University of Southampton

Faculty of Medicine

Understanding the relationship between muscle and bone in older adults: an investigation of two cohorts.

Human Development and Health

by

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Abstract

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Bone and muscle are interconnected tissues forming the 'muscle-bone unit'. Sarcopenia and osteoporosis are common conditions in older adults; the characterisation of the relationship between muscle and bone is fundamental to the development of potential novel preventive and therapeutic strategies that benefit both tissues. This thesis presents data from two cohorts, the Hertfordshire cohort study (HCS) and Southampton Longitudinal Study of Ageing (SaLSA) that consider relationships between muscle and bone in later life.

Using existing data available from the Hertfordshire Cohort Study (HCS), the association between sarcopenia or/and osteoporosis with frailty was assessed. Co-existence of sarcopenia and osteoporosis were associated with a much higher risk of frailty than either condition alone, while sarcopenia and osteoporosis were both closely linked with multimorbidity. The overall prevalence of frailty was 8.1% with the risk increasing with age, while corresponding figures for pre-frailty were 57.5%, with the risk increasing with age only in females.

Furthermore, possible determinants, such as demographic and anthropometric, of muscle density were considered and the relationships of muscle density measures to the clinical outcomes of falls and fractures were reported. Demographic and anthropometric (female sex, older age, and lower adiposity), rather than lifestyle factors such as physical activity and diet, were associated with lower muscle density, approximately 11 years later. Forearm muscle density was associated with previous fracture, rather than falls history.

In addition, the relationships between other sarcopenia components including muscle size, strength and function were considered with the clinically important outcomes of falls and fractures in HCS. Observed relationships between muscle mass and strength but not function with falls and fractures were reported; sexual dimorphism was also described in the above-mentioned relationships.

Finally, we present results from a new community-based cohort of older adults in Southampton, SaLSA. Initially we have investigated the impact of the COVID19 pandemic on lifestyle factors associated with musculoskeletal health in older adults living in their own homes. Greater nutritional risk and sarcopenia risk were associated with being in a worse category for change in diet quality in SaLSA during the 1st year of the pandemic.

Investigating the factors leading to these changes, understanding whether they are reversible, and recognising the consequences to musculoskeletal health is required. Future work is described

using this new cohort of older adults that will allow the investigation of muscle bone interrelationships in greater detail than has been previously possible. Given the interrelation between bone and muscle, future studies, such as SaLSA, might allow us to better understand muscle-bone crosstalk, with the aim of developing preventative strategies to retard or prevent deterioration of both tissues with age.

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Research Thesis: Declaration of Authorship

Print name: Faidra Laskou

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F. Laskou, H. P. Patel, C. Cooper & E. Dennison (2022) A pas de deux of osteoporosis and sarcopenia: osteosarcopenia, Climacteric, 25:1, 88-95, DOI: 10.1080/13697137.2021.1951204

Laskou, F., Fuggle, N. R., Patel, H. P., Jameson, K., Cooper, C., and Dennison, E. (2022) Associations of osteoporosis and sarcopenia with frailty and multimorbidity among participants of the Hertfordshire Cohort Study, Journal of Cachexia, Sarcopenia and Muscle, 13, 220– 229, https://doi.org/10.1002/jcsm.12870

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Faidra Laskou, Gregorio Bevilacqua, Leo D Westbury, Ilse Bloom, Pritti Aggarwal, Cyrus Cooper, Harnish P Patel, Elaine Dennison. A study of the impact of the COVID-19 pandemic on diet in older community-dwelling adults in the UK: findings from the Southampton Longitudinal Study of Ageing (SaLSA), **submitted to Frontiers in Nutrition, July 2022**

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Hertfordshire Cohort Study, Metabolism Open, Volume 12, 2021, 100143, ISSN 2589-9368, https://doi.org/10.1016/j.metop.2021.100143

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Abstracts related to this thesis

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2021

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Associations of sarcopenia and osteoporosis with frailty and multimorbidity among participants of the Hertfordshire Cohort Study, Faidra Laskou, Karen Jameson, Cyrus Cooper, Harnish P Patel, Elaine Dennison, Faculty of Medicine conference

Determinants of muscle density in late adulthood: findings from the Hertfordshire Cohort Study, Faidra Laskou, Leo D Westbury, Nicholas Fuggle, Nicholas C Harvey, Harnish P Patel, Cyrus Cooper, Kate Ward, Elaine Dennison, WCO-IOF-ESCEO

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Bevilacqua, Faidra Laskou, Harnish P Patel, Karen Jameson, Nicholas Fuggle, Cyrus Cooper, Elaine Dennison, Faculty of Medicine conference

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The impact of musculoskeletal conditions and frailty on the ability to self-care or be in receipt of care: a study of community-dwelling older adults from the Hertfordshire Cohort Study, G. Bevilacqua, F. Laskou, H. P. Patel, K. Jameson, N. Fuggle, C. Cooper, E. Dennison, WCO-IOF-ESCEO

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2022

Grip strength, bone mineral density and mortality: lessons from the past and hope for the future? F Laskou, LD Westbury, HP Patel, C Cooper, EM Dennison, WCO-IOF-ESCEO

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Mortality rates in individuals with a history of fracture: does sex matter? Findings from the Hertfordshire Cohort Study UK. Faidra Laskou, Leo Westbury, Harnish Patel, Cyrus Cooper, Elaine Dennison, BSR

The impact of musculoskeletal conditions and frailty on the ability to self-care or be in receipt of care: a study of community dwelling, G Bevilacqua, HJ Denison, F. Laskou, KA Jameson, KA Ward, C Cooper, EM Dennison, BGS 2022

Project Outputs

What impact have therapeutic advances for musculoskeletal health had on mortality risk – do we see differential relationships for muscle and bone? F Laskou, LD Westbury, H Patel, C Cooper, EM Dennison, ANZBMS 2022

