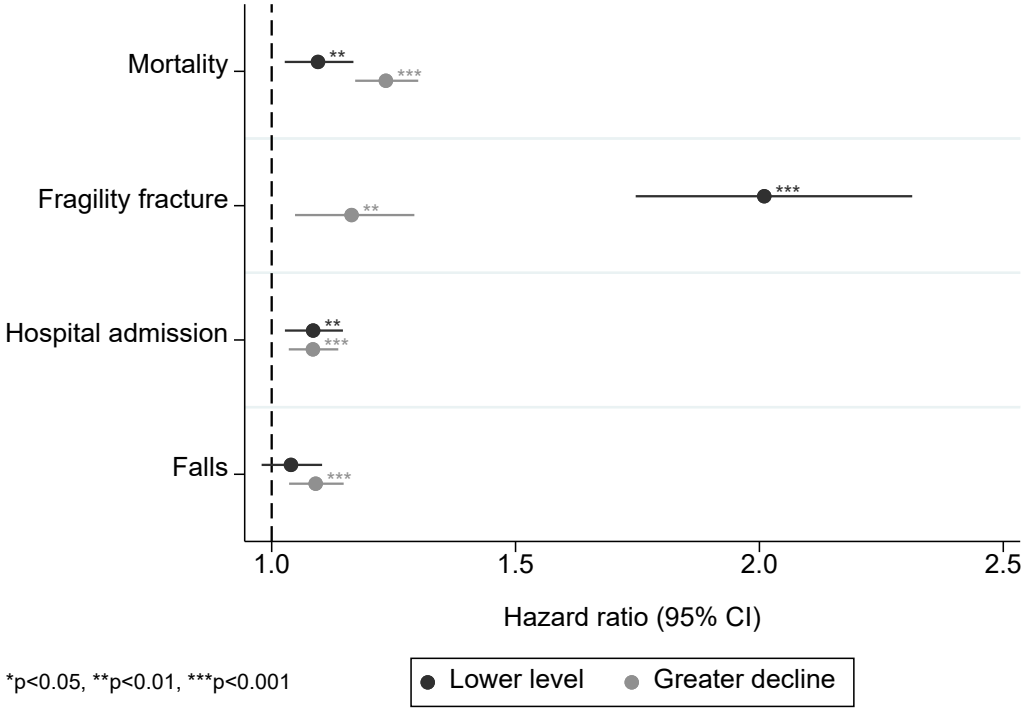
[†]Competing risk analysis for falls was not possible as competing events (deaths occurring before an individual's first fall) would only occur after the censoring date (latest date at which they had experienced no falls and had complete data for previous fall questions).

Significant associations ($p<0.05$) are highlighted in bold and red

3.5.7 Hip BMD level and change in relation to adverse outcomes

Associations between hip BMD level and change in relation to risk of adverse health events are presented in Figure 29 and Table 32. In Cox models, lower level and accelerated loss of hip BMD were associated with greater risk of mortality, fragility fracture and hospital admission; greater decline was also related to increased falls risk. Results from competing risk models were similar apart from a weakening of the association between hip BMD change and risk of fragility fracture.

Figure 29: Risk of adverse outcome per SD decrease in hip BMD level and per SD increase in hip BMD decline



Mean level and change were calculated using data from Years 1, 3 and 5

Change measure was ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Models for level were adjusted for sex, race, age, height, weight-for-height residual, physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were adjusted for sex, race, age and diet quality

For fragility fractures, hospital admissions and falls, an indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models

Table 32: Risk of adverse outcomes per SD decrease in hip BMD level and per SD increase in hip BMD decline

Outcome	Model	Mean hip BMD level over Years 1-6 (z-score)*				Hip BMD decline over Years 1-6 (z-score)**			
		Stratified Cox model		Competing risk model		Stratified Cox model		Competing risk model	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Death	1	**1.13 (1.07,1.20)**	**<0.001**			**1.25 (1.19,1.32)**	**<0.001**		
	2	**1.09 (1.03,1.17)**	**0.006**			**1.23 (1.17,1.30)**	**<0.001**		
Fragility fracture	1	**1.88 (1.67,2.11)**	**<0.001**	**1.77 (1.57,2.00)**	**<0.001**	**1.17 (1.06,1.30)**	**0.002**	1.10 (0.99,1.22)	0.071
	2	**2.01 (1.75,2.31)**	**<0.001**	**1.89 (1.64,2.19)**	**<0.001**	**1.16 (1.05,1.29)**	**0.005**	1.09 (0.98,1.21)	0.096
Hospital admission	1	**1.06 (1.02,1.11)**	**0.008**	**1.07 (1.02,1.11)**	**0.007**	**1.08 (1.04,1.13)**	**0.001**	**1.06 (1.01,1.11)**	**0.012**
	2	**1.09 (1.03,1.15)**	**0.004**	**1.08 (1.03,1.14)**	**0.004**	**1.08 (1.04,1.14)**	**0.001**	**1.06 (1.01,1.11)**	**0.014**
Fall	1	1.02 (0.97,1.07)	0.548			**1.09 (1.04,1.15)**	**<0.001**		
	2	1.04 (0.98,1.10)	0.202			**1.09 (1.04,1.15)**	**0.001**		

HR: Hazard ratio SD: Standard deviation

*Calculated from all available data from Years 1, 3 and 5.

**Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls and as an adjustment in competing risk models for fragility fracture and hospital admission

Model 1: Adjusted for the four-level sex-race variable and age

Model 2: Models for level were additionally adjusted for height, weight-for-height residual, physical activity, alcohol consumption, diet quality, education and number of systems medicated; models for change were additionally adjusted for diet quality

[†]Competing risk analysis for falls was not possible as competing events (deaths occurring before an individual's first fall) would only occur after the censoring date (latest date at which they had experienced no falls and had complete data for previous fall questions).

Significant associations ($p<0.05$) are highlighted in bold and red

3.5.8 Sensitivity analyses

Along with the main analysis, the following sensitivity analyses were performed: models for level adjusted for the change parameter and vice versa; analysis restricted to individuals with complete data from Years 1-6 for each parameter in turn; additionally adjusted for baseline characteristics associated with risk of at least two adverse outcomes to improve precision; and assessment of non-linear relationships between level and change exposures and risk of adverse outcomes by examining statistical significance and effect size of quadratic terms for these exposures. Results that describe the relationship between baseline characteristics and risk of adverse outcomes are presented in the next section as this information informs some of the sensitivity analyses, results of which are presented in Section 3.5.8.2.

The methods for examining the relationship between baseline characteristics and adverse outcomes is outlined in Section 2.6.5.8 and methods for the sensitivity analyses are included in Section 2.6.5.9.

3.5.8.1 Baseline characteristics in relation to risk of adverse outcomes

Associations between baseline participant characteristics and risk of each adverse health outcome were explored for completeness and to determine the characteristics to adjust for to improve precision in sensitivity analysis. A summary of the associations between baseline characteristics and each adverse outcome is presented in Table 33 with a detailed presentation of all relationships in Appendix 31 – Appendix 34.

Older age was associated with increased risk of all adverse outcomes; greater weight-for-height residual was related to reduced risk of death and fragility fracture but increased risk of falls (after adjustment for previous falls); ever smoking was associated with increased risk of mortality and hospital admission; and lower physical activity only predicted increased risk of mortality. Lower educational attainment was related to greater risk of mortality but reduced fall risk and not owner occupying one's home was associated with increased risk of mortality, fragility fracture and hospital admission. A higher number of systems medicated was related to greater risk of all adverse outcomes apart from fragility fractures. All associations described above were significant ($p<0.05$) in mutually-adjusted analyses.

As outlined in Section 2.6.5.6, for the main analysis, models relating levels of musculoskeletal and body composition parameters to risk of adverse outcomes were adjusted for the four-level sex-

race variable, age and the baseline characteristics that were related to the levels of two or more of the musculoskeletal and body composition parameters in mutually-adjusted analysis; an analogous approach was used when the predictor was change in the parameter. Therefore, models for level were additionally adjusted for height, weight-for-height residual (not included for ALM and fat mass due to collinearity), alcohol consumption, physical activity, diet quality, educational attainment and number of systems medicated whereas models for change were only additionally adjusted for diet quality.

Part of the sensitivity analysis involved further adjustment for baseline characteristics that were associated with risk of at least two adverse outcomes in mutually-adjusted analysis, irrespective of their association with the musculoskeletal and body composition parameters. Therefore, for this sensitivity analysis, models for level were additionally adjusted for smoking status and housing tenure whereas models for change were additionally adjusted for weight-for-height residual, smoking status, educational attainment, housing tenure and number of systems medicated. All models included the four-level sex-race variable and age as adjustments.

Table 33: Baseline participant characteristics in relation to risk of adverse health outcomes (pooled and adjusted for age, sex and race)

Baseline characteristic	Death	Fragility fracture		Hospital admission		Falls
	Cox*	Cox*	CR**	Cox*	CR**	Cox*
Older age						
Shorter height						
Greater weight-for-height residual	†	†	†			
Ever smoked						
Higher alcohol consumption	†					
Lower physical activity						
Lower Healthy Eating Index						
Lower educational attainment			†			†
Not owner occupying one's home						
Higher number of systems medicated						

Significant (p<0.05) after adjustment for age, sex and race

Significant (p<0.05)in mutually-adjusted analysis

*Cox model **Competing risk model

† Baseline characteristic was associated with reduced risk of the adverse event; all other associations reflect increases in risk

3.5.8.2 Results from sensitivity analyses

Overall, results from the various sensitivity analyses were similar to those from the main analysis as shown by the comparison of results in Table 34. The sensitivity analysis results that differed most from the main results were those that were restricted to individuals with complete data from Years 1-6 which yielded fewer robust associations. This may be because individuals excluded from the restricted analyses include those leaving the study early with poor health who are more

likely to have lower levels and accelerated declines in musculoskeletal and body composition parameters along with increased risk of poor health outcomes. Therefore, excluding these individuals is likely to underestimate the magnitude of the associations between the musculoskeletal and body composition parameters and adverse health outcomes.

Quadratic effects of levels and changes in grip strength and gait speed were either non-significant or small in magnitude. Some significant quadratic effects were observed for levels and changes in ALM, fat mass and hip BMD in relation to risk of mortality and hospital admission, suggesting that the rate of increase in the risk of these events was somewhat greater with progressively lower levels and greater declines in these parameters. Detailed results for all sensitivity analyses are provided in Appendix 35 – Appendix 41.

Table 34: Level and change in musculoskeletal and body composition parameters in relation to risk of adverse health outcomes (main results and sensitivity analyses)

Analyses	Parameter	Predictor	Death	Fragility fracture		Hospital admission		Falls
			Cox*	Cox*	CR**	Cox*	CR**	Cox*
Main analysis (adjustments included in 'level' models if associated with levels of ≥2 parameters; analogous approach used to determine adjustments for 'change' models)	Grip strength	Lower level	■	■	■	■	■	■
		Greater decline	■			■	■	
	Gait speed	Lower level	■	■		■	■	■
		Greater decline	■			■	■	■
	ALM	Lower level	■	■				
		Greater decline	■			■	■	■
	Fat mass	Lower level	■	■	■			
		Greater decline	■			■	■	
	Hip BMD	Lower level	■	■	■	■	■	
		Greater decline	■	■		■	■	■
Models for level were adjusted for change parameter and vice versa	Grip strength	Lower level	■	■	■	■	■	■
		Greater decline	■			■	⊠	
	Gait speed	Lower level	■	■		■	■	■
		Greater decline	■			■	■	■
	ALM	Lower level	■	■				
		Greater decline	■			■	■	■
	Fat mass	Lower level	■	■	■			
		Greater decline	■			■	■	
	Hip BMD	Lower level	■	■	■	■	■	
		Greater decline	■	■	⊠	■	■	■
Analysis restricted to individuals with complete data from Years 1-6 for the corresponding parameter	Grip strength	Lower level	■	■	■	■	■	■
		Greater decline	■			■	⊠	
	Gait speed	Lower level	■	⊠		■	■	■
		Greater decline	■			■	■	■
	ALM	Lower level	■	■				
		Greater decline	■			■	■	■
	Fat mass	Lower level	■	■	■			
		Greater decline	■			⊠	⊠	
	Hip BMD	Lower level	⊠	■	■	■	■	
		Greater decline	■	■		■	■	■
Additionally adjusted for baseline characteristics associated with risk of ≥2 adverse outcomes[+]	Grip strength	Lower level	■	■	⊠	■	■	■
		Greater decline	■			■	⊠	
	Gait speed	Lower level	■	■		■	■	■
		Greater decline	■	⊠		■	■	■
	ALM	Lower level	■	■				
		Greater decline	■			■	■	■
	Fat mass	Lower level	■	■	■			
		Greater decline	■			■	■	
	Hip BMD	Lower level	■	■	■	■	■	
		Greater decline	■	■		■	■	■

■ Significant ($p<0.05$) in fully-adjusted model

⊠ Association differs compared to corresponding association in main analysis

*Cox model stratified on previous events **Competing risk model adjusted for previous events

Baseline characteristics included in fully-adjusted main analysis models for 'level' were: sex-race variable, age, height, weight-for-height residual (not included in models for ALM and fat mass), alcohol consumption, diet quality, physical activity, education and number of systems medicated. Baseline

characteristics included in fully-adjusted main analysis models for 'change' were: sex-race variable, age, and diet quality.

[+]Models for level were additionally adjusted for smoking status and housing tenure; models for change were additionally adjusted for weight-for-height residual, smoking status, physical activity, education, housing tenure and number of systems medicated.

3.5.9 Associations between previous changes in musculoskeletal and body composition characteristics and risk of adverse outcomes after accounting for current measures of the characteristic

Table 35 presents: the risk of adverse outcomes according to declines in musculoskeletal and body composition parameters after Year 4, conditional on levels at Year 6; and also declines in parameters after Year 2, conditional on levels at Years 4 and 6. These time-points differ for hip BMD which was measured at Years 1, 3 and 5 as opposed to Years 2,4 and 6. Greater grip strength decline after Year 2 was associated with reduced risk of fragility fracture, independent of grip strength at Years 4 and 6. Decline in gait speed from Years 2 and 4 was not strongly related to risk of adverse outcomes after conditioning on current gait speed measurements. Greater decline in ALM after Year 4 was related to increased risk of hospital admission, independent of ALM at Year 6; greater decline in ALM after Year 2 was related to increased risk of mortality and falls, independent of ALM at Years 4 and 6. Greater loss of fat mass from Years 2 and 4 was related to increased risk of mortality, independent of current fat mass. Greater hip BMD decline from Year 3 was associated with greater risk of mortality, hospital admission and falls, independent of hip BMD at Year 5; greater decline in hip BMD after Year 1 was related to increased mortality risk, independent of hip BMD at Years 3 and 5. These associations described were robust after adjustment for sex, race and age and in fully-adjusted analysis.

The methods corresponding to results in this section are included in Section 2.6.5.10.

Table 35: Associations between previous changes in musculoskeletal and body composition characteristics and risk of adverse outcomes after accounting for current measures of the characteristic

Residual	Year	Model	Death		Fragility fracture		Hospital admission		Fall	
			HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Grip strength	*4**	1	1.01 (0.95,1.07)	0.834	1.01 (0.90,1.15)	0.823	1.02 (0.97,1.07)	0.395	0.99 (0.94,1.05)	0.815
		2	1.01 (0.95,1.07)	0.852	1.00 (0.88,1.13)	0.973	1.01 (0.96,1.07)	0.606	0.99 (0.94,1.05)	0.766
	*2***	1	1.05 (0.98,1.11)	0.146	**0.88 (0.78,0.99)**	**0.033**	0.95 (0.90,1.00)	0.052	0.96 (0.91,1.01)	0.152
		2	1.03 (0.97,1.10)	0.311	**0.87 (0.77,0.99)**	**0.030**	**0.94 (0.89,0.99)**	**0.015**	0.95 (0.90,1.01)	0.074
Gait speed	*4**	1	0.96 (0.90,1.03)	0.258	**1.14 (1.01,1.28)**	**0.033**	1.05 (0.99,1.10)	0.079	1.02 (0.97,1.08)	0.397
		2	0.95 (0.89,1.02)	0.148	1.11 (0.99,1.25)	0.086	**1.06 (1.00,1.11)**	**0.042**	1.03 (0.97,1.09)	0.388
	*2***	1	1.04 (0.98,1.10)	0.233	0.97 (0.86,1.09)	0.648	1.01 (0.96,1.06)	0.658	1.03 (0.97,1.09)	0.350
		2	1.04 (0.97,1.10)	0.280	0.96 (0.86,1.09)	0.556	1.00 (0.95,1.06)	0.859	1.03 (0.97,1.09)	0.385
ALM	*4**	1	1.04 (0.98,1.10)	0.245	1.04 (0.92,1.19)	0.501	**1.08 (1.02,1.13)**	**0.004**	1.02 (0.96,1.08)	0.605
		2	1.03 (0.96,1.09)	0.419	1.03 (0.90,1.17)	0.683	**1.08 (1.02,1.13)**	**0.006**	1.01 (0.96,1.08)	0.651
	*2***	1	**1.11 (1.04,1.18)**	**0.001**	0.95 (0.84,1.08)	0.461	**1.05 (1.00,1.11)**	**0.047**	**1.10 (1.04,1.16)**	**0.001**
		2	**1.11 (1.04,1.18)**	**0.002**	0.95 (0.83,1.08)	0.418	1.05 (0.99,1.10)	0.087	**1.11 (1.04,1.17)**	**<0.001**
Fat mass	*4**	1	**1.12 (1.05,1.19)**	**<0.001**	1.01 (0.89,1.14)	0.900	1.05 (1.00,1.11)	0.065	1.02 (0.97,1.08)	0.468
		2	**1.10 (1.03,1.17)**	**0.003**	0.99 (0.87,1.13)	0.891	1.04 (0.98,1.09)	0.166	1.01 (0.95,1.07)	0.760
	*2***	1	**1.11 (1.04,1.18)**	**0.001**	0.98 (0.86,1.12)	0.763	1.05 (1.00,1.10)	0.077	1.03 (0.97,1.09)	0.319
		2	**1.09 (1.03,1.17)**	**0.006**	0.98 (0.86,1.11)	0.731	1.03 (0.98,1.08)	0.304	1.03 (0.97,1.09)	0.333
Hip BMD	*3**	1	**1.22 (1.15,1.29)**	**<0.001**	1.08 (0.96,1.21)	0.197	**1.08 (1.03,1.14)**	**0.002**	**1.08 (1.02,1.14)**	**0.005**
		2	**1.22 (1.15,1.29)**	**<0.001**	1.07 (0.95,1.20)	0.273	**1.07 (1.02,1.13)**	**0.008**	**1.07 (1.01,1.13)**	**0.022**
	*1***	1	**1.12 (1.06,1.18)**	**<0.001**	1.11 (1.00,1.24)	0.052	1.02 (0.97,1.07)	0.365	1.04 (0.99,1.10)	0.128
		2	**1.12 (1.06,1.19)**	**<0.001**	1.11 (0.99,1.24)	0.063	1.04 (0.99,1.09)	0.155	1.05 (1.00,1.11)	0.068

HR: Hazard ratio; P: P-value; ALM: Appendicular lean mass; BMD: Bone mineral density

Hazard ratios per SD greater decline in parameter over various years, conditional on parameter at future years, are presented

*Declines conditional on measurements at Year 6; greater declines correspond to higher levels at Year 4 than expected from Year 6 measurements

**Declines conditional on measurements at Years 4 and 6; greater declines correspond to higher levels at Year 2 than expected from measurements at Years 4 and 6

Hip BMD was ascertained at Years 1, 3 and 5 as opposed to Years 2, 4 and 6

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls

Model 1: Adjusted for the four-level sex-race variable and age

Model 2: Models for level were additionally adjusted for height, weight-for-height residual (not included in models for ALM and fat mass) physical activity, alcohol consumption, diet quality, education and number of systems medicated

Significant associations ($p<0.05$) are highlighted in bold and red

3.5.10 Combined impact of levels of grip strength and hip BMD in relation to adverse outcomes

Of the 2603 participants who were included in this part of the analysis, 1202 (46.2%) had neither low grip strength nor low hip BMD, 533 (20.5%) had low grip strength only, 524 (20.1%) had low hip BMD only and 344 (13.2%) had low grip strength and low hip BMD. For both characteristics, low values were characterised as those in the bottom sex-specific third of the distribution.

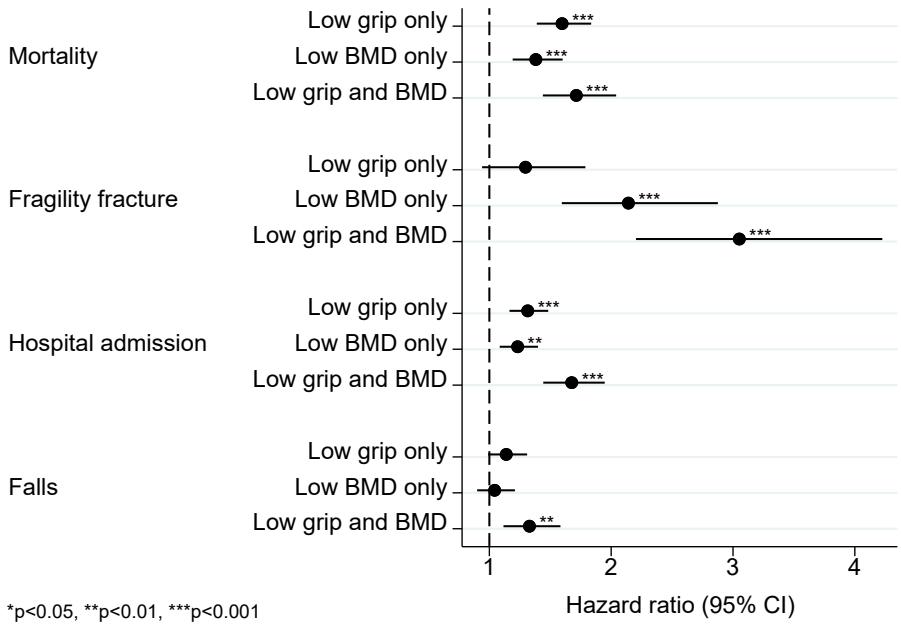
The risk of adverse outcomes according to combinations of levels of grip strength and hip BMD is illustrated in Figure 30. Having both low grip strength and low hip BMD was related to greater risk of mortality and falls compared to participants with low hip BMD only but these differences were not substantial in comparison to participants with low grip strength only. For fragility fracture and hospital admission, having both conditions was related to greater risk of these outcomes compared to having either condition in isolation. For example, compared to participants without low grip strength or hip BMD, fully-adjusted hazard ratios (95% CI) for fragility fracture among those with low grip strength only, low hip BMD only and both low grip strength and hip BMD were 1.30 (0.94,1.79), 2.14 (1.59,2.88) and 3.05 (2.20,4.23) respectively.

It was not possible to conduct analyses using thresholds for sarcopenia and osteoporosis from the EWGSOP2[13] definition (grip strength <27kg and <16 kg among men and women respectively) and the WHO[226] definition (hip BMD ≤0.64 kg/m^2 [2.5 SD or more below the mean of 20-29 year-old non-Hispanic white women from NHANES III]), respectively. This is because only 19 (0.6%) participants had both low grip strength and low hip BMD according to these criteria.

None of the interactions examined between continuously distributed levels of grip strength and hip BMD in relation to the adverse outcomes were statistically significant after adjustment for both sex, race and age and in fully-adjusted analysis.

The methods corresponding to results in this section are included in Section 2.6.5.11.

Figure 30: Risk of adverse outcomes according to combinations of levels of grip strength and hip BMD



Mean levels were calculated using data from Years 1, 2, 4 and 6 for grip strength and Years 1, 3 and 5 for hip BMD

Models were adjusted for sex, race, age, height, weight-for-height residual, alcohol consumption, physical activity, diet quality, education and number of systems medicated

For fragility fractures, hospital admissions and falls, an indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models

Participants with values in the bottom sex-specific third of the distribution were regarded as having low levels.

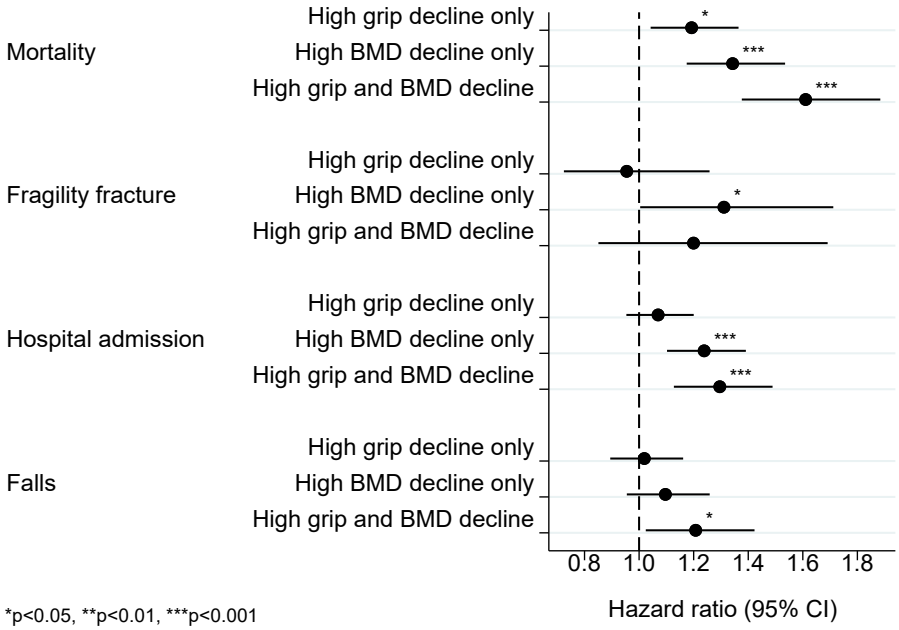
Estimates and p-values are in relation to participants without low grip strength or low hip BMD

3.5.11 Combined impact of changes in grip strength and hip BMD in relation to adverse outcomes

Of the 2603 participants, 1200 (46.1%) had neither high decline (highest sex-specific third of the distribution) in grip strength or hip BMD, 535 (20.6%) had high decline in grip strength only, 535 (20.6%) had high decline in hip BMD only and 333 (12.8%) had high decline in grip strength and hip BMD. The risk of adverse outcomes according to combinations of changes in grip strength and hip BMD is illustrated in Figure 31. Risk of mortality for having high declines in both grip strength and hip BMD was greater than for the other three categories. Compared to participants without high declines in grip strength or hip BMD, fully-adjusted hazard ratios (95% CI) for mortality among those with high declines in grip strength only, hip BMD only and in both grip strength and

hip BMD were 1.19 [1.04,1.36], 1.34 [1.17,1.54] and 1.61 [1.38,1.88] respectively. For fracture and falls, high declines in both characteristics were not associated with greater risk of these outcomes compared to only experiencing declines in either grip strength or hip BMD. Participants with high declines in both characteristics had greater risk of hospital admission compared to those with high decline in grip strength only but similar risks when compared to participants with high declines in hip BMD only.

Figure 31: Risk of adverse outcomes according to combinations of changes in grip strength and hip BMD



Changes were calculated using data from Years 1, 2, 4 and 6 for grip strength and Years 1, 3 and 5 for hip BMD

Change measure was ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Models were adjusted for sex, race, age and diet quality

For fragility fractures, hospital admissions and falls, an indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models

Participants with declines in the top sex-specific third of the distribution were regarded as having high declines

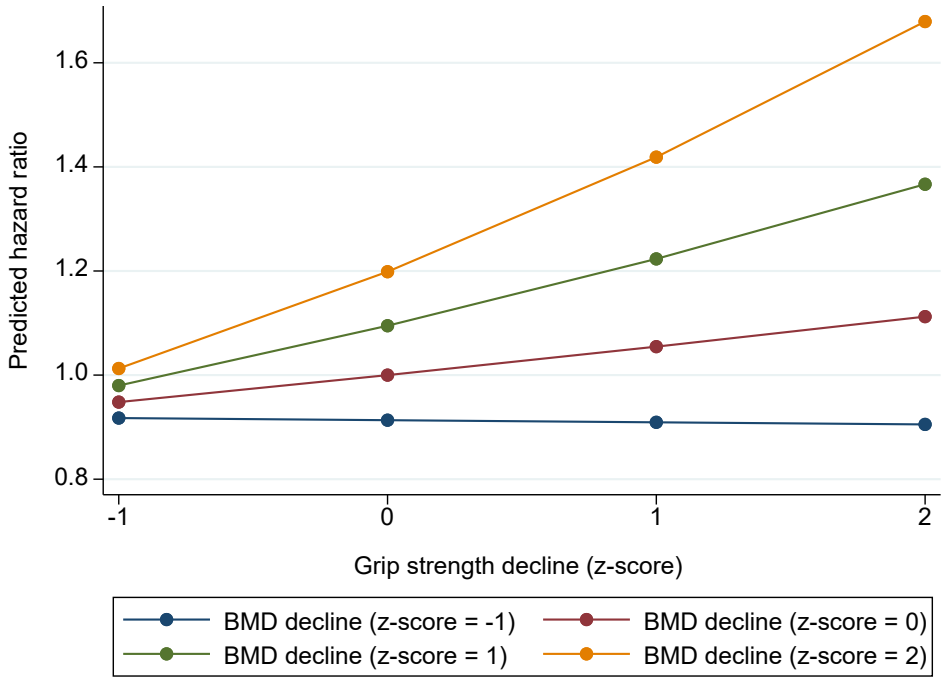
Estimates and p-values are in relation to participants without high declines in grip strength or BMD

Of all continuous interactions examined between the change measures for grip strength and hip BMD, only the interaction in relation to risk of falls was statistically significant both after

adjustment for sex, race and age and in fully-adjusted analysis (p<0.03). The predicted hazard ratios for different combinations of grip strength and BMD changes in relation to this outcome are illustrated in Figure 32. For participants with average changes in hip BMD (z-score=0), changes in grip strength were weakly correlated with risk of falls whereas among participants with high declines in hip BMD (z-score=2), there was a much stronger association between greater declines in grip strength and greater risk of falls. Similarly, degree of decline in hip BMD was more strongly associated with risk of falls among participants experiencing greater losses of grip strength compared to those who were not.

The methods corresponding to results in this section are included in Section 2.6.5.11.

Figure 32: Predicted hazard ratios for combinations of grip strength and hip BMD declines in relation to risk of falls



Changes were calculated using data from Years 1, 2, 4 and 6 for grip strength and Years 1, 3 and 5 for hip BMD

Change measure was ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Higher z-scores indicate greater declines; z-scores of zero for both grip strength and hip BMD are used for the reference category and are assigned a hazard ratio of one.

3.5.12 Summary of findings

3.5.12.1 Summary of findings from the main analysis

A summary of results from the main analysis for level and change in musculoskeletal and body composition parameters in relation to risk of adverse health outcomes is presented in Table 36. Lower levels and greater declines of each musculoskeletal and body composition parameter were associated with increased risk of mortality and, with the exception of ALM and fat mass level, also hospital admission. Lower levels of each parameter and greater declines in hip BMD were related to increased risk of fragility fracture when Cox models were implemented; only associations regarding levels of grip strength, fat mass and hip BMD were similar for competing risk models. Lower levels of grip strength, greater declines in ALM and hip BMD and both lower levels and greater declines in gait speed were related to increased risk of falls.

Table 36: Level and change in musculoskeletal and body composition parameters in relation to risk of adverse health outcomes (results from the main analysis)

Parameter	Predictor	Death	Fragility fracture		Hospital admission		Falls
		Cox*	Cox*	CR**	Cox*	CR**	Cox*
Grip strength	Lower level						
	Greater decline						
Gait speed	Lower level						
	Greater decline						
ALM	Lower level						
	Greater decline						
Fat mass	Lower level						
	Greater decline						
Hip BMD	Lower level						
	Greater decline						

Significant ($p<0.05$) in fully-adjusted model

*Cox model stratified on previous events **Competing risk model adjusted for previous events

Baseline characteristics included in fully-adjusted models for 'level' were: sex-race variable, age, height, weight-for-height residual (not included in models for ALM and fat mass), alcohol consumption, diet quality, physical activity, education and number of systems medicated. Baseline characteristics included in fully-adjusted models for 'change' were: sex-race variable, age and diet quality.

3.5.12.2 Summary of findings from the additional analyses

This subsection summarizes results from Sections 3.5.9-3.5.11 on the relationship between previous changes in musculoskeletal and body composition characteristics and adverse outcomes, after accounting for current measures, and results on the combined impact of grip strength and hip BMD in relation to outcomes.

Even after accounting for most recently available measurements, prior declines in ALM, fat mass and hip BMD were related to increased risk of mortality, and prior declines in ALM and hip BMD were also related to hospital admission and falls. In contrast, relationships between previous declines in grip strength and gait speed and adverse outcomes were weak after accounting for most recent measures.

Having both low grip strength and low hip BMD was related to considerably greater risk of fragility fracture and hospital admission compared to having either condition in isolation; for mortality and falls, this was only the case compared to those with low hip BMD only. Having high declines in both grip strength and hip BMD conferred substantially greater risk of mortality compared to experiencing declines in only one of these characteristics; for hospital admission, this was only the case compared to participants with high declines in grip strength only. Evidence of interactions between levels or changes in grip strength and hip BMD in relation to adverse outcomes was weak.

Chapter 4 Discussion

4.1 Chapter summary

This chapter is structured as follows. First, the main findings from the following analyses are recapped and compared with the published literature: description of longitudinal changes in musculoskeletal and body composition characteristics; examination of baseline determinants of level and change in these characteristics; exploration of interrelationships between changes in characteristics; and examination of level and change in characteristics in relation to risk of adverse health outcomes. Second, insights on the use of statistical methods for the description and analysis of longitudinal changes in parameters are presented. Third, the strengths and weaknesses of the thesis are outlined. Finally, the wider implications of the thesis findings are discussed and recommendations for future research are provided.

4.2 Summary of main thesis findings and comparison with previous literature

4.2.1 Longitudinal changes in characteristics

4.2.1.1 Thesis findings

Declines in grip strength, gait speed and hip BMD accelerated with advancing age whereas declines in ALM were linear; fat mass increased, plateaued, and then decreased. Declines were greatest, and the proportion of variance at follow-up explained by baseline level was lowest for gait speed and grip strength, compared to body composition parameters (including BMD).

4.2.1.2 Previous Health ABC publications

Changes in musculoskeletal and body composition parameters over a 9-year duration had not previously been explored in this cohort. However, the findings in this thesis are consistent with those from earlier Health ABC Study publications which measured changes over a shorter duration of time. For example, 3-year declines in knee extensor strength and both total and leg lean mass were correlated although average percentage declines were smaller for leg lean mass

than strength[93]. In a study of changes in body composition over 5 years, lean mass declined whereas fat mass had a period of increase, maintenance and then decline[92] as reported in this thesis.

4.2.1.3 Findings from other cohorts

These findings are also consistent with those from other cohorts. For example, percentage declines in lean mass were less than declines in gait speed and grip strength over a 4-year follow-up in a Chinese cohort, comprising 3018 participants at least 65 years of age[74], and over a 7-year period in the Hertfordshire Cohort Study[227]. In contrast to the findings in this thesis, changes in grip strength over 5 years were quadratic among women and linear among men in the Newcastle 85+ Study[56] and rate of grip strength decline was constant over a 4-year follow-up among participants aged 50-85 years from a Danish cohort[46]. These different conclusions could be due to the varying follow-up times and age ranges of the study participants. Rates of decline in gait speed and grip strength during an 18-year follow-up accelerated over time in the Cardiovascular Health Study[228] and also in the Osteoporotic Fractures in Men (MrOS) Study[121] for total femoral neck BMD over 5 years; these findings are in agreement with those from this thesis. As discussed in Section 4.2.6, a unique aspect of the Health ABC Study, in comparison with other cohorts, is that a wide range of musculoskeletal and body composition parameters were measured at multiple time-points over a long follow-up (9 years).

4.2.2 Determinants of level and change in characteristics

4.2.2.1 Thesis findings

Key baseline determinants associated with lower levels of musculoskeletal and body composition parameters included older age, anthropometry (shorter stature), and lifestyle risk factors (lower physical activity and poorer diet quality). Higher adiposity was related to higher grip strength and hip BMD but slower walking speed. Greater comorbidity was related to lower levels of grip strength and gait speed and higher levels of fat mass. Some relationships between markers of socioeconomic status in relation to levels of parameters were inconsistent. Fewer baseline determinants were related to declines than levels in parameters. For example, only older age and poorer diet quality were associated with greater declines in two or more parameters.

4.2.2.2 Previous literature on determinants: age and anthropometry

Relationships between older age and both poorer and declining musculoskeletal health are well established[229] along with relationships between shorter height and lower grip strength[47 50 54]. The associations identified in this thesis between shorter height and lower ALM and fat mass are consistent with smaller stature reflecting smaller overall size. In this thesis, lower adiposity, as measured by weight-for-height residuals, was related to lower grip strength and hip BMD and higher gait speed as well as reduced decline in gait speed. These findings are consistent with those from previous studies: lower weight-for-height residuals were associated with lower grip strength in ELSA[47]; low BMI is an established risk factor for low BMD[229]; greater BMI was related to lower gait speed in NHANES[230]; and greater weight was related to greater loss of gait speed in SOF[76].

4.2.2.3 Previous literature on determinants: health behaviours

Relationships between health behaviours and musculoskeletal parameters have also been identified previously. For example, the association between ever smoking and slower gait speed among men and in the pooled sample is in agreement with findings from the Hertfordshire Cohort Study of slower gait speed among men who had smoked (there was no association among women[231]). The positive correlation observed between higher alcohol consumption and faster gait speed is similar to findings from the Swiss-based Lausanne Cohort 65+ Study where slower gait speed was reported among non-drinkers compared to light-to-moderate drinkers[232]. The relationship between higher alcohol consumption and lower ALM was in contrast to results from the MINOS Study which reported no relationship between quartiles of alcohol intake and ALM index[233]. However, in this thesis, the mutually-adjusted association between alcohol consumption and ALM was not significant in sex-stratified analyses, suggesting that these associations are not very robust. The rather counterintuitive observation between lower physical activity and reduced fat mass was a surprising result and possibly due to chance but could also be caused by greater comorbidity driving both lower physical activity and fat mass. Relationships observed between lower physical activity and lower levels of musculoskeletal parameters, and poor diet quality in relation to slower gait speed and both low level and greater decline in ALM and hip BMD, are in agreement with the wide body of evidence for the benefits of both physical activity and high diet quality for muscle and bone health[229].

4.2.2.4 Previous literature on determinants: socioeconomic position and comorbidity

In this thesis, some associations regarding markers of socioeconomic position and comorbidity are in agreement with those from previous literature. For example, not owner occupying one's home was related to lower grip strength and greater comorbidity was related to lower level and accelerated decline in grip strength in the English Longitudinal Study of Ageing[47]. In addition, lower educational attainment and greater comorbidity were associated with lower gait speed in the Hertfordshire Cohort Study[231]. However, associations identified among women in this thesis between higher educational attainment and lower grip strength, and between owner occupying one's home and accelerated decline in grip strength, are in contrast to previous literature[50]. Possible reasons for these counterintuitive associations in the Health ABC Study compared to the UK cohorts cited include differences in how educational attainment and home ownership relate to socioeconomic status between the US and the UK, and age and cohort effects from differences in ages and birth dates of participants between studies. The cross-sectional associations between higher comorbidity and greater fat mass can be explained by the well-established link between obesity and increased risk of comorbidities such as cardiovascular disease and diabetes[37]. The relationship identified in this thesis between increased comorbidity and greater hip BMD was unexpected but perhaps unconvincing given that it was not robust in the sex-specific mutually-adjusted models that were examined as part of the sensitivity analyses.

4.2.3 Interrelationships between changes in characteristics

4.2.3.1 Thesis findings

Significant ($p<0.05$) and positive correlations were observed between changes in musculoskeletal and body composition parameters over the 9-year follow-up which suggests that declines in these characteristics co-occur; the strongest correlations were observed between ALM, fat mass and hip BMD ($0.33<r<0.45$, $p<0.001$). One approach to examine the temporal nature of correlations between these parameters involved examining relationships between changes over Years 1-6 in relation to subsequent changes over Years 6-10. When this approach was implemented, declines in ALM were correlated with subsequent declines in grip strength and gait speed; declines in grip strength were related to subsequent declines in gait speed; and declines in all characteristics were related to subsequent declines in hip BMD. However, these correlations were weak ($r<0.19$ for all associations). A more sophisticated approach to examine temporal changes in musculoskeletal and body composition parameters was implemented which involved the use of bivariate dual change score models. However, the majority of these models failed to converge.

4.2.3.2 Previous literature on interrelationships between changes in characteristics

Interrelationships between changes in musculoskeletal and body composition parameters have been explored previously and support the findings in this thesis. A recent systematic review[234] of relationships between changes in muscle and bone parameters reported statistically significant correlations between changes in BMD and changes in the following parameters among adults: grip strength (all studies reported significant correlations[157 235 236]); gait speed[154]; and lean mass (overall correlation coefficient in hip BMD meta-analysis: 0.34 [95% CI: 0.19-0.48])[156 237-240]. Of the 9 studies in the systematic review: one featured both men and women and one featured only men with the rest comprising only women; ages of participants ranged from mid-life to 97 years with the vast majority comprising participants over 65 years of age; and follow-up times ranged from 1-12 years.

Studies of interrelationships between changes in parameters other than BMD were identified in the epidemiological literature review and broadly support the findings in this thesis. For example, among participants in the Health ABC Study, changes in whole body DXA parameters and CT parameters relating to the abdomen and thigh were examined in relation to changes in gait speed over a 4-year follow-up[75]. Increases in thigh intermuscular fat area and decreases in thigh muscle area were associated with greater decline in gait speed among men and women. Although changes in fat mass and gait speed were not significantly correlated over the 9-year follow-up in this thesis, whole body fat mass, rather than thigh intermuscular fat area, was used in this thesis which could explain the weaker associations observed. In a different cohort of 1710 Afro-Caribbean men, 4.5 year declines in grip strength and arm lean mass were positively correlated[54].

However, these studies[54 75 154 156 157 235-240] only examined changes in one parameter in relation to changes in another parameter over the same time interval. Therefore, the evidence presented in this thesis which suggests that declines in muscle mass, strength and function precede declines in hip BMD appears to be novel.

The epidemiological and statistical literature reviews conducted did not identify any studies which had used bivariate dual change score models to investigate changes in musculoskeletal or body composition parameters.

4.2.3.3 Potential biological mechanisms to explain findings

There are several biological mechanisms that may explain the observed interrelationships between changes in musculoskeletal characteristics. First, bidirectional relationships may exist between declines in muscle strength and lean mass. For example, declines in strength, leading to reductions in physical activity and function, could lead to muscle wasting; simultaneously, reductions in lean mass and quality from inflammaging, skeletal muscle fat infiltration and losses in the number of fast-twitch muscle fibres may result in declines in strength and function[64]. Second, associations between changes in muscle mass, strength and BMD are biologically plausible. For example, osteocytes and myoblasts have a shared mesenchymal stem cell origin[241] and according to the mechanostat hypothesis, losses in bone mass, due to greater resorption than formation, would occur as losses in strength lead to weaker forces on bone[32 227]. Finally, correlations between changes in muscle and bone parameters are also plausible as genetic, developmental and lifestyle factors are known to affect both muscle and bone health in older age[229].

4.2.4 Level and change in characteristics and risk of adverse health outcomes

4.2.4.1 Thesis findings

Lower levels and greater declines in all characteristics predicted hospital admission (excluding ALM and fat mass levels) and mortality. Lower levels of all characteristics and greater hip BMD declines predicted fragility fracture. Lower grip strength, greater declines in ALM and hip BMD, and lower levels and greater declines in gait speed predicted falls.

After accounting for current levels, previous declines in ALM and hip BMD were related to increased risk of mortality, hospital admission and falls. In contrast, relationships between previous declines in grip strength and gait speed and adverse outcomes were weaker after accounting for current measures. Having both low grip strength and low hip BMD, in comparison with having either of these in isolation, was related to substantially greater risk of fragility fracture and hospital admission. Having high declines in both grip strength and hip BMD was associated with increased risk of mortality in comparison with only experiencing high declines in one of these characteristics.

4.2.4.2 Overview of thesis findings in relation to previous literature

Section 4.2.4.2 summarises the findings in this thesis on the relationship between levels and changes in musculoskeletal and body composition parameters and adverse outcomes in relation to previous literature. Sections 4.2.4.3-4.2.4.9 discuss these findings in more detail for each parameter of interest along with references of previous studies.

The findings in this thesis are in broad agreement with those from the published literature. For example, the following relationships in this thesis have also been identified in previous studies: lower levels and greater declines in each characteristic in relation to greater risk of mortality; lower levels of each characteristic in relation to greater risk of fragility fracture; and lower grip strength and gait speed in relation to increased risk of hospital admission and falls. However, whereas previous studies have reported relationships between greater declines in gait speed and ALM and greater risk of fragility fracture, these associations were not evident in this thesis. Few studies were identified from the literature review which had examined levels and changes in body composition or BMD parameters in relation to risk of hospital admission.

There are many potential reasons for differences between the findings in this thesis and results from the published literature. For example, discrepancies may be due to differences in age, health status and ethnicity of participants between Health ABC and cohorts used in previous studies. Differences between the analysis conducted in this thesis and previous studies regarding outcomes (such as use of recurrent falls as opposed to incident falls), adjustments, methods used to derive change measures, and follow-up times may also have resulted in differences in findings.

4.2.4.3 Grip strength level and change and adverse outcomes

Many studies have reported that both low level and accelerated decline in grip strength are associated with mortality[68-71 242 243] with some reporting that low level is a stronger predictor[67 162]. This is in agreement with the findings in this thesis where level and decline were significantly associated with mortality with a larger effect size for level. Although no previous studies have examined grip strength decline in relation to risk of fracture or hospital admission, low grip strength was related to increased risk of osteoporotic fracture in a meta-analysis of the MrOS Study[244] and was predictive of emergency and long stay hospital admission among men and women from HCS[245]. In agreement with the findings of this thesis, upper extremity weakness was associated with increased risk of falls and recurrent falls in a systematic review and meta-analysis[246]. However, rate of grip strength decline predicted subsequent falls in the Women's Health and Aging Study (WHAS) II[73] but no such association was evident in this thesis.

4.2.4.4 Gait speed level and change and adverse outcomes

In agreement with the findings from this thesis, previous literature has established low gait speed[247-249] and greater decline in gait speed[77 88] as risk factors for mortality. Similarly, slow gait speed was a risk factor for hospital admission in a previous analysis of the Health ABC Study during a shorter mean follow-up period of 5 years[218] and predicted future falls in the Einstein Aging Study[250]; the MOBILIZE Boston Study reported greater risk of incident falls among participants with a gait speed decline of more than 0.15 m/s per year[251]. Similar to the findings in this thesis, slow gait speed predicted osteoporotic fracture among men in MrOS[244]. However, no association between gait speed decline and risk of fragility fracture was found in this thesis, whereas accelerated decline in gait speed was related to increased risk of hip fracture among women in the Study of Osteoporotic Fractures (SOF)[252] and increased risk of low trauma fracture among both men and women in the Dubbo Osteoporosis Epidemiology Study[253].

4.2.4.5 Level and change in body composition parameters and mortality

Previous studies have examined level and change in body composition in relation to risk of mortality. In a study comprising 921 Swedish men and women, aged ≥65 years: greater lean mass was protective of mortality among men and women; greater fat mass was protective among women; and very low or very high fat mass increased mortality risk among men[254]. This thesis identified low levels of both appendicular lean and whole body fat mass as risk factors for mortality, although only a linear change in relation to mortality risk was explored and men and women were pooled after no evidence of interaction effects between parameters and sex was found. In agreement with the findings of this thesis: a previous Health ABC analysis of body composition changes in relation to mortality over a shorter follow-up duration found that loss of appendicular lean mass and total fat mass predicted mortality[255]; loss of whole body lean and fat mass was related to higher risk of mortality in the MrOS study[105]; and loss of appendicular lean mass was associated with increased risk of mortality in the MINOS study of older men[106].

4.2.4.6 ALM and fat mass levels in relation to fragility fracture and fall risk

Associations identified in this thesis between lower appendicular lean and fat mass and increased fragility fracture risk are in broad agreement with those in the wider literature. For example, these relationships were observed among women from the Os des Femmes de Lyon (OFELY)

study[256] and among men in MrOS[244]. Conversely, the lack of association in this thesis between appendicular lean and fat mass and falls risk differs from the results of previous studies which have reported low lean mass as a risk factor for falls among men, and identified increased adiposity as a risk factor for falls among men and women[257]. Possible reasons for this discrepancy include the use of different measures of lean mass and adiposity in this thesis in contrast with some previous studies.

4.2.4.7 ALM and fat mass changes in relation to fragility fractures and fall risk

An examination of ALM and fat mass changes in relation to falls and fragility fractures in this thesis only revealed associations between ALM decline and increased risk of falls. Although there are few published studies with which these findings can be compared, greater loss of ALM in relation to fat mass was associated with increased risk of both falls and hip fractures in the Concord Health and Ageing in Men Project (CHAMP)[258].

4.2.4.8 ALM and fat mass and risk of hospital admission

Similar to the findings of this thesis, lean mass level was not related to risk of hospitalization in a previous analysis of the Health ABC study over a shorter follow-up duration of approximately 5 years[218]; no publications examining levels of fat mass or changes in body composition measures in relation to risk of hospital admission were identified in the literature.

4.2.4.9 Hip BMD level and change and adverse outcomes

The findings in this thesis on low and declining hip BMD in relation to increased risk of mortality[144 147 259] and fragility fracture[150 260] are consistent with the wider literature. No studies were found from the literature review which explored BMD level and change in relation to risk of hospital admission or falls.

4.2.4.10 Associations between previous changes in characteristics and adverse outcomes after accounting for current measures

In this thesis, previous declines in hip BMD and body composition parameters were related to risk of adverse outcomes even after accounting for current levels but this was not the case for grip

strength or gait speed. The literature review did not identify any previous studies with which these findings could be directly compared. Although previous publications, outlined in Sections 4.2.4.3 – 4.2.4.9, have identified associations between both lower levels and greater declines in musculoskeletal and body composition parameters in relation to adverse outcomes, the vast majority of these studies which investigated declines in relation to outcomes only accounted for baseline values of parameters; only one study, investigating the relationship between change in femoral neck BMD in relation to mortality in the MrOS Study, adjusted for BMD level at follow-up[144]. The findings from this latter study, in agreement with those from this thesis, reported that declines in BMD were related to greater mortality risk after accounting for BMD level at follow-up. However, no study used the residual approach implemented in this thesis to investigate whether a measure of change in a parameter was related to the adverse outcome, independent of the level at follow-up.

4.2.4.11 Combined impact of grip strength and hip BMD in relation to adverse outcomes

In this thesis, participants with both low grip strength and low hip BMD had considerably greater risk of fragility fracture and hospital admission compared to having either condition in isolation. Having both low grip strength and low hip BMD increased risk of mortality and falls in comparison with having low hip BMD only, but there was no substantial difference in risk compared with those with low grip strength only. In contrast to the findings in this thesis, osteodynapenia (T-scores of the total hip and/or lumbar spine BMD < –1 and grip strength in the bottom fifth of the sex-specific distribution) did not lead to a significantly greater risk of mortality or incident fracture compared to having either condition alone in the Tasmanian Older Adult Cohort Study[261]. Possible reasons for the contrast in findings are the use of different definitions for low grip strength and BMD which resulted in fewer participants having both conditions in the Tasmanian Older Adult Cohort Study (8.3% compared to 13.2% in this thesis) and also the younger age of participants in the Tasmanian Older Adult Cohort Study (Mean [SD]: 62.9 [7.4] vs 74.1 [2.9] in Health ABC).

No previous studies investigating the combined effects of grip strength and BMD levels on hospital admission and falls, or on the combined effects of changes in these parameters in relation to adverse health outcomes, were identified in the literature reviews.

4.2.4.12 Potential biological mechanisms to explain findings

There are several potential mechanisms which may relate levels and changes in musculoskeletal and body composition parameters to risk of adverse health outcomes. As shown in this thesis

(Section 3.3) and in previous literature[229], lower levels and greater declines in these parameters are correlated with low socio-economic position, poor health behaviours and increased comorbidity which are established risk factors for adverse outcomes. However, relationships in this study between these parameters and outcomes remain after accounting for these risk factors which suggests that they do not fully explain the observed associations. Another possibility is that underlying processes such as greater inflammation, oxidative stress and endocrine dysfunction are contributing to both age-related declines in these parameters and greater risk of adverse outcomes[147 247]. Furthermore, reduced function in the musculoskeletal system is usually associated with functional declines in other physiological systems[254]. Therefore, declines in parameters such as BMD and gait speed may act as biomarkers of aging and reflect an overall decline in underlying biological processes.

4.2.5 Statistical techniques for examining longitudinal change in musculoskeletal aging

4.2.5.1 Thesis findings

Valuable insights were gained by examining mean trajectories over time using data from more than two time-points. For example, non-linear changes in gait speed and fat mass could not have been identified from changes based on data from only two repeated measures. Trajectory groups from LCT models were parallel and GMM yielded a dominant group comprising over 85% of the sex-specific sample. This suggested that an LME model with a single population-average trajectory was sufficient for the description of longitudinal change in these parameters among this age group. Applying an LME model to z-scores obtained from the LMS method and then extracting the random slopes was a feasible method for deriving change measures in these characteristics. Bivariate dual change score models were unsuitable for examining musculoskeletal and body composition parameters in this age group as many failed to converge.

4.2.5.2 Use of simple change measures in previous literature

Of the 206 articles from the epidemiological literature review on changes in musculoskeletal and body composition parameters, 139 ascertained change measures using data from only two-time-points. As discussed in Section 1.5.4, this does not account for measurement error and assumes change is linear. Although some publications from this review did implement more sophisticated approaches using data from multiple time-points, simple methods were sometimes used even

when the number of repeated measures available enabled a more robust change analysis to be conducted.

4.2.5.3 Use of growth mixture and latent class trajectory models in previous studies

One article from the epidemiological literature review implemented latent class trajectory models and found that individuals with symptomatic knee osteoarthritis (OA) were at increased risk of being in the 'fast decline' gait speed group[82]. A 2019 paper published after the literature reviews were conducted used latent class trajectory models to derive trajectory groups for grip strength, gait speed and femoral neck BMD and compared mortality risk between groups[262]. This technique was also used in a recent 2020 paper to describe changes in grip strength, gait speed, appendicular lean mass index and hip BMD[263]. Similar to the findings in this thesis, these three articles each identified groups with approximately parallel mean trajectories which differed more with regard to levels of parameters rather than rates of change. Another study applied LCT models to percentage changes in gait speed since baseline, thereby ensuring that all trajectory groups would start at 0%, and then compared risk of mortality between trajectory groups whilst accounting for baseline gait speed[77]. Although these articles illustrate how a high risk 'fast decline' group can sometimes be identified from this statistical technique, they also show that disentangling the effects of baseline levels and changes in characteristics may present challenges when this method is implemented.

Growth mixture models were not used in any articles identified in the epidemiological literature search which suggests that they are rarely used to examine changes in musculoskeletal and body composition parameters among older people.

4.2.5.4 Use of the LMS method

In this thesis, the LMS method was used to derive sex- and age-specific centile curves and z-scores for musculoskeletal and body composition parameters. Previous studies have used this method to derive centiles for normative values of grip strength[264] and physical function[265] among older people. However, no studies identified from the epidemiological or the statistical literature review characterised longitudinal changes in a characteristic by examining changes in the corresponding age-adjusted z-scores obtained from the LMS method. The approach implemented in this thesis accounts for age in the derivation of z-scores and, therefore, results in approximately linear changes in mean z-scores for each characteristic over time which are straightforward for researchers to analyse.

4.2.5.5 Use of bivariate dual change score models

No studies were identified that had implemented these models to explore interrelationships between changes in musculoskeletal or body composition parameters among older people. However, one article from the statistical literature review implemented BDCSM and found that increases in lateral ventricle size were related to larger subsequent declines in memory performance[187] and another article revealed that improvements in self-esteem were associated with subsequent increases in relationship satisfaction[188]; neither study found statistically significant effects in the opposite direction. This illustrates that these models can be used to examine interrelationships between changes in aspects of human functioning but they are clearly not commonly applied in longitudinal studies of musculoskeletal or body composition parameters among older people. The attempted use of BDCSM in this thesis suggests that this may be due to the high likelihood of convergence problems; these models may offer great insights to researchers in some scenarios but they were unsuitable for examining changes in the parameters of interest in this thesis due to the high proportion of models that failed to converge.

4.2.6 How this thesis adds to knowledge from previous literature

This thesis validates the following key findings from previous studies using measurements of musculoskeletal parameters over 9-years of follow-up from the Health ABC Study: age-related declines in muscle strength and function are greater than those for muscle mass; longitudinal declines in musculoskeletal parameters are positively correlated; anthropometric and lifestyle factors and comorbidity are important determinants of levels of musculoskeletal parameters in older age; and lower levels and greater declines in musculoskeletal parameters are associated with increased risk of adverse health outcomes. Previous cohorts, such as the Study of Osteoporotic Fractures (SOF)[76], the Chingford 1000 Women Study[127], the Finnish Osteoporosis Risk Factor and Prevention (OSTPRE) Study[236] and the Hertfordshire Cohort Study[47] have measured some of these musculoskeletal parameters over 9 or more years. However, none of these other cohorts have such a wide range of musculoskeletal and body composition parameters that have been measured over multiple time-points. Therefore, the Health ABC Study enables estimates relating to longitudinal changes in these parameters, such as their percentage changes over time or their strength of association with adverse health outcomes, to be accurately characterised and compared in a single cohort. In contrast, without the use of the Health ABC Study, a comparison of the effects relating to these parameters would have to be performed

between cohorts comprising participants with heterogeneous age ranges and ethnicities which would affect comparability of results.

This thesis also includes novel findings which have not been reported previously. These include: declines in ALM preceded declines in grip strength and gait speed, and declines in all characteristics preceded declines in hip BMD; when accounting for current levels, prior declines in hip BMD and body composition parameters were more strongly related to risk of adverse outcomes, compared to declines in grip strength and gait speed; and having both low grip strength and hip BMD was related to greater risk of hospital admission and fragility fracture compared to having either condition in isolation and this was also the case for mortality in relation to greater declines in both characteristics.

4.3 Strengths and weaknesses

4.3.1 Strengths

A key strength of this study is the measurement of a wide range of musculoskeletal and body composition parameters in a single, well characterised cohort. As outlined in Section 4.2.6, this allows estimates relating to different parameters to be accurately compared as they are ascertained from the same sample of participants. An additional strength is the use of a wide panel of baseline characteristics and adverse health outcomes for analysis of both the determinants and health-related consequences of low levels and greater declines in musculoskeletal and body composition parameters. Other strengths include the measurement of parameters at many time-points along with the use of statistical methods to derive measures of change which incorporate information from all repeated measures, enabling a comprehensive assessment of change, as well as the use of change measures which are only weakly correlated with baseline levels. Another strength is that a suitable temporal sequence in ascertainment of levels and changes in musculoskeletal and body composition parameters and characterisation of adverse health outcomes was ensured. The windows for derivation of these level and change measures were prior to the occurrence of adverse health outcomes; the temporal nature of these measures therefore reduces, although does not totally preclude, the chance of having observed associations due to reverse causation. Finally, results were similar in the many different sensitivity analyses conducted, suggesting that the main findings are robust.

4.3.2 Weaknesses

At baseline, participants were free of mobility disability which limits the generalisability of findings to wider groups of community-dwelling individuals of a similar age. In the nationally-representative US NHANES cohort, mean customary gait speed (0.96 m/s among men and 0.93 m/s among women) was lower than the corresponding values in Health ABC which ranged from 1.01 to 1.23 m/s, depending on race and sex (Table 10). According to the US National Centre for Health Statistics, the prevalence of smoking in 1999-2001 (a similar date to the recruitment of the Health ABC Study) among citizens aged 65 years and older was 10% among white men and women, 11% among black women and 18% among black men[266]; smoking prevalence was lower in Health ABC among white men (5%) and white women (8%) but higher among black men (20%) and black women (12%)[267].

The 'healthy participant' effect in Health ABC may have led to the underestimation of both the magnitude and range of declines in musculoskeletal parameters which typically occur in this age group, and also possible underestimation of the strength of associations between declines in these parameters and risk of adverse health outcomes. Similarly, death and drop-outs during follow-up result in healthier participants remaining in the study who may be more likely to have slower rates of decline in parameters and reduced risk of adverse outcomes. However, wherever possible, participants were included in analyses when the musculoskeletal or body composition parameter of interest was available at two or more time-points. This ensured that most analyses included participants with shorter follow-up times. Moreover, for the analysis of level and change in parameters in relation to adverse outcomes, the similarity of results from the main analysis and those from the sensitivity analysis that only included participants with complete data suggests that the main conclusions are unaffected by these earlier drop-outs. Finally, substantial bias should only have been introduced if the key associations of interest differed markedly between the Health ABC participants who were and who were not included in the analysis sample; this seems unlikely.

Another weakness relates to the availability of participant characteristics in the Health ABC Study. For example, characteristics ascertained in childhood and early to mid-adulthood, such as birth weight, growth in adolescence and physical activity in mid-life are potential determinants of level and change in musculoskeletal parameters in later life, but these were not collected as part of the Health ABC Study; as in all observational studies, there is always a possibility that observed associations may be explained by the influence of unmeasured confounding factors. Furthermore, some of the characteristics that were available could ideally have been assessed with a greater level of accuracy. For example, only self-reported rather than objectively measured physical

activity was available, and exact dates of falls were not recorded but reported on an annual basis; mid-year dates were therefore used as approximations to dates of falls in survival analyses. Despite these limitations, the results obtained were plausible, robust to sensitivity analyses, and the vast majority were in agreement with previous literature.

The statistical analyses implemented also have some limitations. For example, the lower correlation between baseline and follow-up measurements of grip strength and gait speed, compared to body composition parameters, could simply be due to greater measurement error for grip strength and gait speed. In addition, associations regarding ALM in relation to risk of adverse outcomes could be driven by fat mass, and vice versa, because ALM and fat mass are positively correlated. However, relationships were similar when sex-specific ALM residuals were examined in relation to adverse health outcomes (data not shown); these were derived from sex-specific models where ALM was predicted from height and whole body fat mass and residuals were obtained, reflecting whether the amount of ALM was higher or lower than expected, given height and fat mass. Relationships between change in ALM and risk of adverse outcomes were also similar when changes in ALM were adjusted for change in total body weight (data not shown).