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Definitions and abbreviations

ALM	Appendicular Lean Mass
ALM_{BMI}	Appendicular Lean Mass Adjusted for Body Mass Index
AMTS	Abbreviated Mental Test Score
ANOVA	Analysis Of Variance
ASBMR	American Society for Bone and Mineral Research
ASM	Appendicular Skeletal Mass
ATP	Adenosine Triphosphate
AWGS	Asian Working Group for Sarcopenia
BGS	British Geriatrics Society
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index
BMP	Bone Morphogenetic Proteins
BNDF	Brain-Derived Neurotrophic Factors
BRS	Bone Research Society
BSR	British Society of Rheumatology
cBMD	Cortical Bone Mineral Density
CI	Confidence Interval
COVID19	SARS-CoV 19 coronavirus (COVID19)
COX	Cyclooxygenase
CSA	Cross-Sectional Area
CT	Computed Tomography
DALY	Disability Adjusted Life Years
DETERMINE	Disease, Eating Properly, Tooth Loss/Mouth Pain, Economic Hardship, Reduced Social Contact, Multiple Medicines, Involuntary Weight Gain or

	Loss, Needs Assistance in Self-Care, And Elder Years Past Age 80
	Mnemonic
DKK	Calcium Dicckopf-1
DNA	Deoxyribonucleic Acid
dTBA	Distal Total Bone Area
DXA	Dual Energy X Ray Absorptiometry
EC	Endosteal Circumference
ECG	Electrocardiogram
ECTS	European Calcified Tissue Society
eFI	Frailty Index
ELSA	English Longitudinal Study of Ageing
EMIS	Egton Medical Information Systems
EOL	End Of Life
EPOSA	European Project on Osteoarthritis Study
ESCEO	Society For Clinical and Economic Aspects of Osteoporosis, Osteoarthritis
	and Musculoskeletal Diseases
EuGMS	European Geriatric Medicine Society
EWGSOP1	European Working Group on Sarcopenia in Older People 2010
EWGSOP2	European Working Group on Sarcopenia in Older People 2019
FFQ	Short Food Frequency Questionnaire
FGF2	Fibroblast Growth Factor 2
FGF23	Fibroblast Growth Factor 23
FM	Fat Mass
FNIH	Foundation For the National Institutes of Health
FoM	Faculty of Medicine Conference
FRAX	Fracture Risk Assessment Tool
GDF8	Growth Differentiation Factor 8

GH	Growth Hormone
GP	General Practitioner
GWAS	Genome-Wide Association Study
HADS	Hospital Anxiety and Depression Scale
HbA1c	Glycated Haemoglobin
HCRW	Health And Care Research Wales
HCS	Hertfordshire Cohort Study
HEAF	Health And Employment After Fifty Study
HRA	Health Research Authority
HRpQCT	High-Resolution Peripheral Quantitative Computed Tomography
HRT	Hormone Replacement Therapy
IGF1	Insulin Growth Factor- 1
IL6	Interleukin-6
IL7	Interleukin-7
IMAT	Intermuscular Adipose Tissue
IMC	Intramyocellular Lipids
IQR	Interquartile Range
ISTRC	International Sarcopenia Translation Research Conference
IWGS	International Working Group on Sarcopenia
JCSM	Journal of Cachexia, Sarcopenia and Muscle
LAPAQ	Lasa Physical Activity Questionnaire
LBM	Lean Body Mass
LIF	Leukaemia Inhibitory Factor
LMs	Lipid Signalling Mediators
LSNS-6	Six-Item Lubben Social Network Scale
LWP	Living Well Partnership
MAT	Marrow Adipose Tissue

MEMOSA	Multi Ethnic Molecular Determinants of Human Sarcopenia Study
MoCA	Montreal Cognitive Assessment
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal Stem Cell
MSK	Musculoskeletal
MSSP	Maastricht Social Participation Profile
NAPA	Nutrition And Physical Activity Study
NICE	National Institute for Health and Care Excellence
NSAID's	Non-Steroidal Anti-Inflammatory Drugs
OP	Osteoporosis
OPCS	Occupational Classification Scheme for Occupation and Social Class
PASE	Physical Activity Scale for The Elderly
PC	Periosteal Circumference
PG	Prostaglandin
PIS	Participant Information Sheet
PPG	Patient And Public Group
PPI	Patient And Public Involvement
pQCT	Peripheral Quantitative Computed Tomography
QoL	Quality Of Life
RANKL	Receptor Activator of Nuclear Factor-Kappa B Ligand
RNA	Ribonucleic Acid
RSMI	Relative Skeletal Muscle Index
SaLSA	Southampton Longitudinal Study of Ageing
SARC-F	Strength, Assistance with Walking, Rising from A Chair, Climbing Stairs, And Falls Questionnaire

SARCOS	Sarcopenia And Osteoporosis in Older Adults with Cardiovascular Diseases Study
SARCUS	Sarcopenia Measurement by Ultrasound
SARMs	Selective Androgen Receptor Modulators
SarQoL	Sarcopenia And Quality of Life
SARS-Cov-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SDOC	Sarcopenia Definition and Outcomes Consortium
SHARE	Survey Of Health, Aging and Retirement in Europe
SP	Sarcopenia
SPPB	Short Physical Performance Battery
SSI	Strength Strain Index
tBMD	Trabecular Bone Mineral Density
TUG	Timed Up and Go
UK	United Kingdom
USA	United States of America
USS	Ultrasound
VFA	Vertebral Fracture Assessment
VIBES	Vibration To Improve Bone in Elderly Subjects Study
WCO-IOF-ESCEO	World Congress on Osteoporosis, Osteoarthritis, And Musculoskeletal Diseases
$Weak_{BMI}$	Grip Strength Adjusted for Body Mass Index
WHO	World Health Organization
Wnt	Wingless-Related Integration Site

Chapter 1. Introduction

Over the coming years, the number of people over the age of 65 is projected to increase substantially [1]. By 2050, 2 billion people will be over 60 years of age, up from 1 billion in 2020 according to the World Health Organization (WHO) [2]. In England the proportion of people over the age of 65 years is projected to increase from 18.2% to 20.7% of the total population between 2018 and 2028 [2]. The greatest increase will be seen in the number of older people where the number aged 85 years and over is projected to almost double to 2.6 million over the next 25 years [2].This increase is occurring at an unprecedented pace and will accelerate in coming decades, particularly in developing countries.