4.4 Implications of this thesis

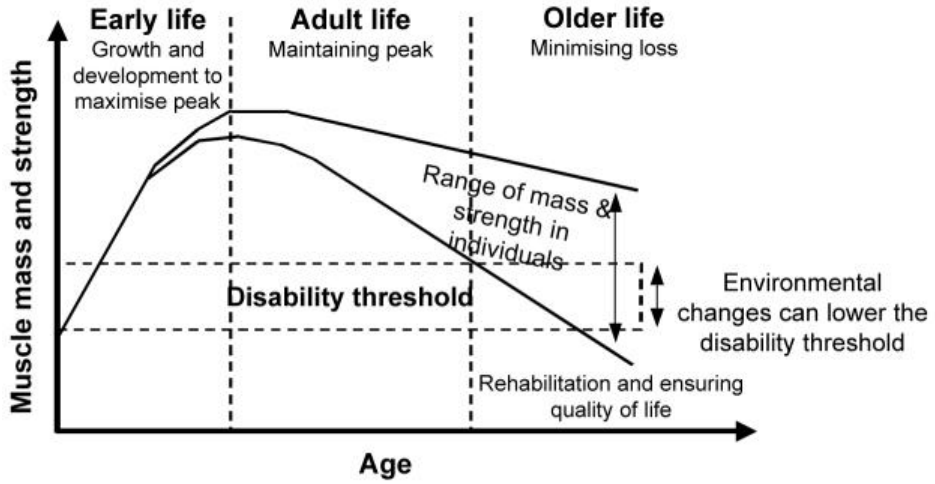
4.4.1 Lifecourse strategies to promote musculoskeletal health

Many of the epidemiological implications of this thesis can be interpreted in the context of a lifecourse perspective on healthy aging. This approach recognises that there are factors acting during gestation, childhood and adult life which influence risk of chronic disease in older age[33]. In the context of musculoskeletal health, risk of physical disability in later life depends partly on the peak levels of musculoskeletal parameters (such as muscle mass, strength and bone density) attained in early adulthood and their subsequent rates of loss following mid-life. Therefore, the lifecourse perspective suggests that interventions early in the lifecourse to maximise peak levels of these parameters and interventions in mid-life onwards to reduce age-related declines will result in better musculoskeletal health in older age (Figure 33).

In this thesis, shorter stature was related to lower levels of most musculoskeletal parameters. As height is a biomarker of lifetime nutrition and standard of living, these findings suggest that developmental factors in utero and in childhood may have influenced the eventual levels of these musculoskeletal parameters in older age among Health ABC participants. This is supported by

systematic reviews and meta-analyses which report robust positive associations between higher birth weight in relation to both higher grip strength[268] and higher bone mass in later life[269]. Therefore, interventions to improve the intrauterine environment, such as improving maternal nutrition, may lead to improvements in musculoskeletal health in older age as well as yielding benefit for the growth and development of the offspring during earlier phases of the lifecourse.

Figure 33: Lifecourse model for musculoskeletal health



Used from *Sayer A.A et al. The developmental origins of sarcopenia. J Nutr Health Aging (2008)*[270]
This figure also applies to bone mass and density

Lifestyle factors were important determinants of level and change in musculoskeletal parameters. Therefore, a lifecourse approach suggests that intervention strategies to improve physical activity and diet quality throughout life are likely to result in better musculoskeletal health in older age. This is supported by findings from the 1946 British Birth Cohort which related higher physical activity and diet quality in mid-adulthood to higher muscle strength and physical performance several decades later[271 272]. Although physical activity was not strongly associated with changes in musculoskeletal parameters in this thesis, positive effects of physical activity and resistance training interventions on muscle strength and physical function among older people have been reported previously[229 273]. This suggests such interventions could delay age-related declines in strength and function. Diet is widely recognised as an important determinant of musculoskeletal health[229]. Associations reported in this thesis regarding better diet quality and reduced declines in ALM and hip BMD suggest that improving diet quality, even in older age, may confer benefits for muscle and bone health.

The findings in this thesis about changes in characteristics over time also have wider implications. Percentage declines in gait speed and grip strength were greater, and the proportion of variance at follow-up explained by baseline level was lower, in comparison with the other characteristics. This suggests that interventions designed to slow loss of muscle strength and physical function in later life might perhaps offer greater benefit among older people than those targeted at body composition parameters, whose values at follow-up are more determined by those at baseline. Although statistically significant, correlations between changes in body composition and changes in grip strength and gait speed were weak in magnitude. This suggests that a range of interventions are required to prevent or delay declines in muscle strength and function in later life. Finally, for all parameters, the substantial proportion of variation at follow-up that was explained by baseline level suggests that maximising peak levels of muscle mass, strength, function and bone density earlier in life is critical for ensuring healthy musculoskeletal aging.

Low levels of musculoskeletal parameters were related to increased risk of adverse health outcomes. This suggests that maximising levels in earlier life and reducing rates of decline in older age may reduce the burden of disease in this age group. This is perhaps particularly important for muscle strength and function, owing to their strong associations with risk of adverse outcomes considered in this thesis, and also for BMD, given its strong association with risk of fragility fractures. Both lower levels and accelerated declines in some parameters were associated with the same adverse health outcome in this thesis. This suggests that the combined use of absolute levels of parameters as well as rates of change over time could be used to improve the identification of individuals most at risk of adverse outcomes and who are likely to benefit most from interventions. This is also supported by results showing that prior declines in ALM, fat mass and hip BMD over a period of 2-4 years were related to greater risk of adverse outcomes even after accounting for the most recently measured value. Overall, a population-based holistic approach to intervention strategies among older people that aims to preserve level and reduce rate of decline in musculoskeletal parameters may be more beneficial than interventions which target specific clinical phenotypes[274 275].

4.4.2 Evidence-based algorithms for sarcopenia

Findings from this thesis also have implications for diagnostic algorithms for sarcopenia (various algorithms for defining sarcopenia are presented in Table 37). In this thesis, low gait speed and grip strength were associated with increased risk of all adverse outcomes whereas low ALM was only related to greater risk of mortality and fragility fracture. These stronger associations between muscle strength and function in relation to adverse outcomes, in comparison with lean mass, are

well established[276], and suggest that these components should be included in definitions of sarcopenia with lean mass having less importance or simply not being included. The Sarcopenia Definitions and Outcomes Consortium (SDOC) apply this rationale and define sarcopenia as having both weak grip strength and slow gait speed[276]. To arrive at this definition, SDOC used data from eight cohorts to identify cut-points for muscle strength (with and without standardisation for body size and composition) and lean mass measures that discriminate older participants with slow gait speed (<0.8 m/s). The predictive capacity of these cut-points in relation to incident adverse outcomes (falls, hip fractures, mobility limitation, and mortality) was then evaluated[277]. Participants with both muscle weakness according to absolute grip strength (<35.5 kg in men and <20 kg in women) and slow gait speed (<0.8 m/s) were more likely to experience each of the adverse outcomes compared to those without either low grip strength or slow gait speed; lean mass measures were not consistently associated with these outcomes and, therefore, were not included in the sarcopenia diagnostic algorithm.

Table 37: Diagnostic algorithms for sarcopenia

Definition	Algorithm	Cut-points used in algorithm
Sarcopenia Definition and Outcomes Consortium (SDOC)[276 277]	Low grip strength and gait speed	Grip strength: <35.5 kg (men) and <20 kg (women) Gait speed: <0.8 m/s
European Working Group on Sarcopenia in Older People (EWGSOP)[278]	Low lean mass and either low grip strength or gait speed	Grip strength: <30 kg (men), <20 kg (women) Gait speed: ≤0.8 m/s ALM/height^2: ≤7.23 kg/m^2 (men), ≤5.67 kg/m^2 (women) Other cut-points for EWGSOP components are also recommended
Revised European Working Group on Sarcopenia in Older People (EWGSOP2)[13]	**Probable sarcopenia**: Low muscle strength **Confirmed sarcopenia:** Low muscle strength and lean mass **Severe sarcopenia:** Low muscle strength, lean mass and physical performance	Different measures of muscle strength, mass and physical performance may be used, depending on the availability of measures **Low muscle strength** Grip strength: <27 kg (men), <16 kg (women) Chair stands: >15 seconds for five rises **Low lean mass** ALM: <20 kg (men), <15 kg (women) ALM/height$^{2:}$ <7.0 kg/m^2 (men), <5.5 kg/m^2 (women) **Low physical performance** Gait speed: ≤0.8 m/s SPPB: ≤8 point score TUG: ≥20 seconds 400m walk: ≥6 minutes or non-completion
Foundation for the National Institutes of Health (FNIH) Sarcopenia Project[279]	Low grip strength and lean mass adjusted for BMI	Grip strength: <26 kg (men), <16 kg (women) ALM/BMI: <0.789 (men), <0.512 (women)
International Working Group on Sarcopenia (IWGS)[14]	Low gait speed and lean mass	Gait speed: <1.0 m/s ALM/height^2: ≤7.23 kg/m^2 (men), ≤5.67 kg/m^2 (women)

ALM: Appendicular lean mass; SPPB: Short physical performance battery; TUG: Timed up-and-go

Although the revised 2019 EWGSOP definition (EWGSOP2) still uses a combination of low muscle strength and lean mass to confirm sarcopenia, muscle strength is regarded as the primary component of sarcopenia and is used alone to define probable sarcopenia; severe sarcopenia is regarded as having low muscle strength, lean mass and physical performance[13]. This approach was based on evidence which suggested that muscle strength and physical performance predict adverse outcomes better than lean mass and that muscle strength is the most reliable measure of muscle function. However SDOC identifies the following limitations with the revised EWGSOP2 definition: cut-points are based on distributions of parameters across the lifecourse, rather than cut-points which optimise the predictions of adverse outcomes; and many different parameters can be used for each sarcopenia component (Table 37). In contrast, the original 2010 EWGSOP definition considered lean mass as a principal component of sarcopenia and defined sarcopenia as having low lean mass along with either low muscle strength or performance[278].

The Foundation for the National Institutes of Health (FNIH) Sarcopenia Project recognised that low lean mass is related to weakness and weakness is associated with reduced function and disability[279]. Therefore, to develop an algorithm to define sarcopenia, the following approach was implemented using several cohort studies: identify optimum grip strength cut-points for mobility impairment (gait speed <0.8 m/s); identify optimum ALM and ALM/BMI cut-points according to these grip strength cut-points; and examine the predictive capacity of these derived cut-points for predicting incident mobility impairment and mortality[280]. Sarcopenia was defined as having both low grip strength (<26kg for men and <16kg for women) and low ALM (kg) / BMI (kg/m^2) (<0.789 for men and <0.512 for women) as each of these were associated with increased risk of incident mobility impairment. Possible limitations of this approach are that low ALM/BMI was not associated with mortality and many important adverse outcomes such as fractures and falls were not examined.

The International Working Group on Sarcopenia (IWGS) defined sarcopenia in 2011 as the 'age-associated loss of skeletal muscle mass and function'[14]. Therefore, they proposed that a diagnosis of sarcopenia should involve screening for low physical function among high risk patients, such as those who are non-ambulatory or who cannot rise from a chair unassisted, followed by an assessment of lean mass using DXA among those with low physical function. Consequently, both low gait speed (<1.0 m/s) and low appendicular lean mass index (≤7.23 kg/m^2 for men and ≤5.67 kg/m^2 for women) are required for a sarcopenia diagnosis according to the IWGS algorithm. A limitation of this approach is that neither of these cut-points were optimised according to their capacity to predict clinically relevant outcomes: the lean mass cut-point corresponds to the

bottom fifth of the sex-specific distribution for healthy young adults and a justification for the gait speed cut-point was not provided. Furthermore, grip strength, now regarded as a key component of sarcopenia, is not included in the diagnostic algorithm.

In summary, the findings in this thesis of stronger associations between muscle strength and function in relation to adverse outcomes, in comparison with lean mass, are in agreement with previous research over the last 10 years. These insights have resulted in the more recent definitions of sarcopenia placing less importance on lean mass (EWGSOP2) or even not including this component of sarcopenia in the definition (SDOC). The findings in this thesis support this approach.

4.4.3 Statistical implications for the analysis of longitudinal change in musculoskeletal aging parameters

The findings of this thesis have implications for the statistical analysis of longitudinal data in the field of musculoskeletal aging. Few insights were gained from the use of advanced techniques to derive trajectory groups (those from LCT models had approximately parallel mean trajectories and those from GMM contained a dominant group comprising over 85% of the sample). As such, an LME model with a single population-average trajectory may be sufficient for the description of longitudinal changes in musculoskeletal parameters among older people. However, if there had been groups in the sample with markedly different mean trajectories, an LME model would have been overly simplistic. Therefore, a more rigorous approach for the analysis of longitudinal changes in musculoskeletal parameters over time may include examining whether there is evidence of multiple trajectory groups using GMM or LCT models and then using an LME model if change can be adequately described using a single population-average trajectory.

Bivariate dual change score models (BDCSM), used to examine temporal relationships between changes in characteristics over time, failed to converge in most scenarios. This outcome, together with the limited insights obtained from the LCT and GMM, perhaps suggests that age-related changes in musculoskeletal and body composition parameters among people of this age group exhibit too little between-individual variation to be suitably analysed using these techniques. This may be more likely in the Health ABC Study, compared to other cohorts, as the selection of participants who were free of mobility disability at baseline is likely to have resulted in a more homogenous sample, perhaps with similar rates of change in parameters. Instead of implementing BDCSM, the temporal correlations between changes in musculoskeletal parameters can be ascertained simply by examining associations between change measures ascertained over

two intervals, as was performed in this thesis. Although simplistic, this approach can be made more robust by deriving change measures from multiple repeated measurements, provided these are available, and by implementing regression approaches to examine associations between change measures whilst accounting for potential confounders.

This thesis has demonstrated that longitudinal changes in parameters can be characterised by analysing changes in the corresponding z-scores obtained using the LMS method. This method accounts for age in the derivation of z-scores and therefore results in approximately linear changes in mean z-scores for each characteristic over time which are straightforward for researchers to analyse. The use of these change measures as predictors or outcomes in statistical models is suitable if quantifying the effect of standard deviation differences in such measures is of interest. However, a disadvantage of this approach is that converting changes in z-scores back to the original scale of measurement is not possible.

4.4.4 Future research

The findings of this thesis have implications for future research on musculoskeletal aging. Significant and positive correlations between changes in musculoskeletal parameters were observed in this thesis which is consistent with the mechanostat hypothesis on the interrelated nature of muscle and bone physiology. Therefore, for a comprehensive understanding of muscle and bone health among older people, future aging cohorts should ascertain data on a wide array of musculoskeletal parameters. Furthermore, for a more accurate characterisation of longitudinal changes in these parameters, cohorts should also measure these parameters at three or more time points; this is the minimum number of repeated measures required to investigate non-linear changes. The Health ABC study was the only cohort identified from the literature reviews that had ascertained a wide range of musculoskeletal parameters at multiple time points.

This thesis validates the position of SDOC that muscle mass is less strongly associated with adverse health outcomes compared to muscle strength or function, so these latter characteristics should feature as components in definitions of sarcopenia. However, neither this thesis nor the research by SDOC, proposes cut-points for both grip strength and gait speed that are based on optimum thresholds for predicting clinically relevant outcomes, for example, by implementing receiver operating characteristic analyses. Therefore, future research could focus on this topic, potentially utilising data from multiple cohorts.

This thesis is based on data from a cohort of community-dwelling older US men and women who were free of mobility disability at baseline which limits the generalisability of findings. Therefore, where data are available, replication of these findings among nationally representative cohorts, such as the US National Health and Nutrition Examination Survey, and among cohorts of different ethnicities and countries, could be performed.

Alongside components of sarcopenia (grip strength, gait speed and ALM), body composition parameters such as BMD and total fat mass, ascertained using DXA, were also examined in this thesis. For a more comprehensive assessment of bone health, future studies could explore similar research questions as in this thesis but using bone microarchitecture parameters, ascertained from peripheral quantitative computed tomography (pQCT) or high resolution peripheral quantitative computed tomography (HRpQCT) scans; information on bone microarchitecture was not available in the Health ABC Study. Similarly, more detailed information on adiposity, such as body fat distribution and measures of visceral adipose tissue, could be examined in future studies of the determinants and health-related consequences of levels and changes in measures of adiposity.

Investigation of the determinants and health-related consequences of different definitions of sarcopenia was beyond the scope of this thesis. However, this could be addressed in future research, ideally using nationally representative cohorts in which a higher prevalence of sarcopenia, than was identified in the Health ABC Study, would enable a more robust investigation of this research area. The determinants and adverse consequences of related conditions such as sarcopenic obesity and osteosarcopenia (coexistence of osteoporosis and sarcopenia) could also be addressed in future research using nationally representative cohorts.

4.4.5 Summary of epidemiological and statistical recommendations from this thesis

Promotion of musculoskeletal health in older age and development of diagnostic algorithms for sarcopenia

- Develop interventions to maximise levels of musculoskeletal parameters attained in early adulthood and to reduce rates of decline from midlife onwards. This may involve improving: the intrauterine environment; health behaviours such as physical activity and diet quality throughout the lifecourse; and muscle strength through the use of resistance exercises.

- Use a combination of absolute levels of parameters and rates of change over time to improve identification of individuals most at risk of adverse outcomes and who are likely to benefit most from interventions.
- Sarcopenia algorithms should be based on grip strength and gait speed, rather than lean mass, due to their greater predictive capacity regarding adverse health outcomes.

Statistical analysis of longitudinal changes in musculoskeletal aging

- Cohort studies which aim to investigate longitudinal changes in musculoskeletal parameters should:
    - include a wide range of parameters relating to muscle strength, function and body composition (including bone);
    - measure these parameters at three or more time-points.
- Before analysing longitudinal changes, evidence of multiple trajectory groups should be explored using GMM or LCT models; use of an LME model is suitable if change can be adequately described using a single population-average trajectory.
- Temporal correlations between changes in parameters could be ascertained by examining associations between change measures ascertained over two intervals, rather than implementing BDCSM which are likely to suffer from convergence problems.
- Examining longitudinal changes in LMS z-scores of musculoskeletal parameters is an effective method to assess change in the age- and sex-specific ranking of a participant's values over time.

Thesis outputs

Publications

Westbury, L.D., Syddall, H.E., Fuggle, N.R., Dennison, E.M., Cauley, J.A., Shiroma, E.J., Fielding, R.A., Newman, A.B. and Cooper, C., 2020. **Long-term rates of change in musculoskeletal aging and body composition: findings from the Health, Aging and Body Composition Study**. *Calcified Tissue International*. 106(6):616-624.doi: 10.1007/s00223-020-00679-2.

Westbury, L.D., Syddall, H.E., Fuggle, N.R., Dennison, E.M., Harvey, N.C., Cauley, J.A., Shiroma, E.J., Fielding, R.A., Newman, A.B. and Cooper, C., 2020. **Relationships between level and change in sarcopenia and other body composition components and adverse health outcomes: findings from the Health, Aging, and Body Composition Study.** *Calcified Tissue International*. 108(3):302-313.doi: 10.1007/s00223-020-00775-3.

Conference abstracts presented

Westbury, L.D., Syddall, H.E., Dennison, E.M., Cooper, C. **Describing change in musculoskeletal aging: a comparison of techniques using data from the Health, Aging and Body Composition Study.** Presented at the *Society for the Study of Human Biology Conference 2019* and at the *Society for Social Medicine Annual Scientific Meeting 2019***.**

Westbury, L.D., Syddall, H.E., Dennison, E.M., Cauley, J.A., Harris, T.B., Shiroma, E.J., Goodpaster, B.H., Newman, A.B., Cooper, C. **Long-term rates of change in musculoskeletal aging: findings from the Health, Aging and Body Composition Study**. Presented at the *World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases 2019* and at the *Southampton Medical and Health Research Conference 2019*.

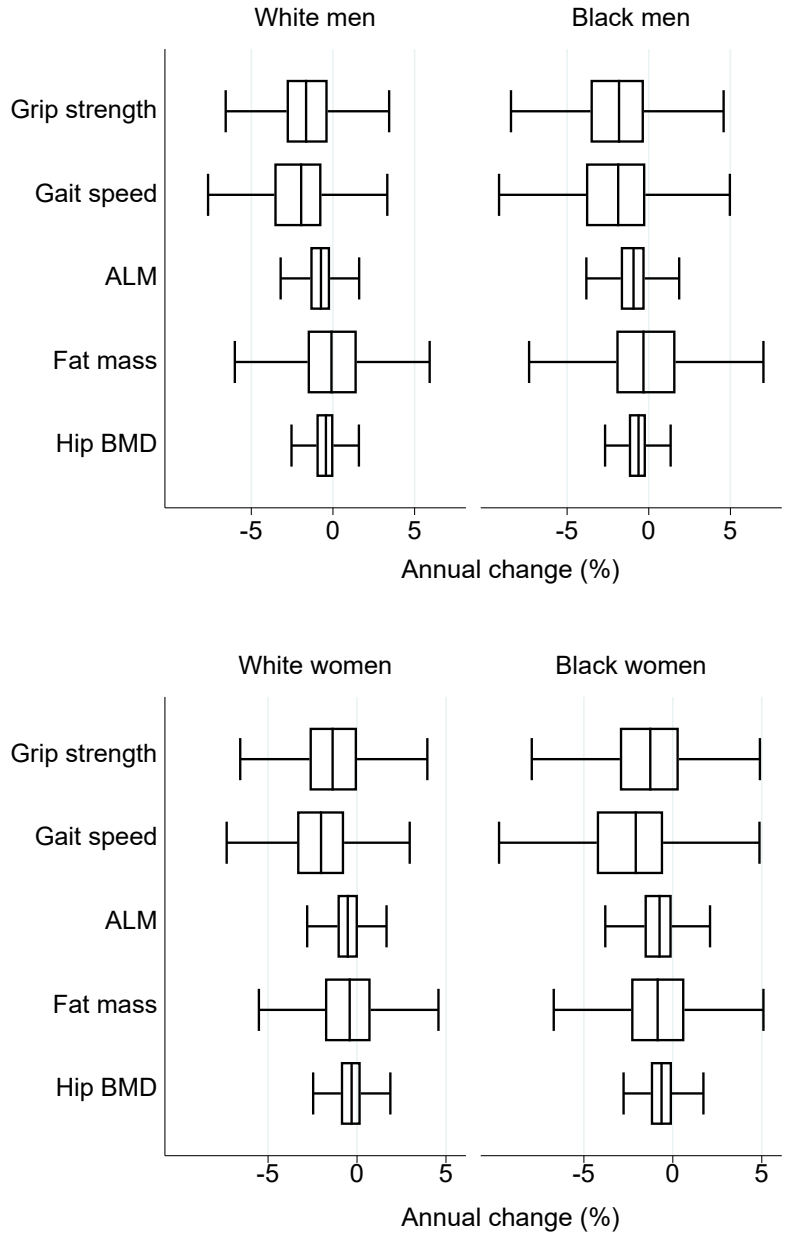
Westbury, L.D., Syddall, H.E., Fuggle, N.R., Dennison, E.M., Harvey, N.C., Cauley, J.A., Shiroma, E.J., Fielding, R.A., Newman, A.B. and Cooper, C. **Level and change in sarcopenia components predict adverse health outcomes: findings from the Health, Aging, and Body Composition Study.** Presented at the *World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases 2020* and at the *Southampton Medical and Health Research Conference 2020*.

Awards

ESCEO-AgNovos Young Investigator Award for abstract at the *World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases 2020*

Supplementary material

Appendix 1: Estimated annual percentage change in characteristics according to sex and ethnicity



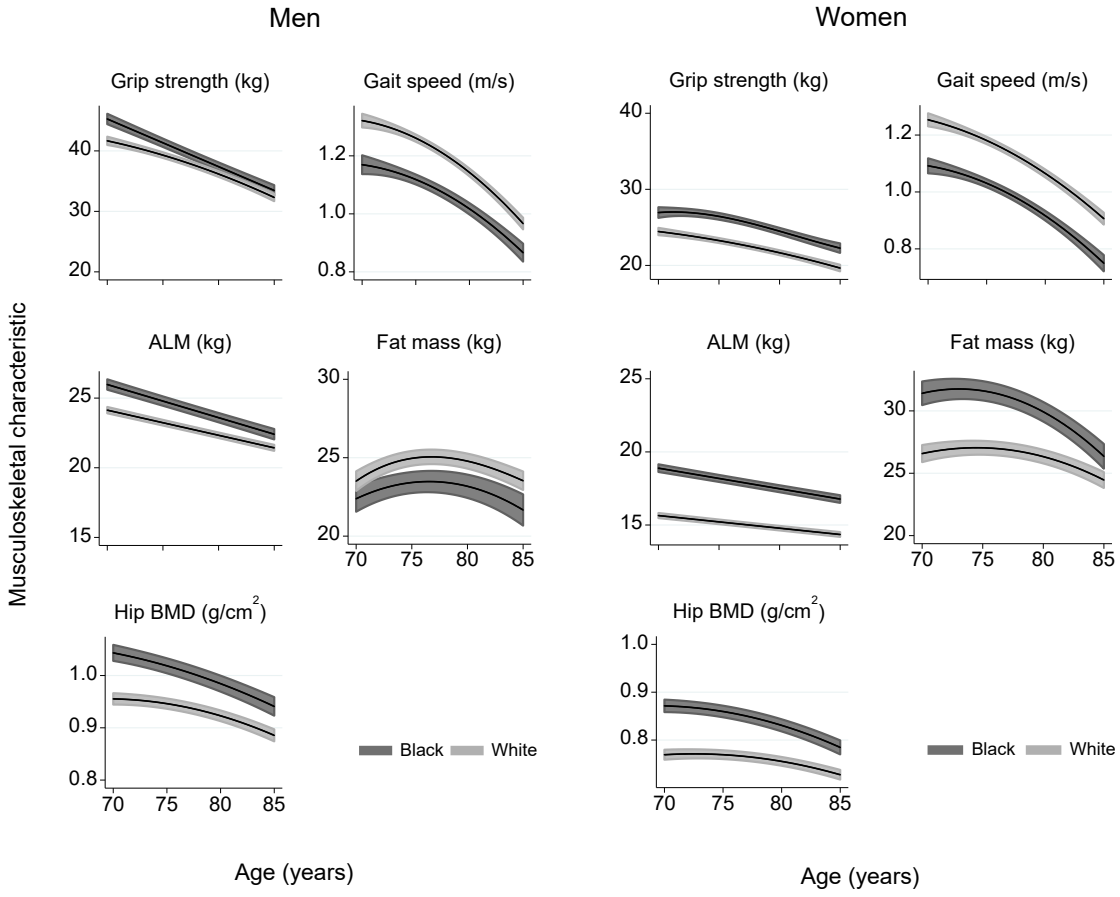
ALM: Appendicular lean mass; BMD: Bone mineral density

The three vertical lines in the box represent the lower quartile (Q1), median and upper quartile (Q3). The lower whisker is the smallest value that is greater than Q1 − 1.5 × IQR and the upper quartile is the largest value which is less than Q3 + 1.5 × IQR, where IQR = Q3-Q1.

Estimates of percentage change for each participant were derived using person-specific linear regression models for percentage change since baseline calculated at each time-point as the outcome with age at each time-point as the only predictor. Annual percentage change is given by the regression coefficient for age.

Analyses restricted to 1418 men (907 white and 511 black) and 1499 women (823 white and 676 black) with data on at least one change measure.

Appendix 2: Mean (95% CI) trajectories of characteristics according to sex and ethnicity

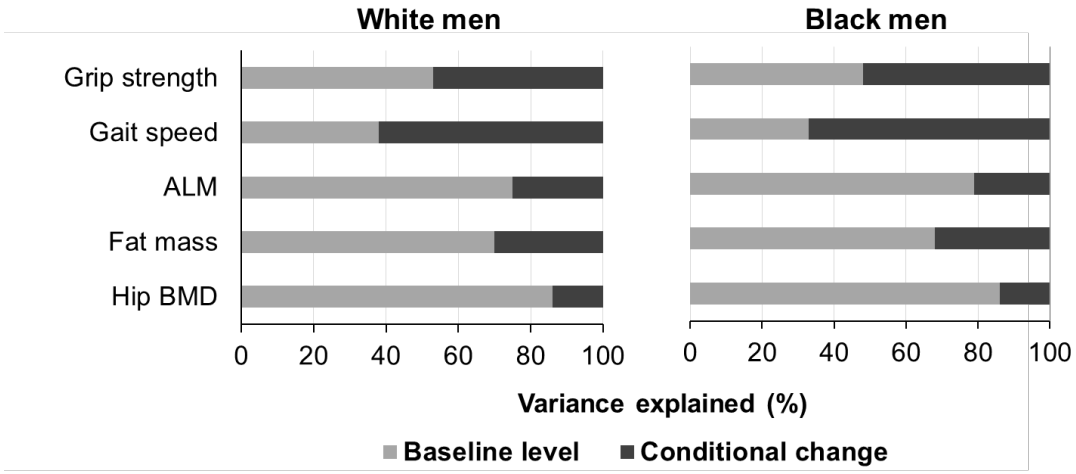


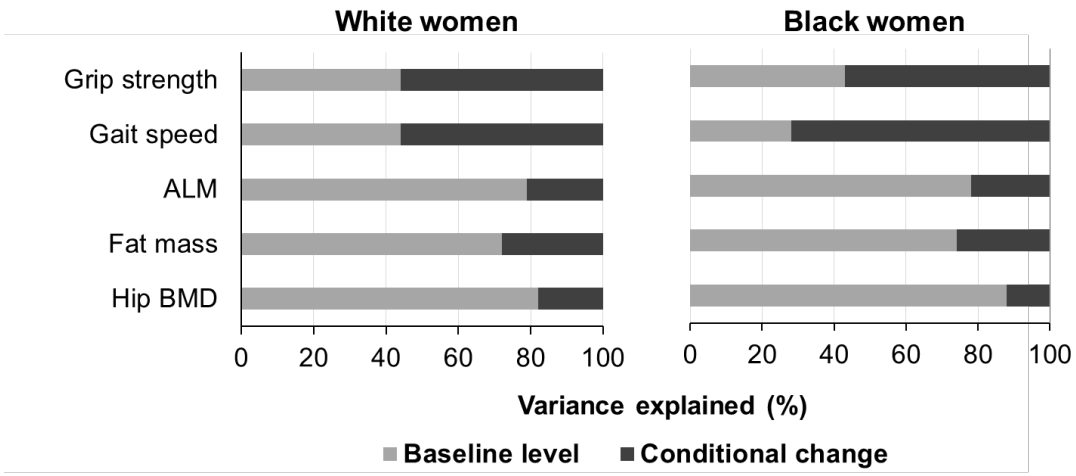
ALM: Appendicular lean mass; BMD: Bone mineral density

Mean trajectories were derived using linear mixed effects models with random intercepts and slopes. Quadratic and cubic age terms were included as fixed effects if significant ($p<0.05$)

For each characteristic, trajectories from participants with at least two observations were included

Appendix 3: Proportion of variance at follow-up (Year 10) explained by baseline level and conditional change since baseline according to sex and ethnicity