Local and worldwide clinical guidance on delivering integrated care for older people at the community level focuses on early interventions to ameliorate or reverse frailty [3]. Frailty is a complex and multidimensional syndrome defined as an increased vulnerability and reduced ability to maintain homeostasis amongst physiological systems [4], and is usually but not exclusively observed with ageing [5]. Individuals living with pre- or with frailty face higher risks of falls, reduced mobility, morbidity and mortality and are consequently at risk of multiple adverse health outcomes [6–8].

The occurrence of musculoskeletal health disorders will also increase commensurate with population ageing. Ageing is closely associated with loss of both bone and muscle, and strong associations between muscle and bone have been reported across the lifespan [9]. The two tissues muscle and bone develop during adolescence, reaching a peak in density that is maintained in midlife and then declines with ageing [10,11]. In fact, after the fourth decade of life, there is a progressive decline in muscle mass (i.e., 1–2% per year) and strength (i.e., 1.5% per year) [12]. Bone mass, on the other hand, steadily increases during childhood, rapidly increases during adolescence to peak between 20-30 years, but this is then followed by a rapid decrease in the postmenopausal period at a rate of nearly 1–1.5%/year, after the age of 60 [13,14]. Few studies have examined the trajectories and associations of muscle and bone change over the life

course (Table 1-1), but available data indicate a linear declining trend with age [15–18]. Conflicting evidence still exists however for the association and crossover between muscle and bone health over the lifecourse [15,16,19].

Since the 19th century, a relationship between muscle and bone has been recognised as it is appreciated that bones have adaptive capability and that structural adaptation is driven by mechanical strain placed on bone by muscle [20,21]. The mechanostat theory was developed by Harold Frost proposing a feedback system that could explain how physiological loads, caused by muscle contraction, cause bone adaptation [22]. Others have since observed a physiological relationship between muscle and bone but the first person to describe the muscle-bone unit as a functional symbiosis was Schiessl in 1998 [23].

A body of evidence now exists in support of the muscle-bone concept and research in the field has been dedicated to understanding the muscle-bone interrelationship and age-related bone and muscle loss. Muscle-bone interactions are of interest for basic, clinical, and translational scientists. Muscle and bone are integrated organs with shared functions, and it might therefore be expected that their development and maintenance are in parallel [18]. The 'muscle-bone unit' is a site of privileged exchanges in which these two tissues communicate and coordinate their development (chemically and metabolically) as well as their response to loading or injury [24].However, although muscle and bone are similar in many ways, important differences exist [25].

Table 1-1: Summary of literature review on muscle and bone changes throughout life and their associations[1].

Author	Year	N	Age	Population	Design	Results
J. L. Ferretti [18]	1998	1450	9-82	F/M	Cross sectional	◦Bone mass was found to be closely and linearly associated with muscle mass throughout life
L. H. Bogl [19]	2011	149	23-31	F/M Twins	Longitudinal	◦Peak BMD is influenced by acquired body weight as well as genetic factors ◦LM and BMD may have more genes in common than do FM and BMD
Westbury [26]	2020	2917	70-79	F/M	Longitudinal	◦Decline in grip strength, gait speed and hip BMD accelerated somewhat with age; decline in ALM was linear ◦Changes in ALM, fat mass and hip BMD were correlated with one another ◦Changes in grip strength and ALM were moderately correlated among men and women
Cawthon [16]	2020	5994	≥65	M	Longitudinal	◦Decline in each trajectory (total hip BMD, ALM, grip strength and walking speed) with age but appeared to have little crossover or convergence of change with age
S. Sipilä [17]	2020	1393	47-55	F	Cross sectional	◦Linear declining trend in muscle mass and bone density across the menopausal groups ◦Significantly lower values in muscle mass and bone density in the postmenopausal compared with premenopausal women ◦Physical activity is beneficial for muscle mass- influence on BMD was weaker

[1] BMD: Bone mineral density; LM: lean mass; FM: fat mass; ALM: appendicular lean mass

A deeper understanding of the pathophysiology of co-existing sarcopenia and osteoporosis has the potential to inform the development of a variety of approaches to improve musculoskeletal health in later life [27].

In Chapter 1.1 I will discuss the coexistence of sarcopenia, osteopenia, or osteoporosis in an individual. Though several terms have been used in the past including sarco-porosis, sarco-osteopenia, sarco-osteoporosis and dysmotility syndrome [28], the most common term describing coexisting poor bone and muscle health currently is osteosarcopenia, also referred to as the next Geriatric Giant [29,30].

1.1 A pas de deux of osteoporosis and sarcopenia: Osteosarcopenia (Appendix I)

1.1.1 Introduction

Musculoskeletal health disorders including osteoporosis and sarcopenia are highly prevalent in older adults. Osteoporosis, a disease characterised by low bone mass and structural deterioration of bone tissue is the most common chronic metabolic bone disease and represents a major global health problem contributing to 8.9 million fractures worldwide on an annual basis [31,32]. Osteoporosis incurred an estimated £1.8 billion in UK health costs in 2000; this is predicted to increase to £2.2 billion by 2025 [33]. Sarcopenia is characterised by progressive and generalised decline in muscle strength, function and muscle mass with increasing age or secondary to disease [34]. It is associated with a range of adverse physical and metabolic outcomes in terms of disability, morbidity, impaired quality of life and mortality [35] and has also been identified as a predictor of fracture risk [36]. In terms of cost, sarcopenia incurred an estimated $18.5billion in health care costs to the USA in 2000 [37]. In the UK, the annual excess cost associated with muscle weakness was estimated to be £2.5 billion [37,38]. Several varying definitions of sarcopenia have contributed to differences in prevalence estimates worldwide, ranging from 3-30% [35,39–41] (Table 1-2). Currently, a global consensus definition for sarcopenia does not exist

but there are well constructed diagnostic algorithms that provide a mechanism for clinical case finding [35].

Growing interest has emerged in the coexistence of osteoporosis and sarcopenia in some individuals, which is often termed osteosarcopenia, and is associated with higher morbidity from falls, fracture, disability as well as mortality [42,43]. Knowledge of the overlap in the pathophysiology of osteoporosis and sarcopenia can inform the development of potential treatments for osteosarcopenia [27]. Given the urgent need to educate clinicians and researchers on the importance of identifying osteosarcopenia early, this article aims to review and appraise relevant and available literature on osteosarcopenia, providing an update on the epidemiology (prevalence, risk factors and diagnosis) and management for osteosarcopenia.

Table 1-2: Sarcopenia cut-off points according to different criteria used (EWGSOP[2], AWGS, IWGS, FNIH and SDOC[2]).

Definition	***Muscle strength***		***Muscle quantity***			***Physical performance***			
	Grip strength (Kg)	**Chair stand (s)**	**$Weak_{BMI}$[3]**	**ASM/ALM (kg)[4]**	**ASM/ht^2 (kg/ht^2)**	**ALM_{BMI}[5]**	**Gait speed (m/s)**	**SPPB [6](points)**	**TUG [7](s)**	**400m walk**
EWGSOP2										
Males	<27	>15		<20	<7.0		≤0.8	≤8	≥20	Non-completion or ≥6 min for completion
Females	<16			<15	<5.5					
AWGS										
Males	< 28	≥ 12			< 7.0		< 1.0	≤ 9		
Females	< 18				< 5.4					
IWGS										
Males					≤ 7.23		< 1.0			
Females					≤ 5.67					

[2] EWGSOP2: European working group on sarcopenia in older people, AWGS: Asian Working Group for Sarcopenia, IWGS: International Working Group on Sarcopenia, FNIH: Foundation for the National Institutes of Health, SDOC: Sarcopenia definition and Outcomes Consortium.
[3] $Weak_{BMI}$: Grip strength adjusted for BMI
4 ALM: appendicular lean mass, ASM: appendicular skeletal mass
5 ALMBMI: Appendicular lean mass adjusted for body mass index
6 SPPB: short physical performance battery
[7] TUG: Timed Up and Go

FNIH						
Males	<26	<1.00	<19.75		<0.789	≤0.8
Females	<16	<0.56	<15.02		<0.512	
SDOC						
Males	<35.5		<19.75	<7.26		≤0.8
Females	<20		<15.02	<5.45		

1.1.2 Coexistence of poor bone and muscle measurements

The concept that individuals with low bone mass might also have low muscle mass has been investigated previously in several studies. For example, in 1998, a study assessed the relationship between whole body BMC and lean mass in males and females between 2 and 87 years of age indicating that bone mass is closely and linearly associated with muscle mass throughout life [18]. In other studies, lean mass was a better predictor of whole-body bone mineral density (BMD) than fat mass as well as incident fractures [44–46]. In the Hertfordshire Cohort Study, muscle size and muscle strength were positively associated with bone size and strength [9]. Greater loss of bone mass was noted in osteosarcopenic patients compared to osteoporotic patients in a study conducted in Ecuador dominated by female participants [47]. A positive relationship between muscle and bone mass decline over a year was recognised in older individuals in the SarcoPhage study[48] whereas an increase in the risk of fracture and decline in muscle strength was associated with a decrease in spine and hip BMD [48]. In the Copenhagen Sarcopenia study , BMD was lower among individuals with sarcopenia [49] and a large study of women in Japan showed that relative skeletal muscle index (RSMI) was positively correlated with BMD of the lumbar spine and total hip [50]. Finally, in a cross-sectional study of pre-, peri- and post-menopausal women, a linear decline in both muscle mass and bone density was noted, showing significant changes in the post- compared to pre-menopausal women [17].

1.1.3 Approaches to defining osteosarcopenia

1.1.3.1 Risk assessment and diagnosis

Awareness of the complex muscle and bone interrelationship will inform construction of diagnostic pathways to identify osteosarcopenia (Figure 1-1). In clinical practice, falls, fractures, slower gait speed, difficulty rising from a chair, weight loss, a low BMI or muscle wasting should all highlight the need for further diagnostic evaluation for osteoporosis and sarcopenia. There are available tools at the clinician's disposal to aid the identification of both sarcopenia and

osteoporosis separately. SARC-F, a 5-point sarcopenia self-questionnaire has high specificity but low sensitivity, making it the most accurate in detecting those with sarcopenia [51] (Table 1-3).

The EWGSOP2 diagnostic algorithm is the most widely used definition for sarcopenia and uses normative grip strength reference values for young healthy adults where possible, with cut-off points usually set –2 or –2.5 standard deviations compared to mean reference values [35]. In recent years, there is much more emphasis on muscle strength as the primary parameter characterising sarcopenia as opposed to muscle mass [35,39]. Sarcopenia is probable when low muscle strength is present; this is assessed by grip strength (measured with the use of a handheld dynamometer), or time taken to compete five chair rises (Table 1-4).

Table 1-3: SARC-F questionnaire; a 5-point sarcopenia self-questionnaire for detecting those with sarcopenia. SARC-F score of ≥4 best predicts the need for further, more comprehensive evaluation to confirm evidence of sarcopenia.