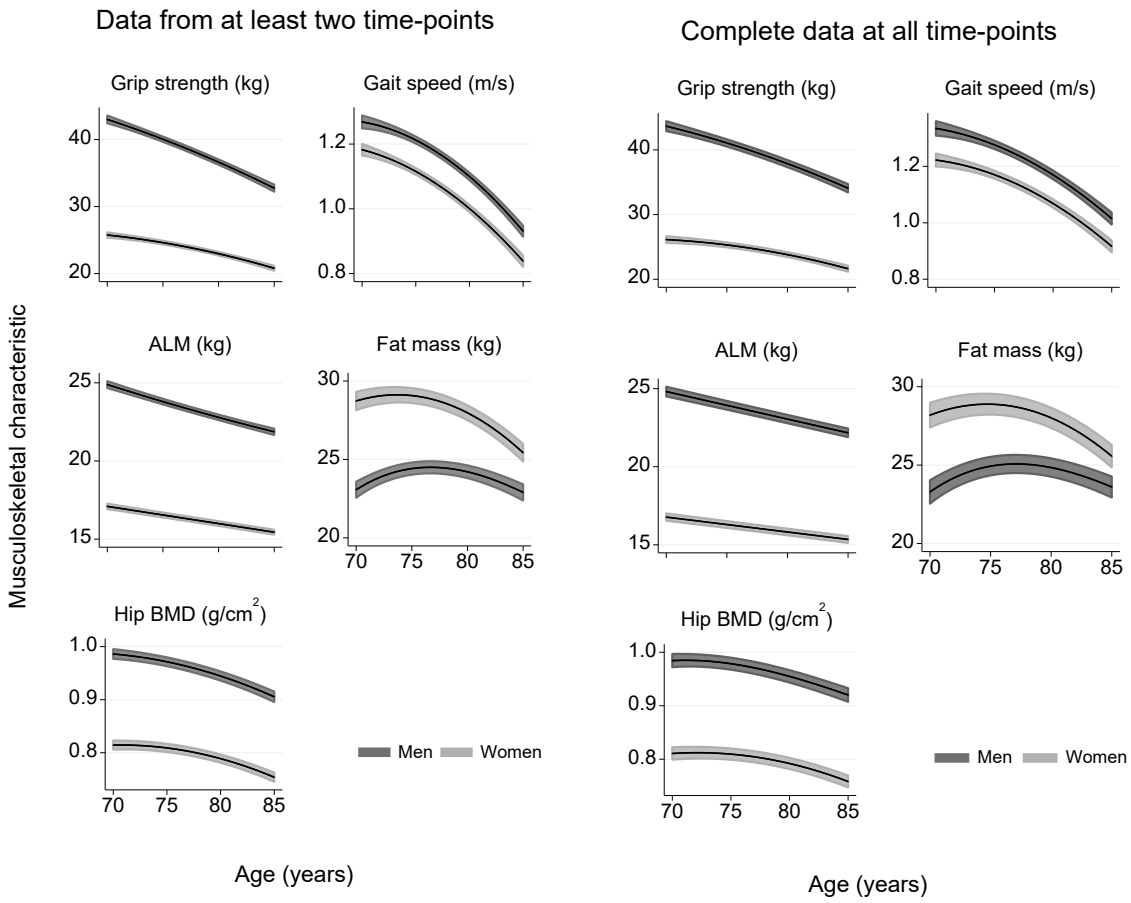




Measures of conditional change were derived using a residual change method and were independent of baseline level

Analyses restricted to 735 men (518 white and 217 black) and 864 women (529 white and 335 black) with data on at least one change measure

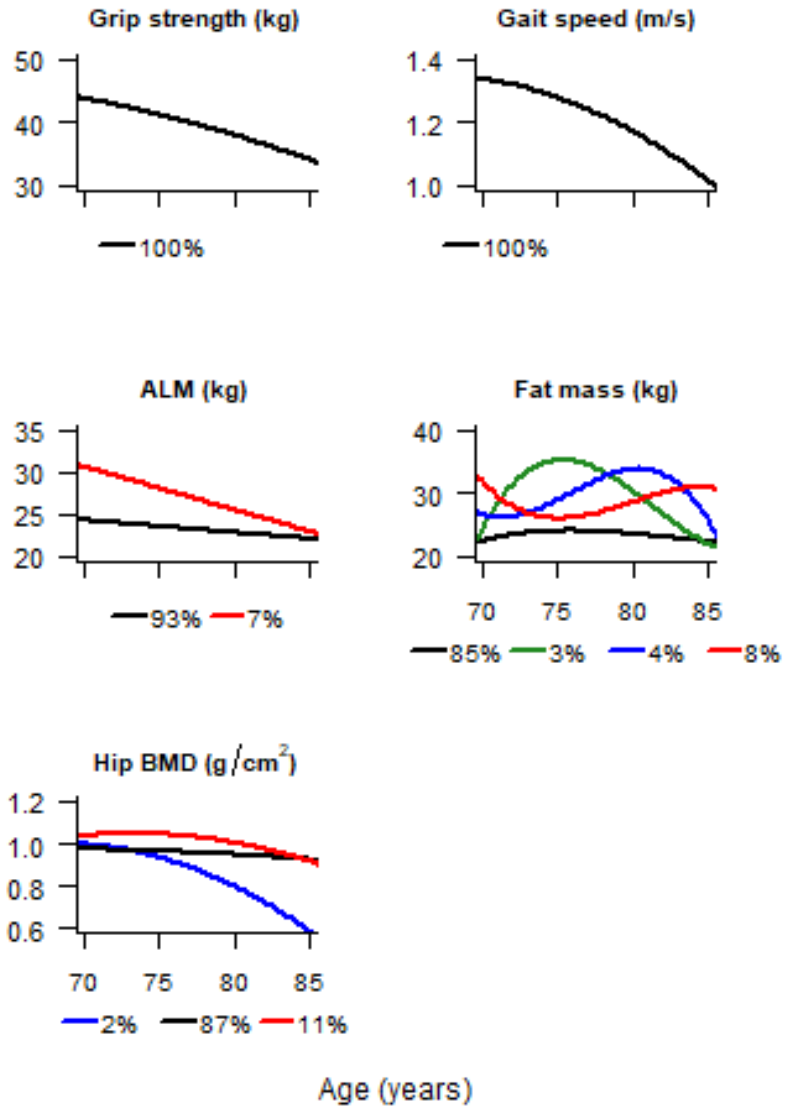
Appendix 4: Mean (95% CI) trajectories among participants with data from at least two time-points compared to trajectories among participants with data at all time-points



Mean trajectories were derived using linear mixed effects models with random intercepts and slopes

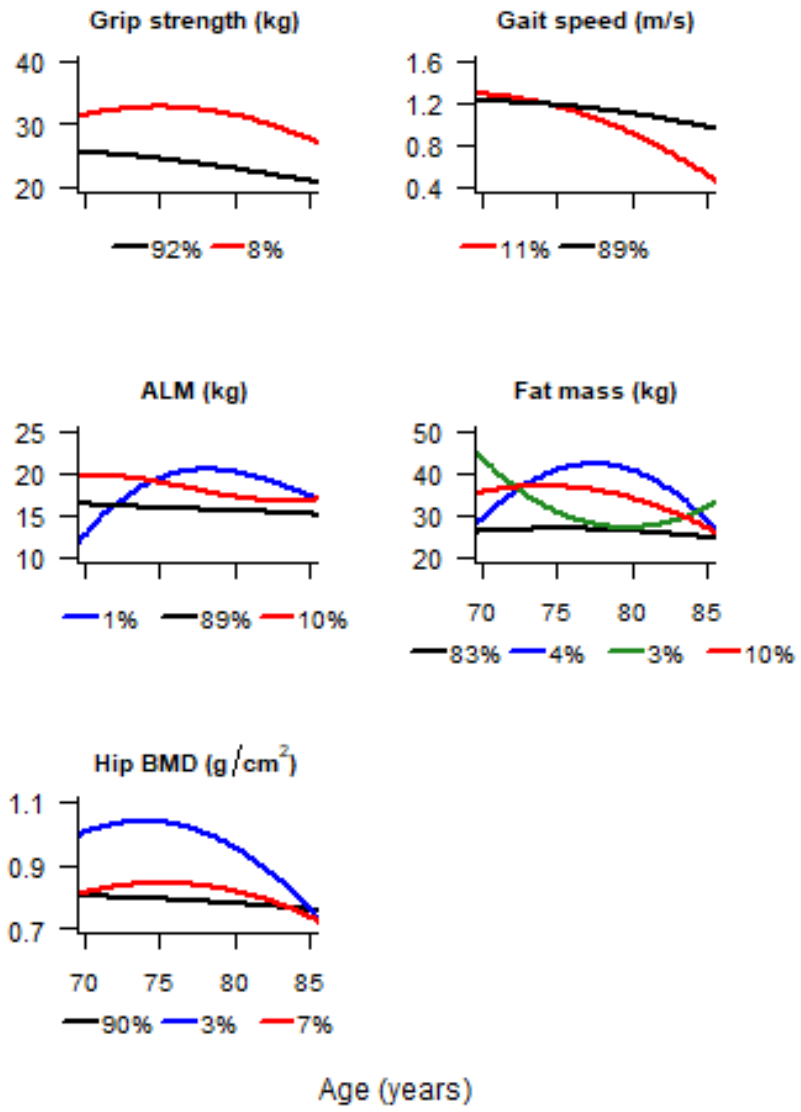
Quadratic and cubic age terms were included as fixed effects if significant ($p<0.05$)

Appendix 5: Mean trajectories of groups from growth mixture models among men with data at all time-points



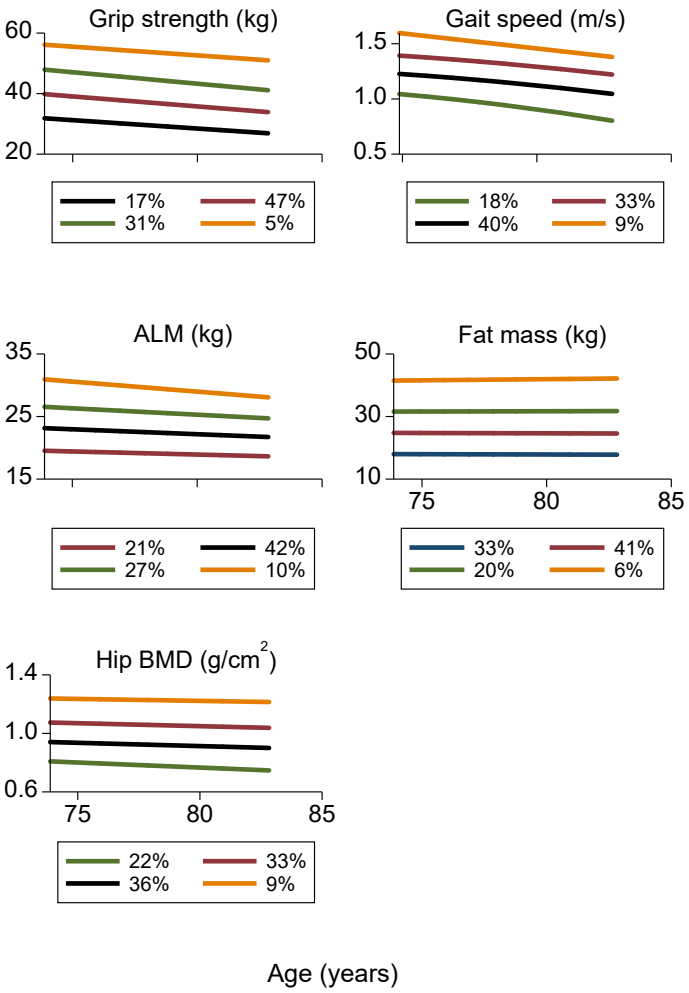
The proportion of men in each group is stated below the graph

Appendix 6: Mean trajectories of groups from growth mixture models among women with data at all time-points



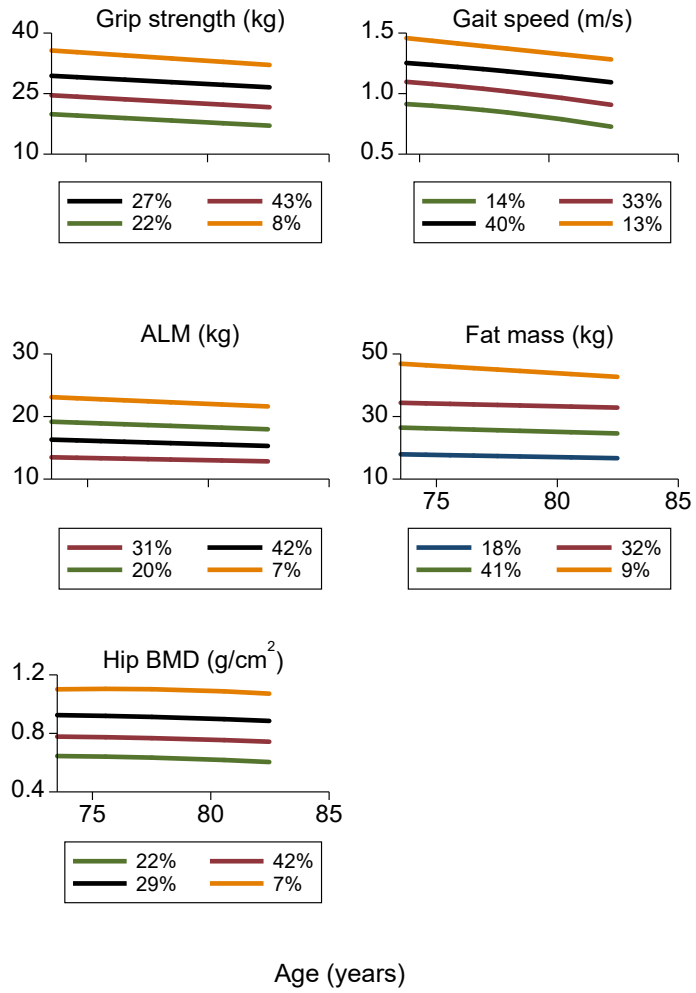
The proportion of women in each group is stated below the graph

Appendix 7: Mean trajectories of groups from latent class trajectory models among men with data at all time-points



The proportion of men in each group is stated below the graph

Appendix 8: Mean trajectories of groups from latent class trajectory models among women with data at all time-points



The proportion of women in each group is stated below the graph

Appendix 9: Sex-stratified associations between participant characteristics and grip strength level

Participant characteristic	Grip strength level among men (z-score)				Grip strength level among women (z-score)			
	Unadjusted		Mutually-adjusted		Unadjusted		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Race (black)	**0.33 (0.22,0.43)**	**<0.001**	**0.36 (0.27,0.46)**	**<0.001**	**0.51 (0.41,0.61)**	**<0.001**	**0.40 (0.30,0.50)**	**<0.001**
Age (z-score)*	**-0.20 (-0.25,-0.15)**	**<0.001**	**-0.15 (-0.20,-0.11)**	**<0.001**	**-0.16 (-0.21,-0.11)**	**<0.001**	**-0.10 (-0.14,-0.05)**	**<0.001**
Height (z-score)*	**0.33 (0.28,0.38)**	**<0.001**	**0.32 (0.28,0.37)**	**<0.001**	**0.36 (0.31,0.40)**	**<0.001**	**0.36 (0.31,0.40)**	**<0.001**
Weight-for-height residual (z-score)*	**0.10 (0.05,0.15)**	**<0.001**	**0.09 (0.05,0.14)**	**<0.001**	**0.10 (0.04,0.15)**	**<0.001**	**0.08 (0.02,0.13)**	**0.003**
Ever smoked	0.08 (-0.03,0.19)	0.168			0.03 (-0.07,0.13)	0.612		
Alcohol consumption**	-0.01 (-0.06,0.04)	0.679			-0.03 (-0.09,0.02)	0.238		
Physical activity (z-score)*	**0.11 (0.06,0.16)**	**<0.001**	**0.06 (0.01,0.11)**	**0.013**	**0.13 (0.08,0.18)**	**<0.001**	**0.09 (0.04,0.14)**	**<0.001**
Healthy Eating Index (z-score)*	0.03 (-0.02,0.09)	0.244			0.05 (-0.01,0.10)	0.081		
Education**	-0.01 (-0.08,0.05)	0.710			**-0.11 (-0.18,-0.04)**	**0.001**	**-0.12 (-0.19,-0.06)**	**<0.001**
Housing tenure (rent/other)	**-0.19 (-0.31,-0.06)**	**0.003**	**-0.17 (-0.28,-0.05)**	**0.004**	**-0.12 (-0.23,-0.01)**	**0.029**	**-0.13 (-0.23,-0.03)**	**0.011**
Number of systems medicated*	**-0.05 (-0.09,-0.02)**	**0.005**	**-0.05 (-0.08,-0.01)**	**0.007**	-0.02 (-0.06,0.02)	0.305		

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

Significant associations (p<0.05) are highlighted in bold and red

Appendix 10: Sex-stratified associations between participant characteristics and grip strength change

Participant characteristic	Grip strength change among men (z-score)				Grip strength change among women (z-score)†			
	Unadjusted		Mutually-adjusted		Unadjusted		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Race (black)	**-0.14 (-0.25,-0.03)**	**0.011**	**-0.16 (-0.27,-0.05)**	**0.005**	-0.04 (-0.15,0.06)	0.429	-0.07 (-0.18,0.03)	0.183
Age (z-score)*	**-0.10 (-0.15,-0.04)**	**<0.001**	**-0.09 (-0.15,-0.04)**	**0.001**	-0.02 (-0.07,0.04)	0.552	-0.03 (-0.08,0.03)	0.311
Height (z-score)*	0.00 (-0.05,0.05)	0.993			**-0.06 (-0.11,-0.01)**	**0.022**	**-0.06 (-0.11,-0.01)**	**0.026**
Weight-for-height residual (z-score)*	-0.01 (-0.06,0.05)	0.827			0.01 (-0.05,0.06)	0.859		
Ever smoked	0.02 (-0.10,0.13)	0.785			0.01 (-0.10,0.11)	0.872		
Alcohol consumption**	-0.03 (-0.08,0.02)	0.247			-0.01 (-0.07,0.05)	0.757		
Physical activity (z-score)*	0.05 (-0.01,0.10)	0.079			-0.02 (-0.07,0.03)	0.481		
Healthy Eating Index (z-score)*	-0.04 (-0.09,0.02)	0.200			-0.01 (-0.06,0.05)	0.786		
Education**	0.00 (-0.07,0.07)	0.932			-0.00 (-0.07,0.07)	0.941		
Housing tenure (rent/other)	-0.02 (-0.15,0.11)	0.764			**0.21 (0.09,0.32)**	**<0.001**	**0.21 (0.10,0.32)**	**<0.001**
Number of systems medicated*	**-0.04 (-0.08,-0.01)**	**0.022**	**-0.04 (-0.08,-0.01)**	**0.022**	**-0.06 (-0.11,-0.02)**	**0.003**	**-0.06 (-0.11,-0.02)**	**0.004**

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

†Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for grip strength change illustrates that an increase/presence of the predictor was associated with reduced loss of grip strength over time and a negative coefficient reflects accelerated loss of grip strength

Significant associations (p<0.05) are highlighted in bold and red

Appendix 11: Sex-stratified associations between participant characteristics and gait speed level

Participant characteristic	Gait speed level among men (z-score)				Gait speed level among women (z-score)			
	Unadjusted		Mutually-adjusted		Unadjusted		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Race (black)	**-0.66 (-0.77,-0.55)**	**<0.001**	**-0.48 (-0.59,-0.36)**	**<0.001**	**-0.71 (-0.81,-0.62)**	**<0.001**	**-0.48 (-0.59,-0.38)**	**<0.001**
Age (z-score)*	**-0.18 (-0.24,-0.13)**	**<0.001**	**-0.19 (-0.24,-0.14)**	**<0.001**	**-0.20 (-0.25,-0.15)**	**<0.001**	**-0.21 (-0.26,-0.16)**	**<0.001**
Height (z-score)*	**0.06 (0.01,0.11)**	**0.030**	0.05 (-0.00,0.10)	0.064	0.03 (-0.02,0.08)	0.250		
Weight-for-height residual (z-score)*	**-0.13 (-0.18,-0.07)**	**<0.001**	**-0.12 (-0.17,-0.07)**	**<0.001**	**-0.20 (-0.26,-0.15)**	**<0.001**	**-0.22 (-0.27,-0.17)**	**<0.001**
Ever smoked	**-0.19 (-0.30,-0.07)**	**0.001**	**-0.16 (-0.28,-0.05)**	**0.004**	-0.02 (-0.12,0.08)	0.696		
Alcohol consumption**	**0.08 (0.03,0.13)**	**0.002**	**0.05 (0.00,0.10)**	**0.035**	**0.11 (0.06,0.17)**	**<0.001**	**0.08 (0.02,0.13)**	**0.008**
Physical activity (z-score)*	**0.15 (0.09,0.20)**	**<0.001**	**0.13 (0.08,0.18)**	**<0.001**	**0.08 (0.03,0.13)**	**0.002**	**0.12 (0.07,0.16)**	**<0.001**
Healthy Eating Index (z-score)*	**0.10 (0.04,0.15)**	**<0.001**	**0.07 (0.02,0.12)**	**0.012**	**0.09 (0.04,0.14)**	**0.001**	**0.08 (0.03,0.13)**	**0.001**
Education**	**0.21 (0.14,0.27)**	**<0.001**	**0.15 (0.08,0.21)**	**<0.001**	**0.16 (0.10,0.23)**	**<0.001**	**0.10 (0.03,0.17)**	**0.003**
Housing tenure (rent/other)	**-0.14 (-0.27,-0.01)**	**0.033**	-0.10 (-0.22,0.02)	0.113	-0.08 (-0.19,0.03)	0.142		
Number of systems medicated*	**-0.05 (-0.09,-0.01)**	**0.011**	**-0.04 (-0.08,-0.00)**	**0.028**	**-0.07 (-0.11,-0.03)**	**<0.001**	**-0.06 (-0.10,-0.02)**	**0.003**

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

Significant associations (p<0.05) are highlighted in bold and red

Appendix 12: Sex-stratified associations between participant characteristics and gait speed change

Participant characteristic	Gait speed change among men (z-score)				Gait speed change among women (z-score)†			
	Unadjusted		Mutually-adjusted		Unadjusted		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Race (black)	**0.17 (0.05,0.29)**	**0.005**	**0.16 (0.04,0.28)**	**0.007**	0.04 (-0.07,0.15)	0.465		
Age (z-score)*	**-0.07 (-0.13,-0.01)**	**0.018**	**-0.07 (-0.13,-0.02)**	**0.012**	-0.02 (-0.07,0.04)	0.550		
Height (z-score)*	-0.03 (-0.09,0.02)	0.265			-0.01 (-0.07,0.04)	0.648		
Weight-for-height residual (z-score)*	**-0.06 (-0.12,-0.00)**	**0.040**	-0.06 (-0.11,0.00)	0.060	-0.06 (-0.12,0.00)	0.055		
Ever smoked	-0.03 (-0.15,0.10)	0.677			-0.01 (-0.12,0.10)	0.847		
Alcohol consumption**	-0.01 (-0.06,0.05)	0.751			0.03 (-0.03,0.10)	0.293		
Physical activity (z-score)*	-0.00 (-0.06,0.06)	0.987			-0.01 (-0.07,0.04)	0.677		
Healthy Eating Index (z-score)*	0.01 (-0.05,0.07)	0.754			-0.05 (-0.10,0.01)	0.093		
Education**	0.00 (-0.07,0.08)	0.956			0.01 (-0.06,0.09)	0.737		
Housing tenure (rent/other)	-0.01 (-0.15,0.14)	0.931			-0.03 (-0.15,0.09)	0.638		
Number of systems medicated*	**-0.04 (-0.08,-0.00)**	**0.049**	-0.04 (-0.08,0.00)	0.075	-0.02 (-0.06,0.03)	0.406		

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

†Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for gait speed change illustrates that an increase/presence of the predictor was associated with reduced loss of gait speed over time and a negative coefficient reflects accelerated loss of gait speed

Significant associations ($p<0.05$) are highlighted in bold and red

Appendix 13: Sex-stratified associations between participant characteristics and appendicular lean mass level

Participant characteristic	ALM level among men (z-score)				ALM level among women (z-score)			
	Unadjusted		Mutually-adjusted		Unadjusted		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Race (black)	**0.46 (0.36,0.57)**	**<0.001**	**0.58 (0.48,0.67)**	**<0.001**	**0.93 (0.84,1.02)**	**<0.001**	**0.86 (0.78,0.95)**	**<0.001**
Age (z-score)*	**-0.16 (-0.21,-0.11)**	**<0.001**	**-0.12 (-0.16,-0.07)**	**<0.001**	**-0.14 (-0.19,-0.10)**	**<0.001**	**-0.08 (-0.12,-0.04)**	**<0.001**
Height (z-score)*	**0.53 (0.49,0.58)**	**<0.001**	**0.52 (0.48,0.57)**	**<0.001**	**0.37 (0.33,0.41)**	**<0.001**	**0.36 (0.32,0.40)**	**<0.001**
Weight-for-height residual (z-score)*	**0.65 (0.61,0.69)**	**<0.001**			**0.68 (0.65,0.71)**	**<0.001**		
Ever smoked	-0.03 (-0.14,0.08)	0.552			-0.03 (-0.12,0.06)	0.451		
Alcohol consumption**	-0.04 (-0.09,0.01)	0.120			**-0.06 (-0.12,-0.01)**	**0.015**	-0.03 (-0.08,0.01)	0.146
Physical activity (z-score)*	**0.21 (0.16,0.25)**	**<0.001**	**0.14 (0.10,0.19)**	**<0.001**	**0.19 (0.14,0.23)**	**<0.001**	**0.17 (0.13,0.21)**	**<0.001**
Healthy Eating Index (z-score)*	**0.06 (0.01,0.11)**	**0.03**	0.04 (-0.00,0.09)	0.059	0.04 (-0.01,0.09)	0.095		
Education**	-0.00 (-0.07,0.06)	0.945			**-0.12 (-0.18,-0.05)**	**<0.001**	**-0.13 (-0.18,-0.07)**	**<0.001**
Housing tenure (rent/other)	**-0.14 (-0.27,-0.02)**	**0.023**	-0.10 (-0.21,0.00)	0.061	0.03 (-0.07,0.13)	0.520		
Number of systems medicated*	-0.01 (-0.05,0.03)	0.547			**0.07 (0.03,0.10)**	**<0.001**	**0.07 (0.03,0.10)**	**<0.001**

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

Significant associations (p<0.05) are highlighted in bold and red

Appendix 14: Sex-stratified associations between participant characteristics and appendicular lean mass change

Participant characteristic	ALM change among men (z-score)				ALM change among women (z-score)†			
	Unadjusted		Mutually-adjusted		Unadjusted		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Race (black)	**-0.17 (-0.28,-0.06)**	**0.003**	-0.11 (-0.23,0.01)	0.074	0.07 (-0.04,0.17)	0.213	0.06 (-0.04,0.17)	0.221
Age (z-score)*	**-0.05 (-0.11,-0.00)**	**0.046**	-0.08 (-0.13,-0.02)	0.005	-0.05 (-0.10,0.01)	0.085	-0.03 (-0.08,0.02)	0.227
Height (z-score)*	-0.00 (-0.06,0.05)	0.937			**0.11 (0.06,0.17)**	**<0.001**	**0.11 (0.06,0.17)**	**<0.001**
Weight-for-height residual (z-score)*	**-0.06 (-0.12,-0.01)**	**0.020**	**-0.07 (-0.12,-0.01)**	**0.016**	0.04 (-0.01,0.10)	0.137		
Ever smoked	-0.10 (-0.22,0.01)	0.088			-0.01 (-0.12,0.09)	0.778		
Alcohol consumption**	0.03 (-0.02,0.08)	0.303			0.01 (-0.05,0.07)	0.782		
Physical activity (z-score)*	**-0.06 (-0.11,-0.01)**	**0.022**	-0.04 (-0.10,0.01)	0.107	0.02 (-0.03,0.07)	0.478		
Healthy Eating Index (z-score)*	**0.07 (0.02,0.13)**	**0.012**	**0.08 (0.02,0.13)**	**0.008**	0.04 (-0.02,0.09)	0.187		
Education**	0.05 (-0.02,0.12)	0.157			-0.00 (-0.07,0.07)	0.991		
Housing tenure (rent/other)	-0.01 (-0.14,0.12)	0.883			0.01 (-0.10,0.12)	0.843		
Number of systems medicated*	-0.02 (-0.06,0.02)	0.248			-0.03 (-0.07,0.01)	0.135		

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

†Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for ALM change illustrates that an increase/presence of the predictor was associated with reduced loss of ALM over time and a negative coefficient reflects accelerated loss of ALM

Significant associations (p<0.05) are highlighted in bold and red

Appendix 15: Sex-stratified associations between participant characteristics and fat mass level

Participant characteristic	Fat mass level among men (z-score)				Fat mass level among women (z-score)			
	Unadjusted		Mutually-adjusted		Unadjusted		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Race (black)	**-0.22 (-0.33,-0.11)**	**<0.001**	**-0.17 (-0.28,-0.07)**	**0.002**	**0.48 (0.38,0.58)**	**<0.001**	**0.39 (0.28,0.49)**	**<0.001**
Age (z-score)*	**-0.06 (-0.11,-0.00)**	**0.038**	-0.03 (-0.08,0.02)	0.248	**-0.12 (-0.16,-0.07)**	**<0.001**	**-0.08 (-0.13,-0.03)**	**0.001**
Height (z-score)*	**0.23 (0.18,0.28)**	**<0.001**	**0.22 (0.17,0.27)**	**<0.001**	**0.15 (0.11,0.20)**	**<0.001**	**0.14 (0.09,0.19)**	**<0.001**
Weight-for-height residual (z-score)*	**0.89 (0.86,0.91)**	**<0.001**			**0.96 (0.94,0.98)**	**<0.001**		
Ever smoked	0.10 (-0.02,0.21)	0.090			-0.02 (-0.12,0.08)	0.681		
Alcohol consumption**	-0.03 (-0.08,0.02)	0.312			**-0.06 (-0.12,-0.00)**	**0.038**	-0.03 (-0.09,0.02)	0.246
Physical activity (z-score)*	**0.10 (0.05,0.15)**	**<0.001**	**0.08 (0.03,0.13)**	**0.001**	**0.20 (0.15,0.25)**	**<0.001**	**0.22 (0.17,0.26)**	**<0.001**
Healthy Eating Index (z-score)*	0.01 (-0.05,0.06)	0.855			0.03 (-0.02,0.08)	0.252		
Education**	-0.01 (-0.08,0.06)	0.737			**-0.11 (-0.18,-0.04)**	**0.001**	**-0.10 (-0.17,-0.03)**	**0.004**
Housing tenure (rent/other)	0.02 (-0.11,0.15)	0.793			**0.14 (0.03,0.25)**	**0.010**	**0.18 (0.08,0.28)**	**0.001**
Number of systems medicated*	**0.05 (0.01,0.08)**	**0.016**	**0.06 (0.02,0.09)**	**0.003**	**0.08 (0.04,0.12)**	**<0.001**	**0.09 (0.05,0.12)**	**<0.001**

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

Significant associations (p<0.05) are highlighted in bold and red

Appendix 16: Sex-stratified associations between participant characteristics and fat mass change

Participant characteristic	Fat mass change among men (z-score)				Fat mass change among women (z-score)†			
	Unadjusted		Mutually-adjusted		Unadjusted		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Race (black)	-0.07 (-0.18,0.04)	0.214	-0.08 (-0.19,0.03)	0.162	**-0.17 (-0.27,-0.06)**	**0.001**	**-0.17 (-0.27,-0.06)**	**0.001**
Age (z-score)*	-0.02 (-0.07,0.03)	0.500	-0.03 (-0.08,0.03)	0.342	**-0.05 (-0.10,-0.00)**	**0.040**	**-0.05 (-0.10,-0.00)**	**0.040**
Height (z-score)*	-0.04 (-0.09,0.01)	0.139			0.05 (-0.00,0.10)	0.061		
Weight-for-height residual (z-score)*	-0.02 (-0.07,0.04)	0.564			-0.00 (-0.06,0.05)	0.982		
Ever smoked	-0.00 (-0.12,0.11)	0.997			0.02 (-0.08,0.13)	0.680		
Alcohol consumption**	-0.01 (-0.07,0.04)	0.567			-0.01 (-0.07,0.05)	0.682		
Physical activity (z-score)*	**-0.08 (-0.13,-0.03)**	**0.003**	**-0.08 (-0.13,-0.03)**	**0.003**	0.02 (-0.03,0.07)	0.485		
Healthy Eating Index (z-score)*	0.03 (-0.02,0.09)	0.256			0.04 (-0.01,0.10)	0.118		
Education**	0.00 (-0.07,0.07)	0.988			0.06 (-0.01,0.13)	0.095		
Housing tenure (rent/other)	0.00 (-0.13,0.14)	0.946			-0.03 (-0.14,0.08)	0.616		
Number of systems medicated*	0.01 (-0.03,0.05)	0.536			-0.01 (-0.05,0.04)	0.805		

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

†Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for fat mass change illustrates that an increase/presence of the predictor was associated with reduced loss of fat mass over time and a negative coefficient reflects accelerated loss of fat mass

Significant associations ($p<0.05$) are highlighted in bold and red

Appendix 17: Sex-stratified associations between participant characteristics and hip BMD level