SARC-F Questionnaire		
Strength	Difficulty in lifting and carrying 10 pounds?	None= 0, Some= 1, A lot or unable = 2
Walking	Difficulty walking across a room?	None= 0, Some= 1, A lot, uses aids or unable = 2
Chair rise	Difficulty transferring from a chair or bed?	None= 0, Some= 1, A lot or unable without help = 2
Stairs	Difficulty climbing a flight of ten stairs?	None= 0, Some= 1, A lot or unable = 2
Falls	Times have you fallen in the past year?	None= 0, 1-3 falls= 1, 4 or more falls = 2

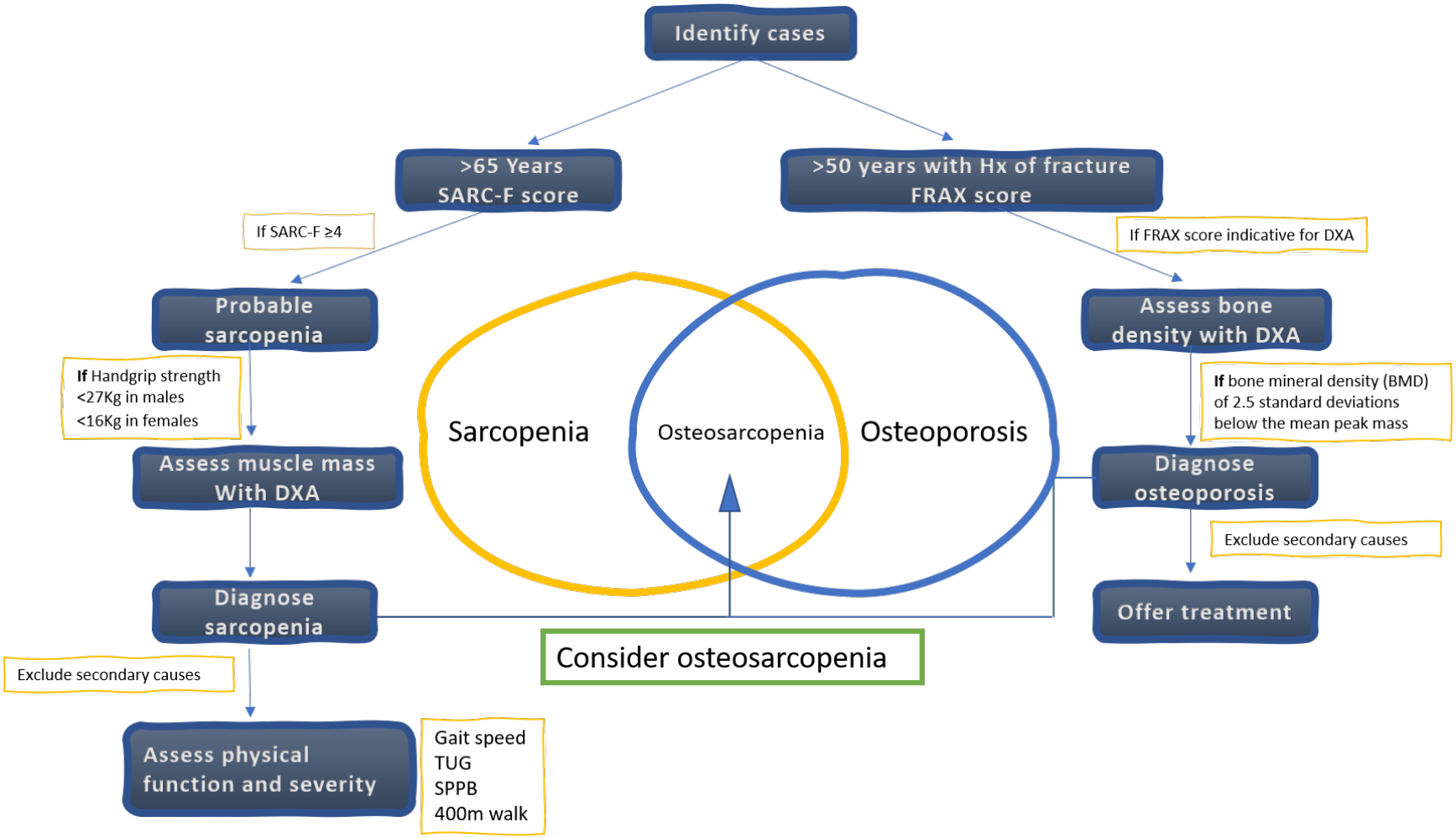


Figure 1-1:Proposed pathway/Risk stratification strategy to identify and diagnose patients with osteosarcopenia based on recent EWGSOP2 criteria for sarcopenia and NICE criteria for osteoporosis. Adapted from Kirk B et al., Osteosarcopenia: epidemiology, diagnosis, and treatment—facts and numbers

A diagnosis of sarcopenia is confirmed by the presence of low muscle quantity measured, for example, by dual energy X ray absorptiometry (DXA). A diagnosis of severe sarcopenia is made when low muscle strength is accompanied by low muscle quantity and decline in physical performance i.e., slower gait speed (Table 1-4).

Table 1-4: Clinical tools and cut offs for measurement of muscle strength, lean mass, and physical performance in sarcopenia according to the EWGSOP2 criteria and pathway [8]

CRITERION		TOOLS	CUT OFFS FOR WOMEN	CUT OFFS FOR MEN
IDENTIFY CASES		SARC-F	⩾ 4	
ASSESS SARCOPENIA	Muscle strength	Grip strength or	<16 kg	<27 kg
		Chair stand test	>15 s for 5 rises	
CONFIRM SARCOPENIA	Muscle quantity or quality	ASM by DXA or	<15 kg	<20 kg
		ASM/height2	<5.5kg/m2	<7kg/m2
ASSESS SEVERITY	Physical performance	Gait speed or	⩽0.8 m/s	
		SPPB or	⩽8 point score	
		TUG or	⩾20 s	
		400 m walk	⩾6 min for completion or noncompletion	

Other modalities of imaging previously used to measure muscle mass include bioelectrical impedance analysis but equations used to derive lean mass values are population and device specific and lack standardisation[52]; the same difficulties apply to ultrasound scanning use but interest in its application is growing, especially in view of the ready access to equipment [53,54]. CT and MRI are mostly used in research settings or when other diseases or conditions are suspected [52].