Participant characteristic	Hip BMD level among men (z-score)				Hip BMD level among women (z-score)			
	Unadjusted		Mutually-adjusted		Unadjusted		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Race (black)	**0.50 (0.39,0.61)**	**<0.001**	**0.55 (0.45,0.66)**	**<0.001**	**0.61 (0.51,0.71)**	**<0.001**	**0.39 (0.29,0.48)**	**<0.001**
Age (z-score)*	**-0.07 (-0.12,-0.01)**	**0.015**	-0.03 (-0.08,0.02)	0.194	**-0.15 (-0.20,-0.10)**	**<0.001**	**-0.07 (-0.11,-0.02)**	**0.003**
Height (z-score)*	**0.12 (0.07,0.18)**	**<0.001**	**0.12 (0.07,0.17)**	**<0.001**	**0.10 (0.05,0.15)**	**<0.001**	**0.12 (0.07,0.16)**	**<0.001**
Weight-for-height residual (z-score)*	**0.40 (0.36,0.45)**	**<0.001**	**0.40 (0.35,0.45)**	**<0.001**	**0.52 (0.47,0.56)**	**<0.001**	**0.49 (0.45,0.54)**	**<0.001**
Ever smoked	-0.06 (-0.18,0.05)	0.266			-0.04 (-0.14,0.06)	0.389		
Alcohol consumption**	0.01 (-0.04,0.06)	0.614			**0.07 (0.01,0.12)**	**0.026**	**0.10 (0.05,0.15)**	**<0.001**
Physical activity (z-score)*	**0.13 (0.08,0.18)**	**<0.001**	**0.07 (0.02,0.11)**	**0.010**	**0.19 (0.14,0.24)**	**<0.001**	**0.08 (0.04,0.13)**	**<0.001**
Healthy Eating Index (z-score)*	**0.09 (0.04,0.15)**	**0.001**	**0.07 (0.02,0.12)**	**0.005**	**0.08 (0.02,0.13)**	**0.004**	**0.05 (0.00,0.09)**	**0.033**
Education**	0.05 (-0.02,0.12)	0.136			-0.02 (-0.09,0.05)	0.618		
Housing tenure (rent/other)	0.01 (-0.12,0.15)	0.844			-0.10 (-0.20,0.01)	0.084		
Number of systems medicated*	**0.04 (0.00,0.08)**	**0.028**	0.02 (-0.02,0.05)	0.293	**0.08 (0.04,0.12)**	**<0.001**	0.03 (-0.00,0.07)	0.058

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

Significant associations (p<0.05) are highlighted in bold and red

Appendix 18: Sex-stratified associations between participant characteristics and hip BMD change

Participant characteristic	Hip BMD change among men (z-score)				Hip BMD change among women (z-score)†			
	Unadjusted		Mutually-adjusted		Unadjusted		Mutually-adjusted	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Race (black)	**-0.27 (-0.39,-0.16)**	**<0.001**	**-0.23 (-0.35,-0.11)**	**<0.001**	**-0.39 (-0.49,-0.28)**	**<0.001**	**-0.39 (-0.49,-0.28)**	**<0.001**
Age (z-score)*	**-0.11 (-0.16,-0.06)**	**<0.001**	**-0.13 (-0.18,-0.07)**	**<0.001**	**-0.08 (-0.13,-0.02)**	**0.004**	**-0.08 (-0.14,-0.03)**	**0.002**
Height (z-score)*	**-0.06 (-0.11,-0.01)**	**0.031**	**-0.06 (-0.12,-0.00)**	**0.041**	-0.00 (-0.06,0.05)	0.912		
Weight-for-height residual (z-score)*	0.03 (-0.03,0.08)	0.303			-0.05 (-0.10,0.01)	0.101		
Ever smoked	0.03 (-0.09,0.15)	0.589			0.10 (0.00,0.21)	0.050		
Alcohol consumption**	0.03 (-0.02,0.08)	0.229			0.01 (-0.05,0.07)	0.791		
Physical activity (z-score)*	-0.03 (-0.08,0.03)	0.347			**-0.06 (-0.11,-0.01)**	**0.018**	**-0.06 (-0.11,-0.01)**	**0.018**
Healthy Eating Index (z-score)*	**0.07 (0.02,0.13)**	**0.012**	**0.08 (0.02,0.13)**	**0.010**	0.04 (-0.02,0.09)	0.202		
Education**	0.04 (-0.03,0.11)	0.242			0.06 (-0.01,0.13)	0.080		
Housing tenure (rent/other)	0.06 (-0.08,0.20)	0.404			0.10 (-0.01,0.21)	0.088		
Number of systems medicated*	-0.01 (-0.05,0.03)	0.770			-0.02 (-0.06,0.02)	0.359		

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

†Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

A positive regression coefficient for hip BMD change illustrates that an increase/presence of the predictor was associated with reduced loss of hip BMD over time and a negative coefficient reflects accelerated loss of hip BMD

Significant associations (p<0.05) are highlighted in bold and red

Appendix 19: Pearson correlations between changes in characteristics over Years 1-10 among white men

	Grip strength	Gait speed	ALM	Fat mass
Gait speed	**0.09**			
P-value	***0.006***			
ALM	**0.28**	**0.11**		
P-value	***<0.001***	***0.001***		
Fat mass	**0.09**	0.06	**0.40**	
P-value	***0.008***	*0.108*	***<0.001***	
Hip BMD	**0.27**	**0.22**	**0.44**	**0.24**
P-value	***<0.001***	***<0.001***	***<0.001***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Changes in gait speed were ascertained from Years 2-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

White men with at least two change measures (n=899) were included; each change measure requires values of the characteristic at two or more time-points from Years 1-10

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Appendix 20: Pearson correlations between changes in characteristics over Years 1-10 among black men

	Grip strength	Gait speed	ALM	Fat mass
Gait speed	**0.12**			
P-value	***0.012***			
ALM	**0.21**	0.03		
P-value	***<0.001***	*0.546*		
Fat mass	0.07	0.05	**0.44**	
P-value	*0.107*	*0.345*	***<0.001***	
Hip BMD	**0.18**	**0.13**	**0.37**	**0.30**
P-value	***<0.001***	***0.007***	***<0.001***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Changes in gait speed were ascertained from Years 2-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

Black men with at least two change measures (n=507) were included; each change measure requires values of the characteristic at two or more time-points from Years 1-10

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Appendix 21: Pearson correlations between changes in characteristics over Years 1-10 among white women

	Grip strength	Gait speed	ALM	Fat mass
Gait speed	**0.17**			
P-value	***<0.001***			
ALM	**0.17**	**0.08**		
P-value	***<0.001***	***0.021***		
Fat mass	**0.08**	0.02	**0.43**	
P-value	***0.028***	*0.675*	***<0.001***	
Hip BMD	**0.12**	**0.13**	**0.30**	**0.40**
P-value	***0.001***	***<0.001***	***<0.001***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Changes in gait speed were ascertained from Years 2-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

White women with at least two change measures (n=814) were included; each change measure requires values of the characteristic at two or more time-points from Years 1-10

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Appendix 22: Pearson correlations between changes in characteristics over Years 1-10 among black women

	Grip strength	Gait speed	ALM	Fat mass
Gait speed	**0.08**			
P-value	***0.043***			
ALM	**0.19**	0.04		
P-value	***<0.001***	*0.385*		
Fat mass	**0.16**	0.02	**0.51**	
P-value	***<0.001***	*0.699*	***<0.001***	
Hip BMD	**0.18**	**0.15**	**0.33**	**0.43**
P-value	***<0.001***	***<0.001***	***<0.001***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Changes in gait speed were ascertained from Years 2-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

Black women with at least two change measures (n=665) were included; each change measure requires values of the characteristic at two or more time-points from Years 1-10

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Appendix 23: Pearson correlations between changes in LMS z-scores over Years 1-6 in relation to changes in LMS z-scores over Years 6-10 among white men

Changes in LMS z-scores over Years 6-10	Changes in LMS z-scores over Years 1-6				
	Grip strength	**Gait speed**	**ALM**	**Fat mass**	**Hip BMD**
Grip strength	**-0.41**	-0.03	0.07	0.05	0.06
P-value	***<0.001***	*0.535*	*0.087*	*0.269*	*0.127*
Gait speed	0.06	**-0.15**	**0.15**	0.07	0.08
P-value	*0.130*	***<0.001***	***<0.001***	*0.091*	*0.074*
ALM	0.04	-0.06	-0.02	0.07	0.03
P-value	*0.324*	*0.188*	*0.716*	*0.119*	*0.449*
Fat mass	-0.02	-0.02	0.01	-0.03	0.07
P-value	*0.709*	*0.686*	*0.779*	*0.468*	*0.086*
Hip BMD	**0.11**	**0.16**	**0.22**	**0.08**	**0.16**
P-value	***0.007***	***<0.001***	***<0.001***	***0.049***	***<0.001***

BMD: Bone mineral density; ALM: Appendicular lean mass

Change in gait speed was derived over Years 2-6 and Years 6-10; change in hip BMD was derived over Years 1-5 and Years 5-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

White men with at least one change measure from both Years 1-6 and Years 6-10 were included (n=581); each change measure requires values of the characteristic at two or more time-points over the interval of assessment

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Appendix 24: Pearson correlations between changes in LMS z-scores over Years 1-6 in relation to changes in LMS z-scores over Years 6-10 among black men

Changes in LMS z-scores over Years 6-10	Changes in LMS z-scores over Years 1-6				
	Grip strength	**Gait speed**	**ALM**	**Fat mass**	**Hip BMD**
Grip strength	**-0.37**	-0.02	-0.01	**-0.16**	-0.05
P-value	***<0.001***	*0.721*	*0.847*	***0.014***	*0.428*
Gait speed	0.12	**-0.16**	-0.05	-0.01	0.07
P-value	*0.059*	***0.014***	*0.489*	*0.866*	*0.272*
ALM	-0.07	-0.06	-0.03	0.10	-0.05
P-value	*0.282*	*0.337*	*0.633*	*0.130*	*0.414*
Fat mass	**-0.13**	-0.03	0.00	-0.03	-0.04
P-value	***0.041***	*0.605*	*0.943*	*0.617*	*0.507*
Hip BMD	0.15	0.04	**0.28**	**0.16**	0.12
P-value	*0.019*	*0.562*	***<0.001***	***0.012***	*0.062*

BMD: Bone mineral density; ALM: Appendicular lean mass

Change in gait speed was derived over Years 2-6 and Years 6-10; change in hip BMD was derived over Years 1-5 and Years 5-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

Black men with at least one change measure from both Years 1-6 and Years 6-10 were included (n=243); each change measure requires values of the characteristic at two or more time-points over the interval of assessment

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Appendix 25: Pearson correlations between changes in LMS z-scores over Years 1-6 in relation to changes in LMS z-scores over Years 6-10 among white women

Changes in LMS z-scores over Years 6-10	Changes in LMS z-scores over Years 1-6				
	Grip strength	**Gait speed**	**ALM**	**Fat mass**	**Hip BMD**
Grip strength	**-0.27**	0.08	**0.10**	0.05	-0.07
P-value	***<0.001***	*0.055*	***0.021***	*0.251*	*0.096*
Gait speed	**0.10**	**-0.25**	0.04	0.03	0.07
P-value	***0.021***	***<0.001***	*0.405*	*0.552*	*0.102*
ALM	0.01	0.01	-0.02	0.07	0.01
P-value	*0.933*	*0.818*	*0.578*	*0.089*	*0.775*
Fat mass	0.01	0.06	0.05	0.05	0.07
P-value	*0.924*	*0.185*	*0.256*	*0.271*	*0.121*
Hip BMD	0.04	0.05	**0.12**	**0.21**	**0.10**
P-value	*0.310*	*0.235*	***0.005***	***<0.001***	***0.016***

BMD: Bone mineral density; ALM: Appendicular lean mass

Change in gait speed was derived over Years 2-6 and Years 6-10; change in hip BMD was derived over Years 1-5 and Years 5-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

White women with at least one change measure from both Years 1-6 and Years 6-10 were included (n=574); each change measure requires values of the characteristic at two or more time-points over the interval of assessment

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Appendix 26: Pearson correlations between changes in LMS z-scores over Years 1-6 in relation to changes in LMS z-scores over Years 6-10 among black women

Changes in LMS z-scores over Years 6-10	Changes in LMS z-scores over Years 1-6				
	Grip strength	Gait speed	ALM	Fat mass	Hip BMD
Grip strength	**-0.25**	0.03	**0.17**	**0.19**	**0.14**
P-value	***<0.001***	*0.582*	***<0.001***	***<0.001***	***0.005***
Gait speed	**0.12**	**-0.10**	0.09	0.03	**0.15**
P-value	***0.029***	***<0.001***	*0.098*	*0.57*	***0.005***
ALM	0.05	-0.08	0.05	0.10	0.05
P-value	*0.406*	*0.136*	*0.364*	*0.065*	*0.327*
Fat mass	-0.06	-0.02	**0.12**	**0.15**	0.097
P-value	*0.279*	*0.734*	***0.026***	***0.006***	*0.075*
Hip BMD	0.03	0.07	**0.18**	**0.21**	0.03
P-value	*0.524*	*0.189*	***<0.001***	***<0.001***	*0.557*

BMD: Bone mineral density; ALM: Appendicular lean mass

Change in gait speed was derived over Years 2-6 and Years 6-10; change in hip BMD was derived over Years 1-5 and Years 5-10

Change measures were ascertained by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Correlations between sex-specific z-scores for these change measures are presented

Black women with at least one change measure from both Years 1-6 and Years 6-10 were included (n=368); each change measure requires values of the characteristic at two or more time-points over the interval of assessment

Significant correlations ($p<0.05$) are in bold; correlations where $r>0.3$ are in bold and underlined

Appendix 27: Descriptive statistics for the survival analysis of adverse health outcomes with gait speed level and change as exposures

Characteristic [N(%) or median (lower quartile, upper quartile)]	All (n=2627)	White men (n=835)	Black men (n=432)	Men (n=1267)	White women (n=770)	Black women (n=590)	Women (n=1360)
Age at start of follow-up	78.3 (76.2, 80.8)	78.8 (76.5, 81.1)	78.3 (76.3, 80.7)	78.6 (76.4, 80.9)	78.5 (76.3, 80.8)	77.6 (75.9, 80.3)	78.1 (76.1, 80.6)
Follow-up time							
Death	9.4 (4.9, 11.6)	8.6 (4.5, 11.5)	7.3 (3.2, 11.4)	8.3 (4.0, 11.5)	10.6 (6.6, 11.7)	9.5 (5.2, 11.6)	10.3 (6.0, 11.7)
Fragility fracture	8.0 (3.8, 9.7)	7.9 (3.9, 9.6)	6.8 (2.9, 9.7)	7.7 (3.5, 9.6)	8.2 (3.8, 9.8)	8.6 (4.4, 9.8)	8.4 (4.1, 9.8)
Hospital admission	2.7 (0.9, 6.0)	2.4 (0.8, 5.4)	2.0 (0.8, 4.6)	2.3 (0.8, 5.2)	3.3 (1.3, 7.1)	2.9 (0.9, 6.4)	3.1 (1.1, 6.9)
Fall	2.5 (0.7, 5.1)	2.5 (0.9, 5.5)	2.5 (1.1, 5.9)	2.5 (1.0, 5.7)	2.0 (0.6, 4.8)	2.5 (0.6, 5.3)	2.4 (0.6, 4.9)
Occurrence during follow-up							
Death	1615 (61.5%)	550 (65.9%)	310 (71.8%)	860 (67.9%)	409 (53.1%)	346 (58.6%)	755 (55.5%)
Fragility fracture	390 (15.2%)	104 (12.7%)	22 (5.1%)	126 (10.1%)	205 (27.7%)	59 (10.3%)	264 (20.1%)
Hospital admission	2184 (83.1%)	711 (85.1%)	363 (84.0%)	1074 (84.8%)	628 (81.6%)	482 (81.7%)	1110 (81.6%)
Fall	1631 (71.4%)	505 (69.3%)	187 (56.5%)	692 (65.3%)	573 (81.4%)	366 (70.5%)	939 (76.8%)
Competing risk variable (fragility fracture)							
No fracture or death	1065 (41.6%)	332 (40.7%)	155 (36.0%)	487 (39.1%)	313 (42.4%)	265 (46.1%)	578 (44.0%)
Death and no fracture**	1106 (43.2%)	380 (46.6%)	254 (58.9%)	634 (50.8%)	221 (29.9%)	251 (43.7%)	472 (35.9%)
Fracture	390 (15.2%)	104 (12.7%)	22 (5.1%)	126 (10.1%)	205 (27.7%)	59 (10.3%)	264 (20.1%)
Competing risk variable (hospital admission)							
No admission or death	310 (11.8%)	75 (9.0%)	38 (8.8%)	113 (8.9%)	113 (14.7%)	84 (14.2%)	197 (14.5%)
Death and no admission**	133 (5.1%)	49 (5.9%)	31 (7.2%)	80 (6.3%)	29 (3.8%)	24 (4.1%)	53 (3.9%)
Admission	2184 (83.1%)	711 (85.1%)	363 (84.0%)	1074 (84.8%)	628 (81.6%)	482 (81.7%)	1110 (81.6%)
Prevalence before follow-up[†]							
Fragility fracture	128 (5.0%)	26 (3.2%)	5 (1.2%)	31 (2.5%)	72 (9.7%)	25 (4.3%)	97 (7.4%)
Hospital admission	1240 (47.2%)	441 (52.8%)	216 (50.0%)	657 (51.9%)	308 (40.0%)	275 (46.6%)	583 (42.9%)
Fall	1450 (63.5%)	450 (61.7%)	156 (47.1%)	606 (57.2%)	511 (72.6%)	333 (64.2%)	844 (69.0%)

N(%) relate to the number and proportion of participants experiencing the corresponding event

**Represent competing events as death prevents the failure event of interest from occurring

[†]Events occurring before participants were regarded as being at risk of adverse events in the survival analyses

252 (64.6%) of those who had a fracture during follow-up also died during follow-up; figures for hospital admission and falls were 1433 (65.6%) and 920 (56.4%)

Appendix 28: Descriptive statistics for the survival analysis of adverse health outcomes with ALM level and change as exposures

Characteristic [N(%) or median (lower quartile, upper quartile)]	All (n=2856)	White men (n=890)	Black men (n=497)	Men (n=1387)	White women (n=809)	Black women (n=660)	Women (n=1469)
Age at start of follow-up	78.2 (76.1, 80.7)	78.7 (76.3, 81.0)	77.9 (75.8, 80.2)	78.4 (76.2, 80.8)	78.4 (76.3, 80.8)	77.5 (75.9, 80.2)	78.0 (76.0, 80.5)
Follow-up time							
Death	8.9 (4.3, 11.6)	8.3 (4.0, 11.5)	6.4 (2.3, 11.2)	7.7 (3.3, 11.5)	10.4 (6.3, 11.7)	9.2 (4.6, 11.6)	10.0 (5.6, 11.7)
Fragility fracture	7.6 (3.2, 9.7)	7.6 (3.2, 9.6)	6.2 (2.2, 9.6)	6.9 (2.8, 9.6)	8.1 (3.4, 9.7)	8.1 (3.8, 9.7)	8.1 (3.6, 9.7)
Hospital admission	2.5 (0.8, 5.7)	2.2 (0.7, 5.2)	1.8 (0.7, 4.1)	2.1 (0.7, 4.9)	3.2 (1.1, 7.1)	2.7 (0.9, 6.2)	3.0 (1.0, 6.8)
Fall	2.4 (0.7, 5.0)	2.5 (0.8, 5.3)	2.5 (1.1, 5.8)	2.5 (1.0, 5.3)	2.0 (0.6, 4.8)	2.4 (0.6, 5.3)	2.1 (0.6, 4.9)
Occurrence during follow-up							
Death	1823 (63.8%)	606 (68.1%)	371 (74.6%)	977 (70.4%)	445 (55.0%)	401 (60.8%)	846 (57.6%)
Fragility fracture	417 (15.0%)	109 (12.5%)	25 (5.0%)	134 (9.8%)	213 (27.4%)	70 (10.9%)	283 (20.0%)
Hospital admission	2380 (83.3%)	758 (85.2%)	415 (83.5%)	1173 (84.6%)	663 (82.0%)	544 (82.4%)	1207 (82.2%)
Fall	1699 (71.1%)	520 (69.6%)	200 (55.9%)	720 (65.2%)	590 (81.0%)	389 (70.0%)	979 (76.2%)
Competing risk variable (fragility fracture)							
No fracture or death	1087 (39.0%)	335 (38.5%)	158 (31.9%)	493 (36.1%)	314 (40.5%)	280 (43.6%)	594 (41.9%)
Death and no fracture**	1280 (46.0%)	426 (49.0%)	313 (63.1%)	739 (54.1%)	249 (32.1%)	292 (45.5%)	541 (38.2%)
Fracture	417 (15.0%)	109 (12.5%)	25 (5.0%)	134 (9.8%)	213 (27.4%)	70 (10.9%)	283 (20.0%)
Competing risk variable (hospital admission)							
No admission or death	316 (11.1%)	77 (8.7%)	40 (8.0%)	117 (8.4%)	113 (14.0%)	86 (13.0%)	199 (13.5%)
Death and no admission**	160 (5.6%)	55 (6.2%)	42 (8.5%)	97 (7.0%)	33 (4.1%)	30 (4.5%)	63 (4.3%)
Admission	2380 (83.3%)	758 (85.2%)	415 (83.5%)	1173 (84.6%)	663 (82.0%)	544 (82.4%)	1207 (82.2%)
Prevalence before follow-up[†]							
Fragility fracture	132 (4.7%)	25 (2.9%)	6 (1.2%)	31 (2.3%)	74 (9.5%)	27 (4.2%)	101 (7.1%)
Hospital admission	1314 (46.0%)	460 (51.7%)	237 (47.7%)	697 (50.3%)	322 (39.8%)	295 (44.7%)	617 (42.0%)
Fall	1500 (62.8%)	456 (61.0%)	168 (46.9%)	624 (56.5%)	527 (72.4%)	349 (62.8%)	876 (68.2%)

N(%) relate to the number and proportion of participants experiencing the corresponding event

**Represent competing events as death prevents the failure event of interest from occurring

[†]Events occurring before participants were regarded as being at risk of adverse events in the survival analyses

277 (66.4%) of those who had a fracture during follow-up also died during follow-up; figures for hospital admission and falls were 1614 (67.8%) and 984 (57.9%)

Appendix 29: Descriptive statistics for the survival analysis of adverse health outcomes with fat mass level and change as exposures

Characteristic [N(%) or median (lower quartile, upper quartile)]	All (n=2857)	White men (n=892)	Black men (n=498)	Men (n=1390)	White women (n=808)	Black women (n=659)	Women (n=1467)
Age at start of follow-up	78.2 (76.1, 80.7)	78.7 (76.3, 81.0)	77.9 (75.8, 80.2)	78.4 (76.2, 80.8)	78.4 (76.3, 80.8)	77.5 (75.9, 80.2)	78.0 (76.0, 80.5)
Follow-up time							
Death	8.9 (4.3, 11.6)	8.3 (4.0, 11.5)	6.4 (2.3, 11.3)	7.7 (3.3, 11.5)	10.4 (6.3, 11.7)	9.2 (4.6, 11.6)	10.0 (5.6, 11.7)
Fragility fracture	7.6 (3.2, 9.7)	7.6 (3.2, 9.6)	6.2 (2.2, 9.6)	6.9 (2.8, 9.6)	8.1 (3.4, 9.7)	8.1 (3.9, 9.8)	8.1 (3.7, 9.7)
Hospital admission	2.5 (0.8, 5.7)	2.3 (0.7, 5.2)	1.8 (0.7, 4.2)	2.1 (0.7, 4.9)	3.2 (1.1, 7.1)	2.7 (0.9, 6.2)	3.0 (1.0, 6.8)
Fall	2.4 (0.7, 5.0)	2.5 (0.8, 5.3)	2.5 (1.1, 5.6)	2.5 (0.9, 5.4)	2.0 (0.6, 4.8)	2.4 (0.6, 5.4)	2.1 (0.6, 4.9)
Occurrence during follow-up							
Death	1821 (63.7%)	606 (67.9%)	371 (74.5%)	977 (70.3%)	444 (55.0%)	400 (60.7%)	844 (57.5%)
Fragility fracture	417 (15.0%)	109 (12.5%)	25 (5.0%)	134 (9.8%)	213 (27.5%)	70 (10.9%)	283 (20.0%)
Hospital admission	2379 (83.3%)	760 (85.2%)	415 (83.3%)	1175 (84.5%)	662 (81.9%)	542 (82.2%)	1204 (82.1%)
Fall	1701 (71.1%)	523 (69.7%)	199 (55.6%)	722 (65.2%)	590 (81.0%)	389 (70.1%)	979 (76.3%)
Competing risk variable (fragility fracture)							
No fracture or death	1090 (39.1%)	336 (38.5%)	160 (32.2%)	496 (36.2%)	314 (40.5%)	280 (43.7%)	594 (41.9%)
Death and no fracture**	1278 (45.9%)	427 (49.0%)	312 (62.8%)	739 (54.0%)	248 (32.0%)	291 (45.4%)	539 (38.1%)
Fracture	417 (15.0%)	109 (12.5%)	25 (5.0%)	134 (9.8%)	213 (27.5%)	70 (10.9%)	283 (20.0%)
Competing risk variable (hospital admission)							
No admission or death	317 (11.1%)	77 (8.6%)	40 (8.0%)	117 (8.4%)	113 (14.0%)	87 (13.2%)	200 (13.6%)
Death and no admission**	161 (5.6%)	55 (6.2%)	43 (8.6%)	98 (7.1%)	33 (4.1%)	30 (4.6%)	63 (4.3%)
Admission	2379 (83.3%)	760 (85.2%)	415 (83.3%)	1175 (84.5%)	662 (81.9%)	542 (82.2%)	1204 (82.1%)
Prevalence before follow-up[†]							
Fragility fracture	132 (4.7%)	26 (3.0%)	6 (1.2%)	32 (2.3%)	73 (9.4%)	27 (4.2%)	100 (7.1%)
Hospital admission	1311 (45.9%)	462 (51.8%)	236 (47.4%)	698 (50.2%)	321 (39.7%)	292 (44.3%)	613 (41.8%)
Fall	1504 (62.9%)	459 (61.2%)	169 (47.2%)	628 (56.7%)	527 (72.4%)	349 (62.9%)	876 (68.3%)

N(%) relate to the number and proportion of participants experiencing the corresponding event

**Represent competing events as death prevents the failure event of interest from occurring

[†]Events occurring before participants were regarded as being at risk of adverse events in the survival analyses

276 (66.2%) of those who had a fracture during follow-up also died during follow-up; figures for hospital admission and falls were 1611 (67.7%) and 983 (57.8%)

Appendix 30: Descriptive statistics for the survival analysis of adverse health outcomes with hip BMD level and change as exposures

Characteristic [N(%) or median (lower quartile, upper quartile)]	All (n=2630)	White men (n=831)	Black men (n=435)	Men (n=1266)	White women (n=763)	Black women (n=601)	Women (n=1364)
Age at start of follow-up	77.5 (75.4, 80.0)	77.9 (75.6, 80.3)	77.5 (75.4, 79.8)	77.8 (75.5, 80.2)	77.6 (75.5, 79.9)	76.9 (75.1, 79.6)	77.3 (75.3, 79.8)
Follow-up time							
Death	10.2 (5.6, 12.5)	9.4 (5.3, 12.5)	8.0 (3.6, 12.3)	9.1 (4.7, 12.4)	11.5 (7.4, 12.7)	10.2 (5.7, 12.5)	11.1 (6.8, 12.6)
Fragility fracture	8.8 (4.3, 10.6)	8.7 (4.5, 10.5)	7.7 (3.4, 10.5)	8.5 (4.1, 10.5)	9.1 (4.0, 10.7)	9.2 (4.8, 10.7)	9.1 (4.4, 10.7)
Hospital admission	2.9 (1.0, 6.3)	2.6 (0.9, 5.7)	2.3 (0.9, 4.8)	2.5 (0.9, 5.5)	3.5 (1.3, 7.7)	3.1 (1.0, 6.6)	3.4 (1.2, 7.3)
Fall	2.5 (0.6, 5.6)	2.5 (0.7, 5.8)	2.5 (1.1, 5.7)	2.5 (0.9, 5.8)	1.9 (0.5, 4.5)	1.9 (0.5, 5.1)	1.9 (0.5, 4.6)
Occurrence during follow-up							
Death	1627 (61.9%)	547 (65.8%)	313 (72.0%)	860 (67.9%)	408 (53.5%)	359 (59.7%)	767 (56.2%)
Fragility fracture	403 (15.7%)	110 (13.5%)	23 (5.3%)	133 (10.7%)	210 (28.6%)	60 (10.3%)	270 (20.5%)
Hospital admission	2227 (84.7%)	719 (86.5%)	370 (85.1%)	1089 (86.0%)	636 (83.4%)	502 (83.5%)	1138 (83.4%)
Fall	1731 (73.4%)	531 (71.0%)	212 (58.6%)	743 (66.9%)	586 (82.3%)	402 (74.9%)	988 (79.1%)
Competing risk variable (fragility fracture)							
No fracture or death	1051 (41.0%)	330 (40.6%)	155 (35.7%)	485 (38.9%)	305 (41.6%)	261 (44.8%)	566 (43.0%)
Death and no fracture**	1109 (43.3%)	373 (45.9%)	256 (59.0%)	629 (50.4%)	218 (29.7%)	262 (44.9%)	480 (36.5%)
Fracture	403 (15.7%)	110 (13.5%)	23 (5.3%)	133 (10.7%)	210 (28.6%)	60 (10.3%)	270 (20.5%)
Competing risk variable (hospital admission)							
No admission or death	280 (10.6%)	68 (8.2%)	33 (7.6%)	101 (8.0%)	102 (13.4%)	77 (12.8%)	179 (13.1%)
Death and no admission**	123 (4.7%)	44 (5.3%)	32 (7.4%)	76 (6.0%)	25 (3.3%)	22 (3.7%)	47 (3.4%)
Admission	2227 (84.7%)	719 (86.5%)	370 (85.1%)	1089 (86.0%)	636 (83.4%)	502 (83.5%)	1138 (83.4%)
Prevalence before follow-up[†]							
Fragility fracture	100 (3.9%)	19 (2.3%)	5 (1.2%)	24 (1.9%)	56 (7.6%)	20 (3.4%)	76 (5.8%)
Hospital admission	1040 (39.5%)	367 (44.2%)	179 (41.1%)	546 (43.1%)	258 (33.8%)	236 (39.3%)	494 (36.2%)
Fall	1376 (58.3%)	419 (56.0%)	158 (43.6%)	577 (52.0%)	476 (66.9%)	323 (60.1%)	799 (64.0%)

N(%) relate to the number and proportion of participants experiencing the corresponding event

**Represent competing events as death prevents the failure event of interest from occurring

[†]Events occurring before participants were regarded as being at risk of adverse events in the survival analyses

263 (65.3%) of those who had a fracture during follow-up also died during follow-up; figures for hospital admission and falls were 1461 (65.6%) and 1000 (57.8%)

Appendix 31: Baseline characteristics in relation to risk of mortality

Baseline characteristic	Adjusted for sex and race		Mutually-adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (z-score)*	**1.31 (1.26,1.37)**	**<0.001**	**1.30 (1.24,1.36)**	**<0.001**
Height (z-score)*	1.02 (0.98,1.07)	0.276		
Weight-for-height residual (z-score)*	**0.93 (0.88,0.97)**	**0.001**	**0.92 (0.87,0.97)**	**0.001**
Ever smoked	**1.28 (1.16,1.40)**	**<0.001**	**1.25 (1.12,1.39)**	**<0.001**
Alcohol consumption**	**0.94 (0.90,0.99)**	**0.012**	0.95 (0.90,1.00)	0.055
Physical activity (z-score)*	**0.86 (0.82,0.90)**	**<0.001**	**0.91 (0.86,0.96)**	**<0.001**
Healthy Eating Index (z-score)*	**0.93 (0.89,0.98)**	**0.004**	0.95 (0.91,1.00)	0.065
Education**	**0.87 (0.83,0.93)**	**<0.001**	**0.93 (0.87,0.99)**	**0.030**
Housing tenure (rent/other)	**1.24 (1.12,1.37)**	**<0.001**	**1.18 (1.05,1.31)**	**0.004**
Number of systems medicated*	**1.08 (1.05,1.12)**	**<0.001**	**1.10 (1.06,1.14)**	**<0.001**