The FRAX score is now widely used as a validated tool for risk stratification for osteoporosis so decisions can be facilitated in the need for treatment in all postmenopausal women and men age 50 or over who have risk factors for fracture [55,56]. The diagnosis of osteopenia and of osteoporosis is made using DXA scanning. According to World Health Organization (WHO) criteria,

[8] ASM, appendicular skeletal muscle mass; DXA, dual-energy X-ray absorptiometry; SPPB, Short Physical Performance Battery; TUG, timed up and go.

T-scores of bone mineral density (BMD) below –1 and –2.5 categorise the patient as osteopenic and osteoporotic respectively [57].

The presence of sarcopenia when accompanied by low BMD (osteopenia or osteoporosis) with or without clinical fracture, has been defined as osteosarcopenia by some researchers (Figure 1-1).

1.1.4 **Prevalence of Osteosarcopenia**

The prevalence of osteosarcopenia among community dwelling populations increases with age and is greater in women than men [58,59]. Estimates vary considerably and range between 5 and 37% depending on the population and definition of sarcopenia used. The highest rates were observed in those with fractures [49,58]. In a study of 316 community-dwelling Chinese adults aged 65 years and over, 10.4% of men and 15.1% of women were found to be osteosarcopenic [60]. The prevalence of osteosarcopenia was found to be 37% in 680 community-dwelling older individuals in Australia with a history of falls [42]. The prevalence of sarcopenia was found to be 58% among 313 older women following hip fractures in an Italian study [61]. BMD values were significantly lower in sarcopenic older women and sarcopenic adults had a 4-fold higher risk of having co-existing osteoporosis compared with non-sarcopenic adults in a Belgian study [62]. Lastly, studies have shown that being diagnosed with sarcopenia was associated with a high risk of having osteoporosis and vice versa [48–50,63–65].

1.1.5 **Risk factors and pathophysiology**

Many factors have been implicated in the pathology of osteosarcopenia. Data from the UK Biobank show that muscle strength is partially genetically regulated and genetic factors are important in the achievement of peak bone mass [66,67]. No single gene or single nucleotide polymorphisms have been associated with the loss of bone mass, muscle strength or mass in conjunction but genome-wide association studies have identified several genes that are associated with bone and muscle wasting, with GDF8 the most well characterised [68]. Genetic background might also determine responsivity of the muscle-bone unit to mechanical stimuli;

several quantitative trait loci have been associated with the specific response to mechanical stimulation [69].

The mechanostat hypothesis suggests that increasing loads imposed by larger muscle forces on bone in childhood and adolescence lead to higher bone strength in midlife [22,70]. Conversely, a decline in muscle strength with age put bones into partial disuse and remodelling [22]. This highlights the importance of mechanical loading in the maintenance of the muscle-bone unit as loss of both bone and muscle mass are intrinsically linked to the reduction in physical performance observed with ageing [71].

Ageing is a significant risk factor for both osteoporosis and sarcopenia [72]. However, the molecular mechanisms linking bone to muscle function as we age are not very well-defined. Factors known as myokines (released from muscle such as myostatin, irisin), and osteokines (released from bone such as osteocalcin) are thought to be the mechanism of communication between the two tissues. Myostatin and the wnt-b–catenin signalling pathway have been extensively studied in mediating muscle-bone crosstalk by controlling both osteoblastic activity and muscle regeneration [73,74].

Inflamm-ageing, the chronic low level and long-term physiological stimulation of the immune system occurs as a consequence of lifelong exposure to antigenic stimuli interacting with complex genetic, environmental and age-related mechanisms including mitochondrial dysfunction [75,76]. These changes can affect muscle proteolysis and lead to a reduction in bone mineralisation [77], while it has been suggested that low grade and chronic inflammation can shift mesenchymal stem cells lineage towards adipogenesis instead of myogenesis and osteoblast genesis, resulting in decreased muscle and bone quality [78]. Finally, fat infiltration is one of the hallmarks of sarcopenia and osteoporosis as high levels of marrow adipose tissue (MAT) are associated with bone loss and osteoporosis whilst myosteatosis is associated with myocyte dysfunction and impaired muscle quality [78].

Sex hormones have several effects on muscle and bone. Notably with ageing, their concentration and activity on tissues alters. Menopause, which is characterised by a sharp decline in circulating

prostaglandin (PG) E2 in women, is an important contributor to the further decline in muscle and bone; the same abrupt decline does not apply to men. Early menopause without treatment is a strong risk factor for future fragility fracture [79] and hormone replacement therapy in post-menopausal women is able to both preserve bone and muscle mass [80]. Growth hormone (GH) and Insulin growth factor- 1 (IGF1) both exert a positive influence on osteoblasts in addition to their anabolic actions on muscle [81].

Lifestyle factors such as nutrition, alcohol and smoking have been shown to have effects on bone and muscle. Active smoking is associated with worse bone health in female smokers [82] and has been linked to the development of sarcopenia [83,84]. While moderate alcohol intake is not thought to be associated with low muscle mass, heavy alcohol consumption is likely to lead to low muscle mass secondary to poor nutrition, lower physical activity, and hormonal abnormalities [85].