HR: Hazard ratio

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

Age at baseline and a four-level sex-race variable were included in all models

Estimates were derived from Cox models

Significant associations ($p<0.05$) are highlighted in bold and red

Appendix 32: Baseline participant characteristics in relation to risk of fragility fracture

Baseline characteristic	Cox model				Competing risk model			
	Adjusted for sex and race		Mutually-adjusted		Adjusted for sex and race		Mutually-adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (z-score)*	**1.26 (1.15,1.37)**	**<0.001**	**1.22 (1.12,1.33)**	**<0.001**	**1.18 (1.08,1.28)**	**<0.001**	**1.15 (1.06,1.26)**	**0.001**
Height (z-score)*	1.03 (0.95,1.13)	0.428			1.03 (0.95,1.12)	0.454		
Weight-for-height residual (z-score)*	**0.86 (0.78,0.94)**	**0.002**	**0.88 (0.80,0.97)**	**0.009**	**0.88 (0.80,0.97)**	**0.009**	**0.89 (0.81,0.98)**	**0.022**
Ever smoked	0.95 (0.80,1.13)	0.564			0.87 (0.73,1.04)	0.127		
Alcohol consumption**	0.91 (0.83,1.00)	0.055			0.93 (0.85,1.02)	0.108		
Physical activity (z-score)*	**0.90 (0.82,0.99)**	**0.025**	0.93 (0.84,1.02)	0.129	0.96 (0.87,1.05)	0.376		
Healthy Eating Index (z-score)*	0.92 (0.84,1.01)	0.07			0.93 (0.85,1.01)	0.098		
Education**	1.12 (1.00,1.27)	0.059			**1.15 (1.02,1.30)**	**0.022**	**1.14 (1.01,1.30)**	**0.038**
Housing tenure (rent/other)	**1.32 (1.09,1.59)**	**0.004**	**1.30 (1.08,1.58)**	**0.006**	**1.23 (1.02,1.49)**	**0.027**	**1.26 (1.04,1.52)**	**0.016**
Number of systems medicated*	1.07 (1.00,1.14)	0.056			1.05 (0.98,1.12)	0.177		

HR: Hazard ratio

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

Age at baseline and a four-level sex-race variable were included in all models

Significant associations (p<0.05) are highlighted in bold and red

Appendix 33: Baseline participant characteristics in relation to risk of hospital admission

Baseline characteristic	Cox model				Competing risk model			
	Adjusted for sex and race		Mutually-adjusted		Adjusted for sex and race		Mutually-adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (z-score)*	**1.09 (1.05,1.13)**	**<0.001**	**1.08 (1.04,1.12)**	**<0.001**	**1.07 (1.03,1.11)**	**<0.001**	**1.07 (1.03,1.11)**	**0.001**
Height (z-score)*	0.99 (0.96,1.03)	0.639			1.00 (0.96,1.03)	0.862		
Weight-for-height residual (z-score)*	1.03 (0.99,1.07)	0.161			1.04 (1.00,1.08)	0.081		
Ever smoked	**1.18 (1.09,1.28)**	**<0.001**	**1.17 (1.08,1.26)**	**<0.001**	**1.14 (1.06,1.24)**	**0.001**	**1.13 (1.05,1.23)**	**0.002**
Alcohol consumption**	0.96 (0.92,1.00)	0.057			0.97 (0.93,1.01)	0.116		
Physical activity (z-score)*	**0.95 (0.92,0.99)**	**0.02**	0.97 (0.93,1.01)	0.153	0.96 (0.93,1.00)	0.067		
Healthy Eating Index (z-score)*	0.96 (0.93,1.00)	0.074			0.98 (0.94,1.02)	0.219		
Education**	0.97 (0.92,1.02)	0.269			0.99 (0.94,1.05)	0.772		
Housing tenure (rent/other)	**1.14 (1.05,1.25)**	**0.002**	**1.13 (1.03,1.23)**	**0.007**	**1.15 (1.05,1.25)**	**0.002**	**1.14 (1.05,1.25)**	**0.003**
Number of systems medicated*	**1.13 (1.10,1.17)**	**<0.001**	**1.14 (1.10,1.17)**	**<0.001**	**1.13 (1.10,1.16)**	**<0.001**	**1.13 (1.10,1.17)**	**<0.001**

HR: Hazard ratio

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

Age at baseline and a four-level sex-race variable were included in all models

Significant associations (p<0.05) are highlighted in bold and red

Appendix 34: Baseline participant characteristics in relation to risk of falls

Baseline characteristic	Cox model with no stratification				Cox model stratified for falls in past 12 months			
	Adjusted for sex and race		Mutually-adjusted		Adjusted for sex and race		Mutually-adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (z-score)*	**1.08 (1.03,1.12)**	**0.001**	**1.09 (1.04,1.13)**	**<0.001**	**1.08 (1.03,1.12)**	**0.001**	**1.08 (1.04,1.13)**	**<0.001**
Height (z-score)*	0.96 (0.92,1.00)	0.069			0.97 (0.93,1.01)	0.174		
Weight-for-height residual (z-score)*	**1.06 (1.01,1.11)**	**0.014**	1.04 (0.99,1.09)	0.086	**1.06 (1.01,1.11)**	**0.013**	**1.05 (1.00,1.10)**	**0.037**
Ever smoked	1.00 (0.92,1.09)	0.955			1.01 (0.93,1.10)	0.796		
Alcohol consumption**	1.01 (0.96,1.05)	0.778			1.00 (0.96,1.05)	0.854		
Physical activity (z-score)*	**1.04 (1.00,1.09)**	**0.046**	1.04 (1.00,1.09)	0.068	1.04 (0.99,1.08)	0.104		
Healthy Eating Index (z-score)*	0.99 (0.95,1.04)	0.665			0.99 (0.94,1.03)	0.537		
Education**	**1.07 (1.01,1.13)**	**0.017**	**1.06 (1.01,1.13)**	**0.031**	**1.06 (1.00,1.12)**	**0.039**	**1.06 (1.00,1.12)**	**0.042**
Housing tenure (rent/other)	0.96 (0.87,1.06)	0.457			0.96 (0.87,1.06)	0.451		
Number of systems medicated*	**1.08 (1.04,1.11)**	**<0.001**	**1.07 (1.04,1.11)**	**<0.001**	**1.08 (1.04,1.12)**	**<0.001**	**1.07 (1.04,1.11)**	**<0.001**

HR: Hazard ratio

*Estimate per unit increase in characteristic; **Estimate per higher band of characteristic; other estimates are for the presence versus absence of the characteristic

Age at baseline and a four-level sex-race variable were included in all models

Significant associations (p<0.05) are highlighted in bold and red

Appendix 35: Risk of adverse outcomes per SD decrease in grip strength level and per SD increase in grip strength decline (fully-adjusted associations for main results and sensitivity analyses are presented)

Outcome	Model	Mean grip strength level over Years 1-6 (z-score)				Grip strength decline over Years 1-6 (z-score)*			
		Stratified Cox model		Competing risk model		Stratified Cox model		Competing risk model	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Death	1	1.25 (1.18,1.32)	<0.001			1.15 (1.10,1.21)	<0.001		
	2	1.22 (1.15,1.30)	<0.001			1.13 (1.08,1.19)	<0.001		
	3	1.22 (1.13,1.32)	<0.001			1.15 (1.09,1.22)	<0.001		
	4	1.25 (1.18,1.33)	<0.001			1.15 (1.09,1.20)	<0.001		
Fragility fracture	1	1.22 (1.08,1.38)	0.001	1.13 (1.01,1.27)	0.040	1.04 (0.94,1.15)	0.418	0.99 (0.90,1.10)	0.883
	2	1.22 (1.08,1.37)	0.001	1.13 (1.01,1.28)	0.037	1.03 (0.93,1.14)	0.561	0.98 (0.89,1.09)	0.763
	3	1.34 (1.15,1.57)	<0.001	1.26 (1.08,1.47)	0.003	1.02 (0.91,1.14)	0.721	0.98 (0.87,1.10)	0.761
	4	1.20 (1.06,1.35)	0.004	1.11 (0.98,1.25)	0.100	1.05 (0.95,1.17)	0.308	1.00 (0.90,1.11)	0.987
Hospital admission	1	1.21 (1.15,1.27)	<0.001	1.18 (1.12,1.24)	<0.001	1.06 (1.02,1.11)	0.006	1.04 (1.00,1.09)	0.044
	2	1.20 (1.14,1.26)	<0.001	1.18 (1.12,1.24)	<0.001	1.05 (1.00,1.09)	0.039	1.03 (0.99,1.07)	0.161
	3	1.17 (1.10,1.25)	<0.001	1.16 (1.08,1.23)	<0.001	1.05 (1.01,1.11)	0.030	1.04 (1.00,1.10)	0.076
	4	1.21 (1.15,1.27)	<0.001	1.18 (1.12,1.24)	<0.001	1.06 (1.02,1.11)	0.006	1.04 (1.00,1.09)	0.053
Fall	1	1.13 (1.07,1.20)	<0.001			1.03 (0.98,1.08)	0.256		
	2	1.13 (1.06,1.20)	<0.001			1.02 (0.97,1.07)	0.394		
	3	1.12 (1.04,1.20)	0.002			1.02 (0.97,1.08)	0.415		
	4	1.14 (1.07,1.20)	<0.001			1.03 (0.98,1.08)	0.289		

HR: Hazard ratio SD: Standard deviation

*Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls and as an adjustment in competing risk models for fragility fracture and hospital admission

Supplementary material

Model 1: Estimates from main analysis
Model 2: Models for level adjusted for change parameter and vice versa
Model 3: Analyses restricted to individuals with complete data from Years 1-6 for the corresponding parameter
Model 4: Additionally adjusted for baseline characteristics associated with risk of ≥2 adverse outcomes

Appendix 36: Risk of adverse outcomes per SD decrease in gait speed level and per SD increase in gait speed decline (fully-adjusted associations for main results and sensitivity analyses are presented)

Outcome	Model	Mean gait speed level over Years 1-6 (z-score)				Gait speed decline over Years 1-6 (z-score)*			
		Stratified Cox model		Competing risk model		Stratified Cox model		Competing risk model	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Death	1	1.54 (1.45,1.63)	<0.001			1.19 (1.13,1.24)	<0.001		
	2	1.50 (1.41,1.59)	<0.001			1.12 (1.06,1.17)	<0.001		
	3	1.49 (1.37,1.61)	<0.001			1.22 (1.15,1.29)	<0.001		
	4	1.52 (1.43,1.61)	<0.001			1.18 (1.12,1.24)	<0.001		
Fragility fracture	1	1.19 (1.05,1.34)	0.006	1.04 (0.93,1.17)	0.514	1.09 (0.99,1.20)	0.082	1.03 (0.93,1.13)	0.604
	2	1.17 (1.03,1.32)	0.013	1.03 (0.92,1.16)	0.589	1.07 (0.97,1.18)	0.182	1.02 (0.93,1.13)	0.655
	3	1.12 (0.96,1.31)	0.146	1.02 (0.88,1.18)	0.774	1.07 (0.96,1.20)	0.217	1.02 (0.91,1.13)	0.761
	4	1.20 (1.06,1.35)	0.004	1.05 (0.93,1.18)	0.413	1.11 (1.00,1.22)	0.043	1.04 (0.95,1.15)	0.378
Hospital admission	1	1.27 (1.21,1.34)	<0.001	1.24 (1.17,1.31)	<0.001	1.16 (1.11,1.21)	<0.001	1.14 (1.09,1.19)	<0.001
	2	1.24 (1.18,1.31)	<0.001	1.21 (1.14,1.28)	<0.001	1.12 (1.07,1.17)	<0.001	1.11 (1.06,1.16)	<0.001
	3	1.20 (1.12,1.28)	<0.001	1.18 (1.09,1.27)	<0.001	1.17 (1.11,1.22)	<0.001	1.16 (1.10,1.22)	<0.001
	4	1.26 (1.20,1.33)	<0.001	1.23 (1.16,1.30)	<0.001	1.15 (1.11,1.21)	<0.001	1.14 (1.09,1.18)	<0.001
Fall	1	1.16 (1.09,1.24)	<0.001			1.13 (1.07,1.18)	<0.001		
	2	1.14 (1.07,1.21)	<0.001			1.11 (1.06,1.16)	<0.001		
	3	1.15 (1.06,1.24)	<0.001			1.14 (1.08,1.20)	<0.001		
	4	1.17 (1.10,1.24)	<0.001			1.12 (1.07,1.18)	<0.001		

HR: Hazard ratio SD: Standard deviation

*Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

Supplementary material

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls and as an adjustment in competing risk models for fragility fracture and hospital admission

Model 1: Estimates from main analysis

Model 2: Models for level adjusted for change parameter and vice versa

Model 3: Analyses restricted to individuals with complete data from Years 1-6 for the corresponding parameter

Model 4: Additionally adjusted for baseline characteristics associated with risk of ≥2 adverse outcomes

Appendix 37: Risk of adverse outcomes per SD decrease in ALM level and per SD increase in ALM decline (fully-adjusted associations for main results and sensitivity analyses are presented)

Outcome	Model	Mean ALM level over Years 1-6 (z-score)				ALM decline over Years 1-6 (z-score)*			
		Stratified Cox model		Competing risk model		Stratified Cox model		Competing risk model	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Death	1	1.18 (1.10,1.26)	<0.001			1.20 (1.14,1.26)	<0.001		
	2	1.14 (1.07,1.22)	<0.001			1.18 (1.13,1.24)	<0.001		
	3	1.15 (1.05,1.25)	0.003			1.20 (1.13,1.28)	<0.001		
	4	1.18 (1.10,1.25)	<0.001			1.19 (1.13,1.25)	<0.001		
Fragility fracture	1	1.18 (1.02,1.37)	0.024	1.11 (0.96,1.29)	0.149	1.07 (0.97,1.18)	0.202	1.00 (0.91,1.10)	0.994
	2	1.17 (1.01,1.36)	0.037	1.12 (0.96,1.31)	0.136	1.04 (0.94,1.15)	0.435	0.98 (0.89,1.08)	0.699
	3	1.26 (1.05,1.52)	0.014	1.20 (0.99,1.46)	0.070	1.09 (0.97,1.23)	0.143	1.03 (0.93,1.15)	0.548
	4	1.19 (1.02,1.38)	0.026	1.12 (0.96,1.30)	0.139	1.06 (0.96,1.18)	0.234	1.00 (0.91,1.10)	0.963
Hospital admission	1	1.05 (1.00,1.11)	0.071	1.05 (0.99,1.11)	0.097	1.10 (1.06,1.15)	<0.001	1.09 (1.04,1.14)	<0.001
	2	1.03 (0.98,1.09)	0.259	1.03 (0.97,1.09)	0.288	1.10 (1.05,1.15)	<0.001	1.09 (1.04,1.14)	<0.001
	3	1.04 (0.97,1.12)	0.296	1.02 (0.95,1.09)	0.600	1.10 (1.04,1.16)	<0.001	1.08 (1.03,1.15)	0.003
	4	1.05 (1.00,1.12)	0.067	1.05 (0.99,1.11)	0.093	1.10 (1.05,1.15)	<0.001	1.09 (1.04,1.14)	<0.001
Fall	1	1.00 (0.93,1.06)	0.898			1.08 (1.03,1.14)	0.002		
	2	0.98 (0.91,1.05)	0.508			1.09 (1.03,1.14)	0.002		
	3	1.00 (0.93,1.08)	0.986			1.09 (1.03,1.16)	0.002		
	4	0.99 (0.92,1.06)	0.693			1.07 (1.02,1.13)	0.006		

HR: Hazard ratio SD: Standard deviation

*Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls and as an adjustment in competing risk models for fragility fracture and hospital admission

Supplementary material

Model 1: Estimates from main analysis
Model 2: Models for level adjusted for change parameter and vice versa
Model 3: Analyses restricted to individuals with complete data from Years 1-6 for the corresponding parameter
Model 4: Additionally adjusted for baseline characteristics associated with risk of ≥2 adverse outcomes

Appendix 38: Risk of adverse outcomes per SD decrease in fat mass level and per SD increase in fat mass decline (fully-adjusted associations for main results and sensitivity analyses are presented)

Outcome	Model	Mean fat mass level over Years 1-6 (z-score)				Fat mass decline over Years 1-6 (z-score)*			
		Stratified Cox model		Competing risk model		Stratified Cox model		Competing risk model	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Death	1	1.15 (1.09,1.21)	<0.001			1.19 (1.14,1.25)	<0.001		
	2	1.11 (1.05,1.17)	<0.001			1.17 (1.11,1.23)	<0.001		
	3	1.11 (1.03,1.19)	0.006			1.22 (1.14,1.30)	<0.001		
	4	1.16 (1.09,1.22)	<0.001			1.19 (1.13,1.25)	<0.001		
Fragility fracture	1	1.22 (1.08,1.37)	0.001	1.16 (1.03,1.31)	0.014	1.09 (0.98,1.21)	0.111	1.01 (0.91,1.11)	0.866
	2	1.20 (1.06,1.36)	0.003	1.17 (1.03,1.32)	0.014	1.05 (0.94,1.17)	0.355	0.98 (0.88,1.08)	0.663
	3	1.22 (1.06,1.42)	0.007	1.18 (1.02,1.38)	0.027	1.11 (0.97,1.26)	0.131	1.03 (0.91,1.16)	0.668
	4	1.21 (1.07,1.37)	0.002	1.15 (1.02,1.30)	0.019	1.09 (0.98,1.22)	0.114	1.01 (0.91,1.12)	0.827
Hospital admission	1	1.03 (0.99,1.08)	0.155	1.02 (0.97,1.07)	0.403	1.07 (1.02,1.11)	0.005	1.06 (1.01,1.11)	0.011
	2	1.02 (0.97,1.07)	0.386	1.01 (0.96,1.05)	0.793	1.07 (1.02,1.11)	0.007	1.06 (1.01,1.12)	0.011
	3	1.01 (0.95,1.07)	0.711	0.99 (0.94,1.05)	0.807	1.05 (0.99,1.11)	0.082	1.03 (0.97,1.09)	0.339
	4	1.04 (0.99,1.09)	0.116	1.02 (0.98,1.07)	0.342	1.07 (1.02,1.11)	0.006	1.06 (1.01,1.11)	0.015
Fall	1	0.97 (0.92,1.03)	0.283			1.02 (0.97,1.07)	0.481		
	2	0.96 (0.91,1.02)	0.204			1.03 (0.97,1.08)	0.326		
	3	0.96 (0.90,1.02)	0.210			0.99 (0.93,1.06)	0.809		
	4	0.96 (0.91,1.02)	0.162			1.02 (0.97,1.08)	0.459		

HR: Hazard ratio SD: Standard deviation

*Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls and as an adjustment in competing risk models for fragility fracture and hospital admission

Supplementary material

Model 1: Estimates from main analysis
Model 2: Models for level adjusted for change parameter and vice versa
Model 3: Analyses restricted to individuals with complete data from Years 1-6 for the corresponding parameter
Model 4: Additionally adjusted for baseline characteristics associated with risk of ≥2 adverse outcomes

Appendix 39: Risk of adverse outcomes per SD decrease in hip BMD level and per SD increase in hip BMD decline (fully-adjusted associations for main results and sensitivity analyses are presented)

Outcome	Model	Mean hip BMD level over Years 1-6 (z-score)				Hip BMD decline over Years 1-6 (z-score)*			
		Stratified Cox model		Competing risk model		Stratified Cox model		Competing risk model	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Death	1	1.09 (1.03,1.17)	0.006			1.23 (1.17,1.30)	<0.001		
	2	1.10 (1.03,1.17)	0.004			1.23 (1.17,1.30)	<0.001		
	3	1.06 (0.99,1.14)	0.110			1.24 (1.17,1.32)	<0.001		
	4	1.10 (1.03,1.18)	0.003			1.25 (1.18,1.32)	<0.001		
Fragility fracture	1	2.01 (1.75,2.31)	<0.001	1.89 (1.64,2.19)	<0.001	1.16 (1.05,1.29)	0.005	1.09 (0.98,1.21)	0.096
	2	2.03 (1.76,2.34)	<0.001	1.90 (1.64,2.19)	<0.001	1.19 (1.08,1.32)	0.001	1.11 (1.00,1.22)	0.043
	3	1.94 (1.66,2.27)	<0.001	1.87 (1.60,2.20)	<0.001	1.18 (1.06,1.32)	0.003	1.11 (1.00,1.25)	0.055
	4	2.10 (1.82,2.42)	<0.001	1.97 (1.70,2.28)	<0.001	1.18 (1.06,1.31)	0.002	1.11 (0.99,1.23)	0.068
Hospital admission	1	1.09 (1.03,1.15)	0.004	1.08 (1.03,1.14)	0.004	1.08 (1.04,1.14)	0.001	1.06 (1.01,1.11)	0.014
	2	1.09 (1.03,1.15)	0.003	1.08 (1.03,1.14)	0.004	1.08 (1.04,1.14)	0.001	1.06 (1.01,1.11)	0.014
	3	1.07 (1.01,1.14)	0.023	1.08 (1.02,1.15)	0.011	1.08 (1.03,1.13)	0.003	1.06 (1.00,1.11)	0.039
	4	1.09 (1.03,1.15)	0.003	1.09 (1.03,1.15)	0.003	1.10 (1.05,1.15)	<0.001	1.07 (1.02,1.12)	0.006
Fall	1	1.04 (0.98,1.10)	0.202			1.09 (1.04,1.15)	0.001		
	2	1.05 (0.99,1.11)	0.133			1.09 (1.04,1.15)	0.001		
	3	1.02 (0.96,1.09)	0.464			1.09 (1.03,1.14)	0.003		
	4	1.05 (0.98,1.11)	0.152			1.09 (1.04,1.15)	0.001		

HR: Hazard ratio SD: Standard deviation

*Derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls and as an adjustment in competing risk models for fragility fracture and hospital admission

Supplementary material

Model 1: Estimates from main analysis
Model 2: Models for level adjusted for change parameter and vice versa
Model 3: Analyses restricted to individuals with complete data from Years 1-6 for the corresponding parameter
Model 4: Additionally adjusted for baseline characteristics associated with risk of ≥2 adverse outcomes

Appendix 40: Quadratic and linear effects for levels of musculoskeletal and body composition characteristics in relation to risk of adverse health outcomes

Characteristic	Term	Death		Fragility fracture		Hospital admission		Fall	
		Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
Grip strength	Linear (β_1)	**0.22 (0.16,0.27)**	**<0.001**	**0.23 (0.10,0.36)**	**0.001**	**0.19 (0.14,0.24)**	**<0.001**	**0.12 (0.07,0.18)**	**<0.001**
	Quadratic (β_2)	0.03 (-0.01,0.06)	0.114	-0.07 (-0.15,0.01)	0.096	0.02 (-0.01,0.05)	0.164	0.00 (-0.03,0.04)	0.934
Gait speed	Linear (β_1)	**0.46 (0.40,0.53)**	**<0.001**	**0.17 (0.05,0.30)**	**0.008**	**0.24 (0.19,0.29)**	**<0.001**	**0.15 (0.09,0.21)**	**<0.001**
	Quadratic (β_2)	**-0.05 (-0.09,-0.01)**	**0.012**	-0.04 (-0.12,0.04)	0.353	0.02 (-0.01,0.05)	0.266	0.02 (-0.01,0.06)	0.179
ALM	Linear (β_1)	**0.18 (0.11,0.25)**	**<0.001**	**0.19 (0.04,0.33)**	**0.011**	**0.08 (0.02,0.14)**	**0.008**	0.00 (-0.07,0.07)	0.971
	Quadratic (β_2)	0.03 (-0.00,0.06)	0.076	0.06 (-0.01,0.13)	0.098	**0.04 (0.01,0.06)**	**0.009**	0.01 (-0.02,0.04)	0.607
Fat mass	Linear (β_1)	**0.16 (0.10,0.21)**	**<0.001**	**0.21 (0.09,0.33)**	**0.001**	**0.06 (0.01,0.11)**	**0.025**	0.02 (-0.04,0.08)	0.568
	Quadratic (β_2)	**0.03 (0.00,0.06)**	**0.027**	0.04 (-0.03,0.11)	0.252	**0.03 (0.00,0.05)**	**0.022**	0.06 (0.03,0.09)	<0.001
Hip BMD	Linear (β_1)	**0.12 (0.05,0.18)**	**<0.001**	**0.68 (0.52,0.84)**	**<0.001**	**0.11 (0.06,0.17)**	**<0.001**	0.04 (-0.02,0.11)	0.151
	Quadratic (β_2)	**0.05 (0.02,0.08)**	**0.001**	0.02 (-0.06,0.10)	0.635	**0.05 (0.02,0.08)**	**<0.001**	0.01 (-0.02,0.04)	0.448

P: P-value; ALM: Appendicular lean mass; BMD: Bone mineral density

Sex-specific z-scores were calculated for mean levels of characteristics over Years 1-6

The hazard ratio for a decrease in the level of the characteristic from x to x-1 on the SD scale is given by $\exp(\beta_1 + \beta_2[2x+1])$

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls

Models were adjusted for the four-level sex-race variable, age, height, weight-for-height residual (not included in models for ALM and fat mass) physical activity, alcohol consumption, diet quality, education and number of systems medicated

Significant associations ($p<0.05$) are highlighted in bold and red

Appendix 41: Quadratic and linear effects for changes in musculoskeletal and body composition characteristics in relation to risk of adverse health outcomes

Characteristic	Term	Death		Fragility fracture		Hospital admission		Fall	
		Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
Grip strength	Linear	**0.15 (0.10,0.19)**	**<0.001**	0.04 (-0.05,0.14)	0.372	**0.06 (0.02,0.10)**	**0.006**	0.03 (-0.02,0.08)	0.266
	Quadratic	-0.02 (-0.05,0.01)	0.211	0.04 (-0.02,0.10)	0.212	0.01 (-0.02,0.03)	0.714	-0.01 (-0.04,0.02)	0.514
Gait speed	Linear	**0.20 (0.14,0.25)**	**<0.001**	0.11 (-0.00,0.21)	0.051	**0.15 (0.10,0.19)**	**<0.001**	**0.13 (0.08,0.18)**	**<0.001**
	Quadratic	**-0.04 (-0.07,-0.01)**	**0.005**	-0.04 (-0.10,0.02)	0.166	-0.00 (-0.03,0.02)	0.758	-0.02 (-0.05,0.01)	0.114
ALM	Linear	**0.15 (0.10,0.20)**	**<0.001**	0.08 (-0.03,0.19)	0.131	**0.08 (0.04,0.12)**	**<0.001**	**0.08 (0.02,0.13)**	**0.004**
	Quadratic	**0.03 (0.01,0.05)**	**0.007**	-0.04 (-0.10,0.03)	0.240	**0.03 (0.01,0.05)**	**0.009**	0.01 (-0.02,0.04)	0.454
Fat mass	Linear	**0.14 (0.09,0.19)**	**<0.001**	0.09 (-0.02,0.21)	0.099	**0.04 (0.00,0.09)**	**0.046**	0.00 (-0.05,0.06)	0.891
	Quadratic	**0.04 (0.02,0.06)**	**<0.001**	-0.02 (-0.08,0.04)	0.542	**0.03 (0.01,0.05)**	**0.001**	**0.03 (0.01,0.05)**	**0.010**
Hip BMD	Linear	**0.17 (0.12,0.23)**	**<0.001**	**0.14 (0.03,0.25)**	**0.010**	0.05 (0.00,0.10)	0.039	**0.08 (0.03,0.13)**	**0.002**
	Quadratic	**0.04 (0.01,0.06)**	**0.002**	0.02 (-0.03,0.07)	0.417	**0.05 (0.03,0.07)**	**<0.001**	0.01 (-0.02,0.04)	0.391

P: P-value; ALM: Appendicular lean mass; BMD: Bone mineral density

Sex-specific z-scores for changes in characteristics were derived by applying linear mixed effects models to z-scores (derived from generalised additive models for location, scale and shape) and extracting random slopes

The hazard ratio for a decrease in the change parameter (greater decline) from x to x-1 on the SD scale is given by $\exp(\beta_1 + \beta_2[2x+1])$

An indicator variable for the corresponding outcomes occurring before follow-up was used as the stratification variable in Cox models for fragility fracture, hospital admission and falls

Models were adjusted for the four-level sex-race variable, age and diet quality

Significant associations ($p<0.05$) are highlighted in bold

Appendix 42: Parameter estimates from an extended bivariate dual change score model for grip strength and gait speed over Years 2-10

Parameter	Estimate (95% CI)	P-value
Prior grip strength level on grip strength change	-0.127 (-0.604, 0.35)	0.601
Prior gait speed level on gait speed change	0.02 (-0.672, 0.713)	0.954
Prior grip strength level on gait speed change	-1.928 (-3.546, -0.31)	0.020
Prior gait speed level on grip strength change	0.042 (-0.047, 0.132)	0.357
Prior grip strength change on grip strength change	1.502 (0.326, 2.677)	0.012
Prior gait speed change on gait speed change	-0.642 (-2.082, 0.798)	0.382
Prior gait speed change on grip strength change	**-0.298 (-0.693, 0.096)**	**0.138**
Prior grip strength change on gait speed change	**6.578 (3.192, 9.964)**	**<0.001**
Grip strength residual variance	0.224 (0.216, 0.232)	<0.001
Gait speed residual variance	0.203 (0.194, 0.212)	<0.001
Grip strength latent intercept variance	0.779 (0.731, 0.826)	<0.001
Gait speed latent intercept variance	0.808 (0.753, 0.862)	<0.001
Grip strength slope variance	0.014 (-0.078, 0.106)	0.763
Gait speed slope variance	3.111 (-1.65, 7.871)	0.200
Cov (grip strength and gait speed intercepts)	0.128 (0.093, 0.164)	<0.001
Cov (grip strength intercept and slope)	0.096 (-0.273, 0.465)	0.610
Cov (gait speed intercept, grip strength slope)	-0.015 (-0.098, 0.068)	0.725
Cov (grip strength intercept, gait speed slope)	1.542 (0.354, 2.73)	0.011
Cov (gait speed intercept and slope)	0.202 (-0.216, 0.619)	0.344
Cov (grip strength and gait speed slopes)	0.197 (-0.626, 1.019)	0.639
Grip strength latent intercept	-0.007 (-0.043, 0.03)	0.712
Gait speed latent intercept	-0.018 (-0.056, 0.019)	0.341
Grip strength slope	-0.062 (-0.08, -0.044)	<0.001
Gait speed slope	-0.04 (-0.119, 0.038)	0.313
Corr (grip strength and gait speed intercepts)	0.162 (0.118, 0.206)	<0.001
Corr (grip strength and gait speed slopes)	0.937 (0.465, 1.408)	<0.001
Corr (grip strength intercept and slope)	0.914 (0.336, 1.492)	0.002
Corr (grip strength intercept, gait speed slope)	0.991 (0.981, 1.001)	<0.001
Corr (gait speed intercept, grip strength slope)	-0.14 (-1.216, 0.936)	0.799
Corr (gait speed intercept and slope)	0.127 (-0.188, 0.443)	0.429

Model was applied to the pooled sample of men and women

Units of analyses were sex-specific z-scores derived using the mean and SD at Year 2

Maximum likelihood estimation was used

Key parameters relating change in one characteristic to change in another are highlighted in bold

Appendix 43: Parameter estimates from an extended bivariate dual change score model for grip strength and ALM over Years 2-10

Parameter	Estimate (95% CI)	P-value
Prior grip strength level on grip strength change	0.03 (-0.363, 0.424)	0.880
Prior ALM level on ALM change	0.636 (0.313, 0.959)	<0.001
Prior grip strength level on ALM change	-0.475 (-0.76, -0.19)	0.001
Prior ALM level on grip strength change	0.21 (-0.155, 0.575)	0.260
Prior grip strength change on grip strength change	0.161 (-0.604, 0.926)	0.680
Prior ALM change on ALM change	-0.862 (-1.215, -0.509)	<0.001
Prior ALM change on grip strength change	**0.402 (-0.166, 0.969)**	**0.166**
Prior grip strength change on ALM change	**-0.296 (-0.84, 0.248)**	**0.286**
Grip strength residual variance	0.22 (0.212, 0.228)	<0.001
ALM residual variance	0.042 (0.04, 0.043)	<0.001
Grip strength latent intercept variance	0.79 (0.742, 0.838)	<0.001
ALM latent intercept variance	0.948 (0.898, 0.999)	<0.001
Grip strength slope variance	0.05 (-0.091, 0.19)	0.488
ALM slope variance	0.342 (0.033, 0.651)	0.030
Cov (grip strength and ALM intercepts)	0.408 (0.37, 0.446)	<0.001
Cov (grip strength intercept and slope)	-0.116 (-0.396, 0.164)	0.417
Cov (ALM intercept, grip strength slope)	-0.21 (-0.518, 0.099)	0.184
Cov (grip strength intercept, ALM slope)	0.108 (-0.083, 0.299)	0.268
Cov (ALM intercept and slope)	-0.429 (-0.688, -0.17)	0.001
Cov (grip strength and ALM slopes)	0.084 (-0.101, 0.269)	0.374
Grip strength latent intercept	-0.007 (-0.043, 0.03)	0.728
ALM latent intercept	-0.002 (-0.039, 0.034)	0.894
Grip strength slope	-0.053 (-0.08, -0.025)	<0.001
ALM slope	-0.144 (-0.172, -0.116)	<0.001
Corr (grip strength and ALM intercepts)	0.471 (0.439, 0.504)	<0.001
Corr (grip strength and ALM slopes)	0.645 (-0.536, 1.825)	0.284
Corr (grip strength intercept and slope)	-0.585 (-1.694, 0.525)	0.302
Corr (grip strength intercept, ALM slope)	0.208 (-0.162, 0.577)	0.270
Corr (ALM intercept, grip strength slope)	-0.965 (-1.169, -0.761)	<0.001
Corr (ALM intercept and slope)	-0.753 (-0.997, -0.509)	<0.001

ALM: Appendicular lean mass

Model was applied to the pooled sample of men and women

Units of analyses were sex-specific z-scores derived using the mean and SD at Year 2

Maximum likelihood estimation was used

Key parameters relating change in one characteristic to change in another are highlighted in bold

Appendix 44: Parameter estimates from an extended bivariate dual change score model for grip strength and fat mass over Years 2-10

Parameter	Estimate (95% CI)	P-value
Prior grip strength level on grip strength change	-0.146 (-0.63, 0.338)	0.555
Prior fat mass level on fat mass change	-0.179 (-0.517, 0.16)	0.301
Prior grip strength level on fat mass change	-0.756 (-1.146, -0.365)	<0.001
Prior fat mass level on grip strength change	-0.04 (-0.324, 0.243)	0.780
Prior grip strength change on grip strength change	1.046 (0.203, 1.889)	0.015
Prior fat mass change on fat mass change	0.569 (-0.049, 1.186)	0.071
Prior fat mass change on grip strength change	**-0.066 (-0.733, 0.601)**	**0.847**
Prior grip strength change on fat mass change	**1.952 (1.287, 2.617)**	**<0.001**
Grip strength residual variance	0.221 (0.213, 0.229)	<0.001
Fat mass residual variance	0.045 (0.044, 0.047)	<0.001
Grip strength latent intercept variance	0.8 (0.752, 0.848)	<0.001
Fat mass latent intercept variance	0.984 (0.931, 1.037)	<0.001
Grip strength slope variance	0.02 (-0.108, 0.147)	0.762
Fat mass slope variance	0.546 (-0.005, 1.097)	0.052
Cov (grip strength and fat mass intercepts)	0.147 (0.11, 0.183)	<0.001
Cov (grip strength intercept and slope)	0.116 (-0.289, 0.521)	0.575
Cov (fat mass intercept, grip strength slope)	0.056 (-0.258, 0.371)	0.725
Cov (grip strength intercept, fat mass slope)	0.64 (0.317, 0.963)	<0.001
Cov (fat mass intercept and slope)	0.274 (-0.069, 0.618)	0.118
Cov (grip strength and fat mass slopes)	0.099 (-0.276, 0.474)	0.605
Grip strength latent intercept	-0.006 (-0.043, 0.03)	0.735
Fat mass latent intercept	-0.003 (-0.04, 0.035)	0.888
Grip strength slope	-0.066 (-0.081, -0.052)	<0.001
Fat mass slope	0.023 (-0.009, 0.055)	0.159
Corr (grip strength and fat mass intercepts)	0.165 (0.126, 0.205)	<0.001
Corr (grip strength and fat mass slopes)	0.954 (0.681, 1.227)	<0.001
Corr (grip strength intercept and slope)	0.923 (0.424, 1.422)	<0.001
Corr (grip strength intercept, fat mass slope)	0.968 (0.877, 1.059)	<0.001
Corr (fat mass intercept, grip strength slope)	0.406 (-1.154, 1.965)	0.610
Corr (fat mass intercept and slope)	0.374 (-0.018, 0.766)	0.061

Model was applied to the pooled sample of men and women

Units of analyses were sex-specific z-scores derived using the mean and SD at Year 2

Maximum likelihood estimation was used

Key parameters relating change in one characteristic to change in another are highlighted in bold

Appendix 45: Parameter estimates from an extended bivariate dual change score model for gait speed and ALM over Years 2-10

Parameter	Estimate (95% CI)	P-value
Prior gait speed level on gait speed change	-0.579 (-0.985, -0.173)	0.005
Prior ALM level on ALM change	0.325 (0.156, 0.495)	<0.001
Prior gait speed level on ALM change	-0.133 (-0.218, -0.048)	0.002
Prior ALM level on gait speed change	-0.656 (-0.99, -0.322)	<0.001
Prior gait speed change on gait speed change	1.681 (0.96, 2.402)	<0.001
Prior ALM change on ALM change	-0.688 (-0.907, -0.47)	<0.001
Prior ALM change on gait speed change	**1.947 (1.179, 2.715)**	**<0.001**
Prior gait speed change on ALM change	**-0.128 (-0.304, 0.049)**	**0.156**
Gait speed residual variance	0.221 (0.212, 0.229)	<0.001
ALM residual variance	0.042 (0.041, 0.044)	<0.001
Gait speed latent intercept variance	0.792 (0.743, 0.841)	<0.001
ALM latent intercept variance	0.95 (0.899, 1.001)	<0.001
Gait speed slope variance	0.607 (0.116, 1.097)	0.015
ALM slope variance	0.152 (0.032, 0.272)	0.013
Cov (gait speed and ALM intercepts)	-0.105 (-0.141, -0.07)	<0.001
Cov (gait speed intercept and slope)	0.387 (0.059, 0.715)	0.021
Cov (ALM intercept, gait speed slope)	0.569 (0.245, 0.894)	0.001
Cov (gait speed intercept, ALM slope)	0.158 (0.085, 0.23)	<0.001
Cov (ALM intercept and slope)	-0.345 (-0.506, -0.185)	<0.001
Cov (gait speed and ALM slopes)	-0.14 (-0.319, 0.039)	0.126
Gait speed latent intercept	-0.001 (-0.038, 0.036)	0.950
ALM latent intercept	0 (-0.037, 0.036)	0.992
Gait speed slope	-0.056 (-0.091, -0.02)	0.002
ALM slope	-0.139 (-0.159, -0.12)	<0.001
Corr (gait speed and ALM intercepts)	-0.122 (-0.162, -0.081)	<0.001
Corr (gait speed and ALM slopes)	-0.46 (-0.89, -0.03)	0.036
Corr (gait speed intercept and slope)	0.558 (0.159, 0.957)	0.006
Corr (gait speed intercept, ALM slope)	0.454 (0.262, 0.646)	<0.001
Corr (ALM intercept, gait speed slope)	0.75 (0.436, 1.064)	<0.001
Corr (ALM intercept and slope)	-0.908 (-0.999, -0.818)	<0.001

ALM: Appendicular lean mass

Model was applied to the pooled sample of men and women

Units of analyses were sex-specific z-scores derived using the mean and SD at Year 2

Maximum likelihood estimation was used

Key parameters relating change in one characteristic to change in another are highlighted in bold

Appendix 46: Parameter estimates from an extended bivariate dual change score model for ALM and fat mass over Years 2-10

Parameter	Estimate (95% CI)	P-value
Prior ALM level on ALM change	-0.324 (-0.425, -0.222)	<0.001
Prior fat mass level on fat mass change	-0.485 (-0.641, -0.33)	<0.001
Prior ALM level on fat mass change	0.147 (0.033, 0.262)	0.012
Prior fat mass level on ALM change	-0.05 (-0.17, 0.07)	0.413
Prior ALM change on ALM change	-0.046 (-0.219, 0.127)	0.602
Prior fat mass change on fat mass change	0.885 (0.509, 1.262)	<0.001
Prior fat mass change on ALM change	**0.479 (0.201, 0.757)**	**0.001**
Prior ALM change on fat mass change	**0.432 (0.202, 0.662)**	**<0.001**
ALM residual variance	0.044 (0.042, 0.046)	<0.001
Fat mass residual variance	0.046 (0.044, 0.048)	<0.001
ALM latent intercept variance	0.957 (0.906, 1.009)	<0.001
Fat mass latent intercept variance	0.975 (0.922, 1.027)	<0.001
ALM slope variance	0.113 (0.023, 0.203)	0.014
Fat mass slope variance	0.166 (0.024, 0.307)	0.022
Cov (ALM and fat mass intercepts)	0.621 (0.578, 0.665)	<0.001
Cov (ALM intercept and slope)	0.312 (0.178, 0.446)	<0.001
Cov (fat mass intercept, ALM slope)	0.223 (0.079, 0.367)	0.002
Cov (ALM intercept, fat mass slope)	0.161 (-0.024, 0.346)	0.089
Cov (fat mass intercept and slope)	0.377 (0.173, 0.581)	<0.001
Cov (ALM and fat mass slopes)	0.063 (-0.034, 0.16)	0.205
ALM latent intercept	-0.005 (-0.042, 0.031)	0.777
Fat mass latent intercept	0.004 (-0.033, 0.041)	0.840
ALM slope	-0.129 (-0.145, -0.113)	<0.001
Fat mass slope	0.022 (0.004, 0.039)	0.015
Corr (ALM and fat mass intercepts)	0.643 (0.62, 0.666)	<0.001
Corr (ALM and fat mass slopes)	0.461 (0.052, 0.87)	0.027
Corr (ALM intercept and slope)	0.949 (0.916, 0.982)	<0.001
Corr (ALM intercept, fat mass slope)	0.404 (0.099, 0.709)	0.009
Corr (fat mass intercept, ALM slope)	0.673 (0.478, 0.868)	<0.001
Corr (fat mass intercept and slope)	0.938 (0.825, 1.05)	<0.001

ALM: Appendicular lean mass

Model was applied to the pooled sample of men and women

Units of analyses were sex-specific z-scores derived using the mean and SD at Year 2

Maximum likelihood estimation was used

Key parameters relating change in one characteristic to change in another are highlighted in bold

List of References

1. Lieberman DE. Musculoskeletal System–Overview. John Wiley & Sons 2001.

2. Cooper C, Dere W, Evans W, et al. Frailty and sarcopenia: definitions and outcome parameters. *Osteoporos Int* 2012;23(7):1839-48.

3. Briggs AM, Woolf AD, Dreinhöfer K, et al. Reducing the global burden of musculoskeletal conditions. *Bull World Health Organ* 2018;96(5):366-68.

4. Vos T, Abajobir AA, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;390(10100):1211-59.

5. United States Bone and Joint Initiative. The Burden of Musculoskeletal Diseases in the United States (BMUS). https://www.boneandjointburden.org/fourth-edition/introduction (accessed 1st June 2021).

6. Roberts HC, Dodds R, Sayer AA. Current clinical care of older adults with sarcopenia. *J Clin Densitom* 2015;18(4):493-98.

7. Cao L, Morley JE. Sarcopenia is recognized as an independent condition by an international classification of disease, tenth revision, clinical modification (ICD-10-CM) code. *J Am Med Dir Assoc* 2016;17(8):675-77.

8. Janssen I, Shepard DS, Katzmarzyk PT, et al. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc* 2004;52(1):80-85.

9. Pinedo-Villanueva R, Westbury LD, Syddall HE, et al. Health care costs associated with muscle weakness: a UK population-based estimate. *Calcif Tissue Int* 2019;104(2):137-44.

10. Shaw S, Dennison E, Cooper C. Epidemiology of Sarcopenia: Determinants Throughout the Lifecourse. *Calcif Tissue Int* 2017;101(3):229-47.

11. Sayer A, Stewart C, Patel H, et al. The developmental origins of sarcopenia: from epidemiological evidence to underlying mechanisms. *J Dev Orig Health Dis* 2010;1(3):150-57.

12. Cooper C, Fielding R, Visser Mv, et al. Tools in the assessment of sarcopenia. *Calcif Tissue Int* 2013;93(3):201-10.

13. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;48(1):16-31.

14. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc* 2011;12(4):249-56.

15. Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* 2011;40(4):423-29.

16. Mehmet H, Robinson SR, Yang AWH. Assessment of gait speed in older adults. *J Geriatr Phys Ther* 2020;43(1):42-52.

17. Shafiee G, Keshtkar A, Soltani A, et al. Prevalence of sarcopenia in the world: a systematic review and meta-analysis of general population studies. *J Diabetes Metab Disord* 2017;16(21) doi: 10.1186/s40200-017-0302-x.

18. Christensen MG, Piper KS, Dreier R, et al. Prevalence of sarcopenia in a Danish geriatric out-patient population. *Dan Med J* 2018;65(6):A5485.

19. Bianchi L, Abete P, Bellelli G, et al. Prevalence and clinical correlates of sarcopenia, identified according to the EWGSOP definition and diagnostic algorithm, in hospitalized older people: the GLISTEN study. *J Gerontol A Biol Sci Med Sci* 2017;72(11):1575-81.

20. Rodriguez-Rejon A, Artacho R, Puerta A, et al. Diagnosis of sarcopenia in long-term care homes for the elderly: the sensitivity and specificity of two simplified algorithms with respect to the EWGSOP consensus. *J Nutr Health Aging* 2018;22(7):796-801.

21. Dennison E, Mohamed MA, Cooper C. Epidemiology of osteoporosis. *Rheum Dis Clin North Am* 2006;32(4):617-29.

22. Fox C, Edwards M, Dennison E, et al. Personal and societal burden of osteoporotic fractures. *Clin Rev Bone Miner Metab* 2015;13(2):53-60.

23. Leal J, Gray A, Prieto-Alhambra D, et al. Impact of hip fracture on hospital care costs: a population-based study. *Osteoporos Int* 2016;27(2):549-58.

24. Judge A, Javaid MK, Leal J, et al. Models of care for the delivery of secondary fracture prevention after hip fracture: a health service cost, clinical outcomes and cost-effectiveness study within a region of England. *Health Services and Delivery Research* 2016;4(28)

25. Burge R, Dawson-Hughes B, Solomon DH, et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res* 2007;22(3):465-75.

26. Hernlund E, Svedbom A, Ivergård M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. *Arch Osteoporos* 2013;8(1):136.

27. Kanis J, Johnell O, Odén A, et al. FRAX™ and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008;19(4):385-97.

28. Kanis JA, Harvey NC, Johansson H, et al. A decade of FRAX: how has it changed the management of osteoporosis? *Aging Clin Exp Res* 2020;32(2):187-96.

29. Kanis JA, Oden A, Johansson H, et al. FRAX® and its applications to clinical practice. *Bone* 2009;44(5):734-43.

30. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organ Tech Rep Ser* 1994;843:1-129.

31. Wade S, Strader C, Fitzpatrick L, et al. Estimating prevalence of osteoporosis: examples from industrialized countries. *Arch Osteoporos* 2014;9(182) doi: 10.1007/s11657-014-0182-3.

32. Frost HM. Bone's mechanostat: a 2003 update. *Anat Rec A Discov Mol Cell Evol Biol* 2003;275(2):1081-101.

33. Kuh D, Cooper R, Hardy R, et al. A Life Course Approach to Healthy Ageing. Oxford University Press 2013.

34. Wells J, Fewtrell M. Measuring body composition. *Arch Dis Child* 2006;91(7):612-17.

35. St-Onge MP, Gallagher D. Body composition changes with aging: the cause or the result of alterations in metabolic rate and macronutrient oxidation? *Nutrition* 2010;26(2):152-55.

36. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. *Nat Rev Endocrinol* 2018;14(9):513-37.

37. Houston DK, Nicklas BJ, Zizza CA. Weighty concerns: the growing prevalence of obesity among older adults. *J Am Diet Assoc* 2009;109(11):1886-95.

38. Visser M, Langlois J, Guralnik JM, et al. High body fatness, but not low fat-free mass, predicts disability in older men and women: the Cardiovascular Health Study. *Am J Clin Nutr* 1998;68(3):584-90.

39. Bigaard J, Frederiksen K, Tjønneland A, et al. Body fat and fat-free mass and all-cause mortality. *Obes Res* 2004;12(7):1042-49.

40. Kim DD, Basu A. Estimating the medical care costs of obesity in the United States: systematic review, meta-analysis, and empirical analysis. *Value Health* 2016;19(5):602-13.

41. Hajek A, Lehnert T, Ernst A, et al. Prevalence and determinants of overweight and obesity in old age in Germany. *BMC Geriatr* 2015;15(83) doi: 10.1186/s12877-015-0081-5.

42. Kaplan MS, Huguet N, Newsom JT, et al. Prevalence and correlates of overweight and obesity among older adults: findings from the Canadian National Population Health Survey. *J Gerontol A Biol Sci Med Sci* 2003;58(11):1018-30.

43. Grujić V, Dragnić N, Mijatović-Jovanović V, et al. Predictors of overweight and obesity among adults aged 50 years and above: Serbian national health survey. *Vojnosanit Pregl* 2016;74(1):38-45.

44. Peralta M, Ramos M, Lipert A, et al. Prevalence and trends of overweight and obesity in older adults from 10 European countries from 2005 to 2013. *Scand J Public Health* 2018;46(5):522-29.

45. Ogden CL, Carroll MD, Kit BK, et al. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014;311(8):806-14.

46. Frederiksen H, Hjelmborg J, Mortensen J, et al. Age trajectories of grip strength: cross-sectional and longitudinal data among 8,342 Danes aged 46 to 102. *Ann Epidemiol* 2006;16(7):554-62.

47. Syddall HE, Westbury L, Shaw S, et al. Correlates of Level and Loss of Grip Strength in Later Life: Findings from the English Longitudinal Study of Ageing and the Hertfordshire Cohort Study. *Calcif Tissue Int* 2018;102(1):53-63.

48. Botoseneanu A, Bennett JM, Nyquist L, et al. Cardiometabolic risk, socio-psychological factors, and trajectory of grip strength among older Japanese adults. *J Aging Health* 2015;27(7):1123-46.

49. Sternang O, Reynolds CA, Finkel D, et al. Factors associated with grip strength decline in older adults. *Age Ageing* 2015;44(2):269-74.

50. Starr JM, Deary IJ. Socio-economic position predicts grip strength and its decline between 79 and 87 years: the Lothian Birth Cohort 1921. *Age Ageing* 2011;40(6):749-52.

51. Kröger H, Fritzell J, Hoffmann R. The association of levels of and decline in grip strength in old age with trajectories of life course occupational position. *PloS one* 2016;11(5):e0155954.

52. Forrest KY, Zmuda JM, Cauley JA. Patterns and correlates of muscle strength loss in older women. *Gerontology* 2007;53(3):140-47.

53. Forrest KY, Zmuda JM, Cauley JA. Patterns and determinants of muscle strength change with aging in older men. *Aging Male* 2005;8(3-4):151-56.

54. Forrest KY, Bunker CH, Sheu Y, et al. Patterns and correlates of grip strength change with age in Afro-Caribbean men. *Age Ageing* 2012;41(3):326-32.

55. Rantanen T, Masaki K, Foley D, et al. Grip strength changes over 27 yr in Japanese-American men. *J Appl Physiol (1985)* 1998;85(6):2047-53.

56. Granic A, Davies K, Jagger C, et al. Grip strength decline and its determinants in the very old: Longitudinal findings from the Newcastle 85+ Study. *PloS one* 2016;11(9):e0163183.

57. Yokoyama Y, Nishi M, Murayama H, et al. Dietary variety and decline in lean mass and physical performance in community-dwelling older Japanese: A 4-year follow-up study. *J Nutr Health Aging* 2017;21(1):11-16.

58. McLean RR, Mangano KM, Hannan MT, et al. Dietary protein intake is protective against loss of grip strength among older adults in the Framingham offspring cohort. *J Gerontol A Biol Sci Med Sci* 2015;71(3):356-61.

59. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. *J Clin Endocrinol Metab* 2003;88(12):5766-72.

60. Granic A, Hill TR, Davies K, et al. Vitamin D Status, Muscle Strength and Physical Performance Decline in Very Old Adults: A Prospective Study. *Nutrients* 2017;9(4):379.

61. Rantanen T, Penninx BW, Masaki K, et al. Depressed mood and body mass index as predictors of muscle strength decline in old men. *J Am Geriatr Soc* 2000;48(6):613-17.

62. Stijntjes M, Aartsen MJ, Taekema DG, et al. Temporal relationship between cognitive and physical performance in middle-aged to oldest old people. *J Gerontol A Biol Sci Med Sci* 2016;72(5):662-68.

63. Cooper R, Richards M, Kuh D. Childhood Cognitive Ability and Age-Related Changes in Physical Capability From Midlife: Findings From a British Birth Cohort Study. *Psychosom Med* 2017;79(7):785-91.

64. Westbury L, Fuggle N, Syddall HE, et al. Relationships between markers of inflammation and muscle mass, strength and function: findings from the Hertfordshire Cohort Study. *Calcif Tissue Int* 2018;102(3):287-95.

65. Schaap LA, Pluijm SM, Deeg DJ, et al. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *Am J Med* 2006;119(6):9-17.

66. Stenholm S, Maggio M, Lauretani F, et al. Anabolic and catabolic biomarkers as predictors of muscle strength decline: the InCHIANTI study. *Rejuvenation Res* 2010;13(1):3-11.

67. Metter EJ, Talbot LA, Schrager M, et al. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *J Gerontol A Biol Sci Med Sci* 2002;57(10):359-65.

68. Ling CHY, Taekema D, De Craen AJM, et al. Handgrip strength and mortality in the oldest old population: The Leiden 85-plus study. *CMAJ* 2010;182(5):429-35.

69. Proctor DN, Fauth EB, Hoffman L, et al. Longitudinal changes in physical functional performance among the oldest old: Insight from a study of Swedish twins. *Aging Clin Exp Res* 2006;18(6):517-30.

70. Xue QL, Beamer BA, Chaves PHM, et al. Heterogeneity in rate of decline in grip, hip, and knee strength and the risk of all-cause mortality: the Women's Health and Aging Study II. *J Am Geriatr Soc* 2010;58(11):2076-84.

71. Syddall HE, Westbury LD, Dodds R, et al. Mortality in the Hertfordshire Ageing Study: association with level and loss of hand grip strength in later life. *Age Ageing* 2017;46(3):407-12.

72. Hirsch CH, Buzkova P, Robbins JA, et al. Predicting late-life disability and death by the rate of decline in physical performance measures. *Age Ageing* 2012;41(2):155-61.

73. Xue Q-L, Walston JD, Fried LP, et al. Prediction of risk of falling, physical disability, and frailty by rate of decline in grip strength: the women's health and aging study. *Arch Intern Med* 2011;171(12):1119-21.

74. Auyeung TW, Lee SWJ, Leung J, et al. Age-associated decline of muscle mass, grip strength and gait speed: A 4-year longitudinal study of 3018 community-dwelling older Chinese. *Geriatr Gerontol Int* 2014;14(S1):76-84.

75. Beavers KM, Beavers DP, Houston DK, et al. Associations between body composition and gait-speed decline: results from the Health, Aging, and Body Composition study. *Am J Clin Nutr* 2013;97(3):552-60.

76. Forrest KY, Zmuda JM, Cauley JA. Correlates of decline in lower extremity performance in older women: a 10-year follow-up study. *J Gerontol A Biol Sci Med Sci* 2006;61(11):1194-200.

77. White DK, Neogi T, Nevitt MC, et al. Trajectories of gait speed predict mortality in well-functioning older adults: the Health, Aging and Body Composition study. *J Gerontol A Biol Sci Med Sci* 2013;68(4):456-64.

78. Semanik PA, Lee J, Song J, et al. Accelerometer-monitored sedentary behavior and observed physical function loss. *Am J Public Health* 2015;105(3):560-66.

79. Shahar DR, Houston DK, Hue TF, et al. Adherence to mediterranean diet and decline in walking speed over 8 years in community-dwelling older adults. *J Am Geriatr Soc* 2012;60(10):1881-88.

80. Gale CR, Allerhand M, Sayer AA, et al. The dynamic relationship between cognitive function and walking speed: the English Longitudinal Study of Ageing. *Age (Dordr)* 2014;36(4):9682.

81. Watson NL, Rosano C, Boudreau RM, et al. Executive function, memory, and gait speed decline in well-functioning older adults. *J Gerontol A Biol Sci Med Sci* 2010;65(10):1093-100.

82. White DK, Niu J, Zhang Y. Is symptomatic knee osteoarthritis a risk factor for a trajectory of fast decline in gait speed? Results from a longitudinal cohort study. *Arthritis Care Res (Hoboken)* 2013;65(2):187-94.

83. Rosano C, Longstreth WT, Boudreau R, et al. High Blood Pressure Accelerates Gait Slowing in Well-Functioning Older Adults over 18-Years of Follow-Up. *J Am Geriatr Soc* 2011;59(3):390-97.

84. Welmer A-K, Rizzuto D, Parker MG, et al. Impact of tooth loss on walking speed decline over time in older adults: a population-based cohort study. *Aging Clin Exp Res* 2017;29(4):793-800.

85. Tsakos G, Watt RG, Rouxel PL, et al. Tooth loss associated with physical and cognitive decline in older adults. *J Am Geriatr Soc* 2015;63(1):91-99.

86. Verghese J, Holtzer R, Oh-Park M, et al. Inflammatory markers and gait speed decline in older adults. *J Gerontol A Biol Sci Med Sci* 2011;66(10):1083-89.

87. Ferrucci L, Penninx BW, Volpato S, et al. Change in Muscle Strength Explains Accelerated Decline of Physical Function in Older Women With High Interleukin-6 Serum Levels. *J Am Geriatr Soc* 2002;50(12):1947-54.

88. Sabia S, Dumurgier J, Tavernier B, et al. Change in fast walking speed preceding death: results from a prospective longitudinal cohort study. *J Gerontol A Biol Sci Med Sci* 2013;69(3):354-62.

89. Artaud F, Singh-Manoux A, Dugravot A, et al. Decline in fast gait speed as a predictor of disability in older adults. *J Am Geriatr Soc* 2015;63(6):1129-36.

90. Best JR, Liu-Ambrose T, Boudreau RM, et al. An evaluation of the longitudinal, bidirectional associations between gait speed and cognition in older women and men. *J Gerontol A Biol Sci Med Sci* 2016;71(12):1616-23.

91. Dumurgier J, Artaud F, Touraine C, et al. Gait speed and decline in gait speed as predictors of incident dementia. *J Gerontol A Biol Sci Med Sci* 2017;72(5):655-61.

92. Ding J, Kritchevsky SB, Newman AB, et al. Effects of birth cohort and age on body composition in a sample of community-based elderly. *Am J Clin Nutr* 2007;85(2):405-10.

93. Goodpaster BH, Park SW, Harris TB, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci* 2006;61(10):1059-64.

94. Koster A, Ding J, Stenholm S, et al. Does the amount of fat mass predict age-related loss of lean mass, muscle strength, and muscle quality in older adults? *J Gerontol A Biol Sci Med Sci* 2011;66(8):888-95.

95. Newman AB, Lee JS, Visser M, et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. *Am J Clin Nutr* 2005;82(4):872-78.

96. Reinders I, Murphy RA, Martin KR, et al. Body mass index trajectories in relation to change in lean mass and physical function: The Health, Aging and Body Composition Study. *J Am Geriatr Soc* 2015;63(8):1615-21.

97. Koster A, Visser M, Simonsick EM, et al. Association between fitness and changes in body composition and muscle strength. *J Am Geriatr Soc* 2010;58(2):219-26.

98. Houston DK, Nicklas BJ, Ding J, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. *Am J Clin Nutr* 2008;87(1):150-5.

99. Liu G, Lu L, Sun Q, et al. Poor vitamin D status is prospectively associated with greater muscle mass loss in middle-aged and elderly Chinese individuals. *J Acad Nutr Diet* 2014;114(10):1544-51.

100. Visser M, Kritchevsky SB, Newman AB, et al. Lower serum albumin concentration and change in muscle mass: the Health, Aging and Body Composition Study. *Am J Clin Nutr* 2005;82(3):531-7.

101. Fried LF, Boudreau R, Lee JS, et al. Kidney function as a predictor of loss of lean mass in older adults: health, aging and body composition study. *J Am Geriatr Soc* 2007;55(10):1578-84.

102. Lee CG, Boyko EJ, Strotmeyer ES, et al. Association between insulin resistance and lean mass loss and fat mass gain in older men without diabetes mellitus. *J Am Geriatr Soc* 2011;59(7):1217-24.

103. Teros MTL, Alemán-Mateo H. Hyperinsulinemia is associated with the loss of appendicular skeletal muscle mass at 4.6 year follow-up in older men and women. *Clinical Nutrition* 2015;34(5):931-36.

104. Jung HW, Kim SW, Lim JY, et al. Frailty status can predict further lean body mass decline in older adults. *J Am Geriatr Soc* 2014;62(11):2110-17.

105. Lee CG, Boyko EJ, Nielson CM, et al. Mortality risk in older men associated with changes in weight, lean mass, and fat mass. *J Am Geriatr Soc* 2011;59(2):233-40.

106. Szulc P, Munoz F, Marchand F, et al. Rapid loss of appendicular skeletal muscle mass is associated with higher all-cause mortality in older men: the prospective MINOS study. *Am J Clin Nutr* 2010;91(5):1227-36.

107. Cespedes Feliciano EM, Tinker L, Manson JE, et al. Change in dietary patterns and change in waist circumference and DXA trunk fat among postmenopausal women. *Obesity* 2016;24(10):2176-84.

108. Ma J, McKeown NM, Hwang S-J, et al. Sugar-sweetened beverage consumption is associated with change of visceral adipose tissue over 6 years of follow-up. *Circulation* 2016;133(4):370-7.

109. Ankarfeldt MZ, Gottliebsen K, Ängquist L, et al. Dietary protein and urinary nitrogen in relation to 6-year changes in fat mass and fat-free mass. *Int J Obes (Lond)* 2015;39(1):162-8.

110. Sims ST, Kubo J, Desai M, et al. Changes in physical activity and body composition in postmenopausal women over time. *Med Sci Sports Exerc* 2013;45(8):1486-92.