Specific nutrients affect both bone and muscle. Low levels of Vitamin D are commonly found in osteosarcopenic patients [42]. In a study conducted in Korea, Vitamin D deficiency was associated with low BMD and was more pronounced in those with sarcopenia [86] while low ALM was associated with low Vitamin D in the MINOS Study [83]. Low Vitamin D levels are likely to contribute to muscle weakness and increased risk of falls in addition to increased bone fragility [87,88]. Finally, vitamin K is essential for the effective function of proteins including those involved for bone remodelling and it has been shown that in vitro vitamin K improves the proliferation and migration of primary bovine muscle satellite cells, with the potential of maintaining normal muscle function, as well as facilitating several molecular pathways the underpin muscle-bone cross talk [89,90].

1.1.6 Management of osteosarcopenia

1.1.6.1 Non-Pharmacological Management- Lifestyle and nutritional modifications

Both sarcopenia and osteoporosis are amenable to preventative and therapeutic interventions in the form of exercise and nutritional support, the multicomponent nature of which remain the core of osteosarcopenia management.

Physical exercise has been shown to have a positive impact on muscle mass and function with greater benefits on physical performance in adults over the age of 60 [91]. Furthermore, a meta-analysis of 14 prospective studies has shown a significant inverse relationship between increasing level of physical activity and risk of hip fracture in older women [92]. Randomised controlled trials have demonstrated the efficacy of progressive resistance exercise to stimulate osteoblastogenesis and muscle protein synthesis [93,94]. Low repetition, light load power training also showed improved pelvis BMD and knee extensor strength over the course of 6 weeks in a small study of postmenopausal women with sarcopenia [95]. Emphasis on resistance training for individuals with osteoporosis is also given [96]. A recent systematic review showed that chronic resistance training is safe and effective in improving characteristics of osteosarcopenia such as lumbar spine BMD, muscle mass, strength, and quality but not physical performance [97]. Multi-modal programs which incorporate traditional and high velocity progressive resistance training, weight bearing exercises and balance/mobility activities might be the best approach for osteosarcopenia [98].

A nutritional approach focuses on Vitamin D, calcium, and protein intake. Despite the lack of information regarding the intake of high-quality protein in older individuals, it has been suggested that adequate intake should be ensured. The recommended dietary allowance of protein of 0.8 g protein/Kg/day might be inadequate for older people to meet their metabolic and physiological needs and should be increased to 1.5g protein/Kg/day [99]. Higher protein intake was protective against physical function decline in older individuals, including those with a previously sufficient protein intake, independent of physical activity [100]. Protein supplementation above the recommended daily amount in combination with resistance exercise or endurance type exercises is advised [101]. This combination has demonstrated increase in muscle and bone mass, muscle

strength, balance and functional capacity [94,102]. A recent systematic review suggested that protein supplementation and muscle strengthening exercise was associated with gain in lean muscle mass in people at risk of sarcopenia [103]. Enhanced protein intake has benefited patients with osteosarcopenia [104]. Dairy food provides nutrients such as calcium, phosphate and protein that are important in the maintenance of bone health [105] but there have been mixed reports regarding their benefit [102,106,107].

An adequate vitamin D status is associated with better BMD, muscle mass and function [108,109], and reduced number of falls in postmenopausal women [110]. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends a vitamin D intake of 800IU/daily to maintain 25(OH)D levels >50 nmol/l in post-menopausal women [111]. Conversely, an annual oral administration of high-dose colecalciferol was associated with an increased risk of falls and fractures [112]. However, to date no interventional and randomised controlled studies have been performed to assess its effect on osteosarcopenic patients [113]. Finally creatine has also been reported to increase muscle mass and strength as well as bone density but studies are required to show benefit in osteosarcopenic patients [101].

1.1.6.2 Pharmacologic treatments

Commonalities in pathophysiology could lead to the identification of potential pharmacological targets for treatment of osteosarcopenia. [24,114]. Currently however, there are no randomised controlled trials for drug treatments for osteosarcopenia.

Interventions with drugs that have anti-inflammatory properties including non-steroidal anti-inflammatory drugs (NSAID's) have been examined in sarcopenia [115]. Their exact mechanism of action is still not clearly described, but some studies have shown that COX-inhibiting NSAID's might be effective in improving muscle protein metabolism [116], and participants in a cross sectional study taking long term NSAID's had a lower risk of sarcopenia compared to non NSAID's users [117]. On the contrary, a negative effect of skeletal muscle regeneration has also been

reported [118]. Due to conflicting results from studies and the potential side effects associated with NSAIDs, long term use is not recommended, especially in older adults.

Testosterone replacement in men has demonstrated positive effects in muscle strength, gait and volumetric BMD [119,120]. Hormone replacement therapy (HRT) in women at the onset of menopause has been shown to preserve muscle strength [121] and prolonged use is associated with high muscle mass [122]. HRT use also reduces fractures although the unfavourable risk/benefit balance in older postmenopausal women limits its use to younger postmenopausal women who are at high risk of fracture and also have menopausal symptoms [55]. Side effects and variable anabolic actions seen in studies of SARMs, classes of androgen receptor ligands that display tissue selective anabolic and androgenic activity, have precluded their widespread use. For example, though Andarine and Ostarine use were associated with an increase of lean mass and physical function in older males and post-menopausal females [123,124] no clear advantage was shown for bone health.

Growth hormone (GH) supplementation has shown no clear benefit to improve muscle mass, function or strength, despite initial reports that low GH levels contribute to decrease lean mass and increase in adipose tissue [24]. GH replacement has been shown to be possibly beneficial in the management of postmenopausal women with osteoporosis; a recent meta-analysis indicated a role in fracture prevention although not an increase in BMD [125]. In conclusion, there are currently no approved pharmacological agents for osteosarcopenia, although treatments for osteoporosis have been explored to understand if they have a concomitant effect on muscle. For example, Denosumab has shown beneficial effects on falls risk [126], has been associated with increased handgrip strength and LBM [127], reduced fear of falling, better balance and physical action [128] when compared to IV zoledronic acid.