111. Scott D, Ebeling PR, Sanders KM, et al. Vitamin D and physical activity status: associations with five-year changes in body composition and muscle function in community-dwelling older adults. *J Clin Endocrinol Metab* 2015;100(2):670-78.

112. Kim CH, Kim HK, Kim EH, et al. Association between changes in body composition and risk of developing type 2 diabetes in Koreans. *Diabetic Medicine* 2014;31(11):1393-98.

113. Koh-Banerjee P, Wang Y, Hu FB, et al. Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men. *Am J Epidemiol* 2004;159(12):1150-59.

114. Lee JJ, Pedley A, Hoffmann U, et al. Association of changes in abdominal fat quantity and quality with incident cardiovascular disease risk factors. *J Am Coll Cardiol* 2016;68(14):1509-21.

115. Grinker J, Tucker K, Vokonas P, et al. Changes in patterns of fatness in adult men in relation to serum indices of cardiovascular risk: the Normative Aging Study. *Int J Obes Relat Metab Disord* 2000;24(10):1369-78.

116. Rossi AP, Watson NL, Newman AB, et al. Effects of body composition and adipose tissue distribution on respiratory function in elderly men and women: the health, aging, and body composition study. *J Gerontol A Biol Sci Med Sci* 2011;66(7):801-08.

117. Oh SW, Ahn SY, Jianwei X, et al. Relationship between changes in body fat and a decline of renal function in the elderly. *PloS one* 2014;9(1):e84052.

118. West NA, Lirette ST, Cannon VA, et al. Adiposity, Change in Adiposity, and Cognitive Decline in Mid-and Late Life. *J Am Geriatr Soc* 2017;65(6):1282-88.

119. Zaslavsky O, Rillamas-Sun E, Li W, et al. Association of dynamics in lean and fat mass measures with mortality in frail older women. *J Nutr Health Aging* 2017;21(1):112-19.

120. Burger H, De Laet C, Van Daele P, et al. Risk factors for increased bone loss in an elderly population the rotterdam study. *Am J Epidemiol* 1998;147(9):871-79.

121. Cawthon PM, Ewing SK, McCulloch CE, et al. Loss of hip BMD in older men: the osteoporotic fractures in men (MrOS) study. *J Bone Miner Res* 2009;24(10):1728-35.

122. Hannan MT, Felson DT, Dawson-Hughes B, et al. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. *J Bone Miner Res* 2000;15(4):710-20.

123. Cauley JA, Lui LY, Stone KL, et al. Longitudinal study of changes in hip bone mineral density in Caucasian and African-American women. *J Am Geriatr Soc* 2005;53(2):183-89.

124. Tracy JK, Meyer WA, Flores RH, et al. Racial differences in rate of decline in bone mass in older men: the Baltimore men's osteoporosis study. *J Bone Miner Res* 2005;20(7):1228-34.

125. Araujo AB, Yang M, Suarez EA, et al. Racial/ethnic and socioeconomic differences in bone loss among men. *J Bone Miner Res* 2014;29(12):2552-60.

126. Kaptoge S, Reid D, Scheidt-Nave C, et al. Geographic and other determinants of BMD change in European men and women at the hip and spine. A population-based study from the Network in Europe for Male Osteoporosis (NEMO). *Bone* 2007;40(3):662-73.

127. Zhai G, Hart D, Valdes A, et al. Natural history and risk factors for bone loss in postmenopausal Caucasian women: a 15-year follow-up population-based study. *Osteoporos Int* 2008;19(8):1211-17.

128. Nguyen T, Sambrook P, Eisman J. Bone loss, physical activity, and weight change in elderly women: the Dubbo Osteoporosis Epidemiology Study. *J Bone Miner Res* 1998;13(9):1458-67.

129. Bleicher K, Cumming R, Naganathan V, et al. Predictors of the rate of BMD loss in older men: findings from the CHAMP study. *Osteoporos Int* 2013;24(7):1951-63.

130. Orchard T, Yildiz V, Steck SE, et al. Dietary Inflammatory Index, bone mineral density, and risk of fracture in postmenopausal women: Results from the Women's Health Initiative. *J Bone Miner Res* 2017;32(5):1136-46.

131. Sahni S, Broe KE, Tucker KL, et al. Association of total protein intake with bone mineral density and bone loss in men and women from the Framingham Offspring Study. *Public Health Nutr* 2014;17(11):2570-76.

132. Isanejad M, Sirola J, Mursu J, et al. Association of protein intake with bone mineral density and bone mineral content among elderly women: The OSTPRE fracture prevention study. *J Nutr Health Aging* 2017;21(6):622-30.

133. Vogel JM, Davis JW, Nomura A, et al. The Effects of Smoking on Bone Mass and the Rates of Bone Loss Among Elderly Japanese-American Men. *J Bone Miner Res* 1997;12(9):1495-501.

134. Diem S, Harrison S, Haney E, et al. Depressive symptoms and rates of bone loss at the hip in older men. *Osteoporos Int* 2013;24(1):111-19.

135. Diem SJ, Blackwell TL, Stone KL, et al. Depressive symptoms and rates of bone loss at the hip in older women. *J Am Geriatr Soc* 2007;55(6):824-31.

136. Gebara MA, Shea ML, Lipsey KL, et al. Depression, antidepressants, and bone health in older adults: a systematic review. *J Am Geriatr Soc* 2014;62(8):1434-41.

137. Kuipers AL, Egwuogu H, Evans RW, et al. Renal Function and Bone Loss in a Cohort of Afro-Caribbean Men. *J Bone Miner Res* 2015;30(12):2215-20.

138. Fried LF, Shlipak MG, Stehman-Breen C, et al. Kidney function predicts the rate of bone loss in older individuals: the Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci* 2006;61(7):743-48.

139. Cappuccio FP, Meilahn E, Zmuda JM, et al. High blood pressure and bone-mineral loss in elderly white women: a prospective study. *Lancet* 1999;354(9183):971-75.

140. den Uyl D, Nurmohamed MT, van Tuyl LH, et al. (Sub) clinical cardiovascular disease is associated with increased bone loss and fracture risk; a systematic review of the association between cardiovascular disease and osteoporosis. *Arthritis Res Ther* 2011;13(1):R5.

141. Schwartz AV, Ewing SK, Porzig AM, et al. Diabetes and change in bone mineral density at the hip, calcaneus, spine, and radius in older women. *Front Endocrinol (Lausanne)* 2013;4(62) doi: 10.3389/fendo.2013.00062.

142. Schwartz AV, Sellmeyer DE, Strotmeyer ES, et al. Diabetes and bone loss at the hip in older black and white adults. *J Bone Miner Res* 2005;20(4):596-603.

143. Ding C, Parameswaran V, Udayan R, et al. Circulating levels of inflammatory markers predict change in bone mineral density and resorption in older adults: a longitudinal study. *J Clin Endocrinol Metab* 2008;93(5):1952-8.

144. Cawthon PM, Patel S, Ewing SK, et al. Bone loss at the hip and subsequent mortality in older men: the osteoporotic fractures in men (MrOS) study. *JBMR Plus* 2017;1(1):31-35.

145. Szulc P, Chapurlat R, Delmas PD. Accelerated bone loss, but not low periosteal expansion, is associated with higher all-cause mortality in older men–prospective MINOS study. *J Mens Health* 2010;7(3):199-210.

146. Marques EA, Elbejjani M, Gudnason V, et al. Proximal Femur Volumetric Bone Mineral Density and Mortality: 13 Years of Follow-Up of the AGES-Reykjavik Study. *J Bone Miner Res* 2017;32(6):1237-42.

147. Kado DM, Browner WS, Blackwell T, et al. Rate of bone loss is associated with mortality in older women: a prospective study. *J Bone Miner Res* 2000;15(10):1974-80.

148. Shen C, Deng J, Zhou R, et al. Relation between bone mineral density, bone loss and the risk of cardiovascular disease in a Chinese cohort. *Am J Cardiol* 2012;110(8):1138-42.

149. Campos-Obando N, Kavousi M, van Lennep JER, et al. Bone health and coronary artery calcification: the Rotterdam study. *Atherosclerosis* 2015;241(1):278-83.

150. Nguyen TV, Center JR, Eisman JA. Femoral neck bone loss predicts fracture risk independent of baseline BMD. *J Bone Miner Res* 2005;20(7):1195-201.

151. Berry SD, McLean RR, Hannan MT, et al. Changes in bone mineral density may predict the risk of fracture differently in older adults according to fall history. *J Am Geriatr Soc* 2014;62(12):2345-49.

152. Machado K, Domiciano D, Machado L, et al. Persistent hypovitaminosis D and loss of hip bone mineral density over time as additional risk factors for recurrent falls in a population-based prospective cohort of elderly persons living in the community. The São Paulo Ageing & Health (SPAH) Study. *Osteoporos Int* 2015;26(5):1535-42.

153. Lui LY, Stone K, Cauley JA, et al. Bone loss predicts subsequent cognitive decline in older women: the study of osteoporotic fractures. *J Am Geriatr Soc* 2003;51(1):38-43.

154. Kwon J, Suzuki T, Yoshida H, et al. Association Between Change in Bone Mineral Density and Decline in Usual Walking Speed in Elderly Community-Dwelling Japanese Women During 2 Years of Follow-Up. *J Am Geriatr Soc* 2007;55(2):240-44.

155. Blain H, Carriere I, Favier F, et al. Body weight change since menopause and percentage body fat mass are predictors of subsequent bone mineral density change of the proximal femur in women aged 75 years and older: results of a 5 year prospective study. *Calcif Tissue Int* 2004;75(1):32-39.

156. Bleicher K, Cumming RG, Naganathan V, et al. The role of fat and lean mass in bone loss in older men: findings from the CHAMP study. *Bone* 2011;49(6):1299-305.

157. Sirola J, Tuppurainen M, Honkanen R, et al. Associations between grip strength change and axial postmenopausal bone loss—a 10-year population-based follow-up study. *Osteoporos Int* 2005;16(12):1841-48.

158. Edwards LJ. Modern statistical techniques for the analysis of longitudinal data in biomedical research. *Pediatr Pulmonol* 2000;30(4):330-44.

159. Parsons C, Judge A, Meyer R, et al. Determining individual trajectories of joint space loss: improved statistical methods for monitoring knee osteoarthritis disease progression. *Osteoarthritis Cartilage* 2021;29(1):59-67.

160. Twisk JW. Longitudinal data analysis. A comparison between generalized estimating equations and random coefficient analysis. *Eur J Epidemiol* 2004;19(8):769-76.

161. Preacher KJ, Wichman AL, Briggs NE, et al. Latent growth curve modeling. SAGE 2008.

162. Oksuzyan A, Maier H, McGue M, et al. Sex differences in the level and rate of change of physical function and grip strength in the Danish 1905-cohort study. *J Aging Health* 2010;22(5):589-610.

163. Deary IJ, Johnson W, Gow AJ, et al. Losing one's grip: a bivariate growth curve model of grip strength and nonverbal reasoning from age 79 to 87 years in the Lothian Birth Cohort 1921. *J Gerontol B Psychol Sci Soc Sci* 2011;66(6):699-707.

164. Ghisletta P, Lindenberger U. Static and dynamic longitudinal structural analyses of cognitive changes in old age. *Gerontology* 2004;50(1):12-16.

165. Nagin DS. Analyzing developmental trajectories: a semiparametric, group-based approach. *Psychol Methods* 1999;4(2):139–57.

166. Andruff H, Carraro N, Thompson A, et al. Latent class growth modelling: a tutorial. *Tutor Quant Methods Psychol* 2009;5(1):11-24.

167. Tian Q, An Y, Resnick SM, et al. The relative temporal sequence of decline in mobility and cognition among initially unimpaired older adults: Results from the Baltimore Longitudinal Study of Aging. *Age Ageing* 2016;46(3):445-51.

168. Laursen B, Little TD, Card NA. Handbook of developmental research methods. The Guilford Press 2012.

169. Whitesell NR, Asdigian NL, Kaufman CE, et al. Trajectories of substance use among young American Indian adolescents: Patterns and predictors. *J Youth Adolesc* 2014;43(3):437-53.

170. Munthali RJ, Kagura J, Lombard Z, et al. Childhood adiposity trajectories are associated with late adolescent blood pressure: birth to twenty cohort. *BMC Public Health* 2016;16(665)

171. Jung T, Wickrama K. An introduction to latent class growth analysis and growth mixture modeling. *Soc Personal Psychol Compass* 2008;2(1):302-17.

172. Connell AM, Frye AA. Growth mixture modelling in developmental psychology: Overview and demonstration of heterogeneity in developmental trajectories of adolescent antisocial behaviour. *Infant Child Dev* 2006;15(6):609-21.

173. Wang M, Li Z, Lee EY, et al. Predicting the multi-domain progression of Parkinson's disease: a Bayesian multivariate generalized linear mixed-effect model. *BMC Med Res Methodol* 2017;17(1):147.

174. Baja ES, Schwartz JD, Coull BA, et al. Structural equation modeling of parasympathetic and sympathetic response to traffic air pollution in a repeated measures study. *Environ Health* 2013;12(1):81.

175. Nahhas RW, Choh AC, Lee M, et al. Bayesian longitudinal plateau model of adult grip strength. *Am J Hum Biol* 2010;22(5):648-56.

176. Nandram B, Choi JW. Hierarchical Bayesian nonignorable nonresponse regression models for small areas: An application to the NHANES data. *Surv Methodol* 2005;31(1):73-84.

177. Zhao R, Catalano P, DeGruttola VG, et al. Estimating mono-and bi-phasic regression parameters using a mixture piecewise linear Bayesian hierarchical model. *PloS one* 2017;12(7):e0180756.

178. Huang Y, Chen J, Yin P. Hierarchical mixture models for longitudinal immunologic data with heterogeneity, non-normality, and missingness. *Stat Methods Med Res* 2017;26(1):223-47.

179. Li Z, Tosteson TD, Bakitas MA. Joint modeling quality of life and survival using a terminal decline model in palliative care studies. *Stat Med* 2013;32(8):1394-406.

180. Terrera GM, Piccinin AM, Johansson B, et al. Joint Modeling of Longitudinal Change and Survival: An Investigation of the Association Between Change in Memory Scores and Death. *GeroPsych (Bern)* 2011;24(4):177-85.

181. Asar Ö, Ritchie J, Kalra PA, et al. Joint modelling of repeated measurement and time-to-event data: an introductory tutorial. *Int J Epidemiol* 2015;44(1):334-44.

182. Chandra S, Chandra M. Do consumers substitute opium for hashish? An economic analysis of simultaneous cannabinoid and opiate consumption in a legal regime. *Drug Alcohol Depend* 2015;1(156):170-75.

183. Samimi P, Jenatabadi HS. Globalization and economic growth: Empirical evidence on the role of complementarities. *PloS one* 2014;9(4):e87824.

184. Gerstorf D, Lövdén M, Röcke C, et al. Well-being affects changes in perceptual speed in advanced old age: Longitudinal evidence for a dynamic link. *Dev Psychol* 2007;43(3):705-18.

185. Infurna FJ, Gerstorf D, Ryan LH, et al. Dynamic links between memory and functional limitations in old age: Longitudinal evidence for age-based structural dynamics from the ahead study. *Psychol Aging* 2011;26(3):546-58.

186. Ghisletta P, Bickel J-F, Lövdén M. Does activity engagement protect against cognitive decline in old age? Methodological and analytical considerations. *J Gerontol B Psychol Sci Soc Sci* 2006;61(5):253-61.

187. Grimm KJ, An Y, McArdle JJ, et al. Recent changes leading to subsequent changes: Extensions of multivariate latent difference score models. *Struct Equ Modeling* 2012;19(2):268-92.

188. Mund M, Nestler S. Beyond the cross-lagged panel model: Next-generation statistical tools for analyzing interdependencies across the life course. *Adv Life Course Res* 2019;41(100249)

189. Stasinopoulos MD, Rigby RA, Heller GZ, et al. Flexible Regression and Smoothing: Using GAMLSS in R. Chapman and Hall/CRC 2017.

190. Nagin DS. Group-based modeling of development. Harvard University Press 2005.

191. Proust-Lima C, Philipps V, Liquet B. Estimation of Extended Mixed Models Using Latent Classes and Latent Processes: The R Package lcmm. *J Stat Softw* 2017;78(2)

192. Dunn PK, Smyth GK. Randomized quantile residuals. *J Comput Graph Stat* 1996;5(3):236-44.

193. Angus JE. The probability integral transform and related results. *SIAM Review* 1994;36(4):652-54.

194. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med* 1992;11(10):1305-19.

195. Rigby RA, Stasinopoulos DM. Using the Box-Cox t distribution in GAMLSS to model skewness and kurtosis. *Stat Modelling* 2006;6(3):209-29.

196. Bolker BM, Brooks ME, Clark CJ, et al. Generalized linear mixed models: a practical guide for ecology and evolution. *Trends Ecol Evol* 2009;24(3):127-35.

197. Faraway JJ. Extending the linear model with R. CRC Press 2006.

198. Raudenbush SW. Comparing personal trajectories and drawing causal inferences from longitudinal data. *Annu Rev Psychol* 2001;52(1):501-25.

199. Sweeten G. Group-Based Trajectory Models. Encyclopedia of Criminology and Criminal Justice (pages 1991-2003). Springer New York 2014.

200. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol* 2010;6:109-38.

201. Bauer DJ. Observations on the use of growth mixture models in psychological research. *Multivariate Behav Res* 2007;42(4):757-86.

202. Colder CR, Mehta P, Balanda K, et al. Identifying trajectories of adolescent smoking: an application of latent growth mixture modeling. *Health Psychol* 2001;20(2):127-35.

203. Li F, Duncan TE, Hops H. Examining developmental trajectories in adolescent alcohol use using piecewise growth mixture modeling analysis. *J Stud Alcohol* 2001;62(2):199-210.

204. Marquardt DW. An algorithm for least-squares estimation of nonlinear parameters. *J Soc Ind Appl Math* 1963;11(2):431-41.

205. Kievit RA, Brandmaier AM, Ziegler G, et al. Developmental cognitive neuroscience using latent change score models: A tutorial and applications. *Dev Cogn Neurosci* 2018;33:99-117.

206. National Institute on Aging. Introducing the Health ABC Study: The Dynamics of Health, Aging, and Body Composition. https://healthabc.nia.nih.gov/ (accessed 1st June 2021).

207. Houston DK, Ding J, Lee JS, et al. Dietary fat and cholesterol and risk of cardiovascular disease in older adults: the Health ABC Study. *Nutr Metab Cardiovasc Dis* 2011;21(6):430-7.

208. Butler J, Rodondi N, Zhu Y, et al. Metabolic syndrome and the risk of cardiovascular disease in older adults. *J Am Coll Cardiol* 2006;47(8):1595-602.

209. Rooks RN, Simonsick EM, Miles T, et al. The association of race and socioeconomic status with cardiovascular disease indicators among older adults in the health, aging, and body composition study. *J Gerontol B Psychol Sci Soc Sci* 2002;57(4):247-56.

210. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;32(9 Suppl):498-504.

211. Visser M, Simonsick EM, Colbert LH, et al. Type and intensity of activity and risk of mobility limitation: the mediating role of muscle parameters. *J Am Geriatr Soc* 2005;53(5):762-70.

212. Pettee KK, Brach JS, Kriska AM, et al. Influence of marital status on physical activity levels among older adults. *Med Sci Sports Exerc* 2006;38(3):541-6.

213. Hilmer SN, Mager DE, Simonsick EM, et al. Drug burden index score and functional decline in older people. *Am J Med* 2009;122(12):1142-49.

214. Kennedy E, Ohls J, Carlson S, et al. The Healthy Eating Index: design and applications. *J Am Diet Assoc* 1995;95(10):1103-08.

215. Hengeveld LM, Wijnhoven HA, Olthof MR, et al. Prospective associations of poor diet quality with long-term incidence of protein-energy malnutrition in community-dwelling older adults: the Health, Aging, and Body Composition (Health ABC) Study. *Am J Clin Nutr* 2018;107(2):155-64.

216. Klepin HD, Geiger AM, Tooze JA, et al. Physical performance and subsequent disability and survival in older adults with malignancy: results from the health, aging and body composition study. *J Am Geriatr Soc* 2010;58(1):76-82.

217. Raphael KL, Murphy RA, Shlipak MG, et al. Bicarbonate concentration, acid-base status, and mortality in the Health, Aging, and Body Composition Study. *Clin J Am Soc Nephrol* 2016;11(2):308-16.

218. Cawthon PM, Fox KM, Gandra SR, et al. Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? *J Am Geriatr Soc* 2009;57(8):1411-9.

219. Yenchek RH, Joachim H Ix, Shlipak MG, et al. Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol* 2012;7(7):1130-6.

220. Twisk J. Applied Longitudinal Data Analysis for Epidemiology. A Practical Guide. Cambridge University Press 2013.

221. Joliffe I, Morgan B. Principal component analysis and exploratory factor analysis. *Stat Methods Med Res* 1992;1(1):69-95.

222. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94(446):496-509.

223. Kanis J, Johansson H, Harvey N, et al. The effect on subsequent fracture risk of age, sex, and prior fracture site by recency of prior fracture. *Osteoporos Int* 2021 doi: 10.1007/s00198-020-05803-4.

224. Inouye SK, Zhang Y, Jones RN, et al. Risk factors for hospitalization among community-dwelling primary care older patients: development and validation of a predictive model. *Med Care* 2008;46(7):726-31.

225. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. *Maturitas* 2013;75(1):51-61.

226. Looker AC, Melton III LJ, Harris TB, et al. Prevalence and trends in low femur bone density among older US adults: NHANES 2005–2006 compared with NHANES III. *J Bone Miner Res* 2010;25(1):64-71.

227. Patel A, Edwards M, Jameson K, et al. Longitudinal Change in Peripheral Quantitative Computed Tomography Assessment in Older Adults: The Hertfordshire Cohort Study. *Calcif Tissue Int* 2018;103(5):476-82.

228. Newman AB, Sanders JL, Kizer JR, et al. Trajectories of function and biomarkers with age: the CHS All Stars Study. *Int J Epidemiol* 2016;45(4):1135-45.

229. Curtis E, Litwic A, Cooper C, et al. Determinants of muscle and bone aging. *J Cell Physiol* 2015;230(11):2618-25.

230. Bohannon RW. Population representative gait speed and its determinants. *J Geriatr Phys Ther* 2008;31(2):49-52.

231. Syddall HE, Westbury LD, Cooper C, et al. Self-reported walking speed: a useful marker of physical performance among community-dwelling older people? *J Am Med Dir Assoc* 2015;16(4):323-28.

232. Seematter-Bagnoud L, Büla C, Santos-Eggimann B. The association between different levels of alcohol use and gait under single and dual task in community-dwelling older persons aged 65 to 70 years. *Curr Gerontol Geriatr Res* 2016;2016(2018507) doi: 10.1155/2016/2018507.

233. Szulc P, Duboeuf F, Marchand F, et al. Hormonal and lifestyle determinants of appendicular skeletal muscle mass in men: the MINOS study. *Am J Clin Nutr* 2004;80(2):496-503.

234. Locquet M, Beaudart C, Durieux N, et al. Relationship between the Changes over Time of Bone and Muscle Health in Children and Adults: A Systematic Review and Meta-Analysis. *BMC Musculoskelet Disord* 2019;20(1):429.

235. Sirola J, Rikkonen T, Tuppurainen M, et al. Maintenance of muscle strength may counteract weight-loss-related postmenopausal bone loss—a population-based approach. *Osteoporos Int* 2006;17(5):775-82.

236. Sirola J, Rikkonen T, Tuppurainen M, et al. Association of grip strength change with menopausal bone loss and related fractures: a population-based follow-up study. *Calcif Tissue Int* 2006;78(4):218-26.

237. Arabi A, Baddoura R, El-Rassi R, et al. PTH level but not 25 (OH) vitamin D level predicts bone loss rates in the elderly. *Osteoporos Int* 2012;23(3):971-80.

238. Chen Z, Lohman TG, Stini WA, et al. Fat or lean tissue mass: which one is the major determinant of bone mineral mass in healthy postmenopausal women? *J Bone Miner Res* 1997;12(1):144-51.

239. Liu-Ambrose T, Kravetsky L, Bailey D, et al. Change in lean body mass is a major determinant of change in areal bone mineral density of the proximal femur: a 12-year observational study. *Calcif Tissue Int* 2006;79(3):145-51.

240. Milliken L, Cussler E, Zeller R, et al. Changes in soft tissue composition are the primary predictors of 4-year bone mineral density changes in postmenopausal women. *Osteoporos Int* 2009;20(2):347-54.

241. Singer NG, Caplan AI. Mesenchymal stem cells: mechanisms of inflammation. *Annu Rev Pathol* 2011;6:457-78.

242. Prasitsiriphon O, Pothisiri W. Associations of Grip Strength and Change in Grip Strength With All-Cause and Cardiovascular Mortality in a European Older Population. *Clin Med Insights Cardiol* 2018;12:1179546818771894.

243. Granic A, Davies K, Jagger C, et al. Initial level and rate of change in grip strength predict all-cause mortality in very old adults. *Age Ageing* 2017;46(6):970-76.

244. Harvey NC, Odén A, Orwoll E, et al. Measures of Physical Performance and Muscle Strength as Predictors of Fracture Risk Independent of FRAX, Falls, and aBMD: A Meta-Analysis of the Osteoporotic Fractures in Men (MrOS) Study. *J Bone Miner Res* 2018;33(12):2150-57.

245. Simmonds SJ, Syddall HE, Westbury LD, et al. Grip strength among community-dwelling older people predicts hospital admission during the following decade. *Age Ageing* 2015;44(6):954-59.

246. Moreland JD, Richardson JA, Goldsmith CH, et al. Muscle weakness and falls in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2004;52(7):1121-29.

247. Cooper R, Kuh D, Hardy R. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ* 2010;341:c4467. doi: 10.1136/bmj.c4467.

248. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA* 2011;305(1):50-58.

249. Dumurgier J, Elbaz A, Ducimetière P, et al. Slow walking speed and cardiovascular death in well functioning older adults: prospective cohort study. *BMJ* 2009;339:b4460. doi: 10.1136/bmj.b4460.

250. Verghese J, Holtzer R, Lipton RB, et al. Quantitative gait markers and incident fall risk in older adults. *J Gerontol A Biol Sci Med Sci* 2009;64(8):896-901.

251. Quach L, Galica AM, Jones RN, et al. The nonlinear relationship between gait speed and falls: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston study. *J Am Geriatr Soc* 2011;59(6):1069-73.

252. Barbour KE, Lui L-Y, McCulloch CE, et al. Trajectories of lower extremity physical performance: effects on fractures and mortality in older women. *J Gerontol A Biol Sci Med Sci* 2016;71(12):1609-15.

253. Alajlouni D, Bliuc D, Tran T, et al. Decline in muscle strength and performance predicts fracture risk in elderly women and men. *J Clin Endocrinol Metab* 2020;105(9):dgaa414.

254. Toss F, Wiklund P, Nordström P, et al. Body composition and mortality risk in later life. *Age Ageing* 2012;41(5):677-81.

255. Santanasto AJ, Goodpaster BH, Kritchevsky SB, et al. Body Composition Remodeling and Mortality: The Health Aging and Body Composition Study. *J Gerontol A Biol Sci Med Sci* 2017;72(4):513-19.

256. Sornay-Rendu E, Duboeuf F, Boutroy S, et al. Muscle mass is associated with incident fracture in postmenopausal women: The OFELY study. *Bone* 2017;94:108-13.

257. Xu C, Ebeling PR, Scott D. Body Composition and Falls Risk in Older Adults. *Curr Geri Rep* 2019;8:210–22.

258. Scott D, Seibel MJ, Cumming R, et al. Associations of Body Composition Trajectories with Bone Mineral Density, Muscle Function, Falls, and Fractures in Older Men: The Concord Health and Ageing in Men Project. *J Gerontol A Biol Sci Med Sci* 2019;75(5):939-45.

259. Kim KM, Moon JH, Choi SH, et al. Lower baseline value and greater decline in BMD as independent risk factors for mortality in community dwelling elderly. *Bone* 2019;121:204-11.

260. Berger C, Langsetmo L, Joseph L, et al. Association between change in BMD and fragility fracture in women and men. *J Bone Miner Res* 2009;24(2):361-70.

261. Balogun S, Winzenberg T, Wills K, et al. Prospective associations of osteosarcopenia and osteodynapenia with incident fracture and mortality over 10 years in community-dwelling older adults. *Arch Gerontol Geriatr* 2019;82:67-73.

262. Niiranen TJ, Enserro DM, Larson MG, et al. Multisystem Trajectories Over the Adult Life Course and Relations to Cardiovascular Disease and Death. *J Gerontol A Biol Sci Med Sci* 2019;74(11):1778-85.

263. Cawthon PM, Parimi N, Langsetmo L, et al. Individual and joint trajectories of change in bone, lean mass and physical performance in older men. *BMC Geriatr* 2020;20(1):161.

264. Dodds RM, Syddall HE, Cooper R, et al. Grip strength across the life course: normative data from twelve British studies. *PloS one* 2014;9(12):e113637.

265. Kenny RA, Coen RF, Frewen J, et al. Normative values of cognitive and physical function in older adults: findings from the Irish Longitudinal Study on Ageing. *J Am Geriatr Soc* 2013;61(Suppl 2):S279-S90.

266. National Center for Health Statistics. Health, United States, 2013: With Special Feature on Prescription Drugs. https://www.cdc.gov/nchs/data/hus/2013/058.pdf (accessed 1st June 2021).

267. Thorpe RJ, Jr., Koster A, Bosma H, et al. Racial differences in mortality in older adults: factors beyond socioeconomic status. *Ann Behav Med* 2012;43(1):29-38.

268. Dodds R, Denison H, Ntani G, et al. Birth weight and muscle strength: a systematic review and meta-analysis. *J Nutr Health Aging* 2012;16(7):609-15.

269. Baird J, Kurshid MA, Kim M, et al. Does birthweight predict bone mass in adulthood? A systematic review and meta-analysis. *Osteoporos Int* 2011;22(5):1323-34.

270. Sayer AA, Syddall H, Martin H, et al. The developmental origins of sarcopenia. *J Nutr Health Aging* 2008;12(7):427-32.

271. Robinson SM, Westbury LD, Cooper R, et al. Adult lifetime diet quality and physical performance in older age: findings from a British birth cohort. *J Gerontol A Biol Sci Med Sci* 2017;73(11):1532-37.

272. Dodds R, Kuh D, Aihie Sayer A, et al. Physical activity levels across adult life and grip strength in early old age: updating findings from a British birth cohort. *Age Ageing* 2013;42(6):794-98.

273. Lim S, Cox N, Tan QY, et al. Volunteer-led physical activity interventions to improve health outcomes for community-dwelling older people: a systematic review. *Aging Clin Exp Res* 2020;33(4):843-53.

274. Harvey N, Dennison E, Cooper C. Osteoporosis: a lifecourse approach. *J Bone Miner Res* 2014;29(9):1917-25.

275. Dodds RM, Roberts HC, Cooper C, et al. The epidemiology of sarcopenia. *J Clin Densitom* 2015;18(4):461-66.

276. Bhasin S, Travison TG, Manini TM, et al. Sarcopenia Definition: The Position Statements of the Sarcopenia Definition and Outcomes Consortium. *J Am Geriatr Soc* 2020;68(7):1410-18.

277. Cawthon PM, Manini T, Patel SM, et al. Putative Cut-Points in Sarcopenia Components and Incident Adverse Health Outcomes: An SDOC Analysis. *J Am Geriatr Soc* 2020;68(7):1429-37.

278. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;39(4):412-23.

279. Studenski SA, Peters KW, Alley DE, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci* 2014;69(5):547-58.

280. McLean RR, Shardell MD, Alley DE, et al. Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality:

the foundation for the National Institutes of Health (FNIH) sarcopenia project. *J Gerontol A Biol Sci Med Sci* 2014;69(5):576-83.