Considering novel therapies, lower levels of Myostatin, a negative regulator of muscle development and growth [129], have been found in animal and human studies of increased musculature and strength[130–132]. Myostatin inhibitors have been suggested as a possible treatment for osteosarcopenia. However, in a phase II trial in older adults with a history of falls,

myostatin inhibition was associated with an increased in LBM and improved functional measures but no benefit in bone health [133]. Initial reports of Bimagrumab, a human monoclonal antibody which binds to type II activin receptors and prevents the binding of myostatin and activin A, has demonstrated significant increases in lean body mass and strength in older adults [134], but those results were not sustained [135]. Irisin, another myokine, has also been suggested as a target to treat osteosarcopenic subjects as it retrieves disuse-induced bone loss and muscle atrophy in mice[136] and it is proposed as a biomarker for sarcopenia in postmenopausal women [137]. Finally prevention of fat infiltration [138], use of melatonin [139], adiponectin [140] and exosomes [141] have been proposed as potential therapeutic targets but further research and studies are needed.

1.1.7 **Conclusion**

Osteoporosis and sarcopenia are age related conditions and are associated with significant morbidity and mortality. Their prevalence is expected to increase over the years with important consequences for individuals and healthcare systems. These two conditions share common pathophysiological mechanisms, resulting in an interest and attempts to treat and manage these pathologies simultaneously. Early recognition and intervention of both conditions is important to decrease morbidity and mortality and preserve independence of older individuals. Combined resistance and balance exercises with nutritional supplementation and treatment of osteoporosis are the current strategies to manage osteosarcopenia. Further basic science research to gain a better insight into biomarkers with potential diagnostic and therapeutic value as well as epidemiological studies to understand the lifecourse influences leading to osteosarcopenia are needed.

1.2 Aims and objectives of this thesis

It is hence apparent that osteoporosis and sarcopenia are related diseases and are highly prevalent in the ageing population. Their prevalence is expected to increase in coming years, leading to devastating consequences for individuals and healthcare systems globally. In this thesis we characterise the relationship between muscle and bone health in greater detail both in the Hertfordshire Cohort Study, and in a newly established cohort of older adults in Southampton (Southampton Longitudinal Study of Ageing-(SaLSA)).

This thesis has four research aims:

1. To assess the association of sarcopenia or/and osteoporosis with frailty and multimorbidity, an important contributor to ability to live independently in late adulthood,
2. To consider possible determinants, such as modifiable lifestyle factors, of muscle density and report relationships between muscle density with falls and fractures,
3. To consider the relationships of other sarcopenia components such as muscle size, muscle strength and function with the clinically important outcomes of falls and fractures, and
4. To report COVID19 pandemic-related changes in diet, and correlates of change, in diet quality in SaLSA.

Chapter 2. Methodology

2.1 Hertfordshire Cohort Study Profile

Much of the work presented in this thesis is based on information already collected as part of the Hertfordshire Cohort Study. Due to concerns over the health of the British public, in 1911, birth and early life information was collected in Hertfordshire with the aim of using the collected data to improve paediatric health. These data were collated by local midwives and health visitors under the direction of Ethel Margaret Burnside, the 'Lady Director of the Midwives and Chief Health Visitor' in the county at the time.

The information collected from 1911 included the weight at birth, whether the child was breast-fed or bottle-fed, childhood conditions and the weight at 1 year, and was transcribed into ledgers which were stored in the council buildings. Births were recorded until 1948, though the data collection was potentially affected by the advent of the Second World War.

The ledgers were discovered in 1986 by researchers from the forerunner to the MRC Lifecourse Epidemiology Centre, who aimed to study the developmental origins of health and disease and focused on the cohort born 1931-1939 [142]. There were 42,974 births recorded during this period, including 39,764 live births. Of those, 24,130 were traced through the National Health Service Central Registry and 8,650 were found to be still living in the county and 7,113 were registered with a Hertfordshire General Practice surgery. Letters of invitation were sent to General Practitioners, to acquire permission to contact the potential participants, and this led to 6,099 being invited to participate. Of these 3,225 (53%) agreed to take part and 2,997 were visited. Those in the East Hertfordshire area were identified for specialist musculoskeletal phenotyping (1,482 visited at home), and of these, 966 attended the baseline clinic.

The first visits included lifestyle questionnaires, physical performance measures, grip strength, DXA and phlebotomy. These blood samples were processed, DNA extracted and stored at -80°C.

Since the initial contact in 1998-2004, HCS cohort members have been involved with numerous subsequent studies involving postal questionnaires, clinic visits, home visits, intervention studies, and focus groups, as summarised in Figure 2-1. Detailed musculoskeletal phenotyping of the cohort has taken place at many time points [143,144], and includes DXA at baseline in 1998-2000; 2005; 2011;2017 and peripheral quantitative computed tomography of the radius and tibia in 2005, 2011 and 2017. Lifestyle questionnaires have been completed in each wave of the study, together with anthropometry and physical performance tests (Figure 2-1).

For this thesis, data collected in 1998-2004, as part of the East Hertfordshire cohort, and those collected in 2011-2012, as part of the HCS European Project on Osteoarthritis (EPOSA) study, were used for analysis. EPOSA involves six cohort studies each performed in a different country: Germany, United Kingdom (UK), Italy, The Netherlands, Spain, and Sweden. Random samples from these population-based cohorts are included. In each cohort, around 750 potential participants were contacted with the aim of recruiting 500 participants. In Italy, a new sample was drawn, with recruitment procedures and age/sex-distributions similar to those in the other studies. Further details are available from the EPOSA design paper [142]. The overall age range was 65-85 years (with oversampling of the oldest respondents 80-85 years) in all cohorts except for the UK, which has an age range of 71-79 years. Data collection started between November 2010 and March 2011 in all countries and ended between September and November 2011. HCS fieldwork conducted by a nurse in a home visit followed by x-rays at Hertford County Hospital. HCS EPOSA participants were recruited from men and women who had previously participated in the musculoskeletal follow-up study.

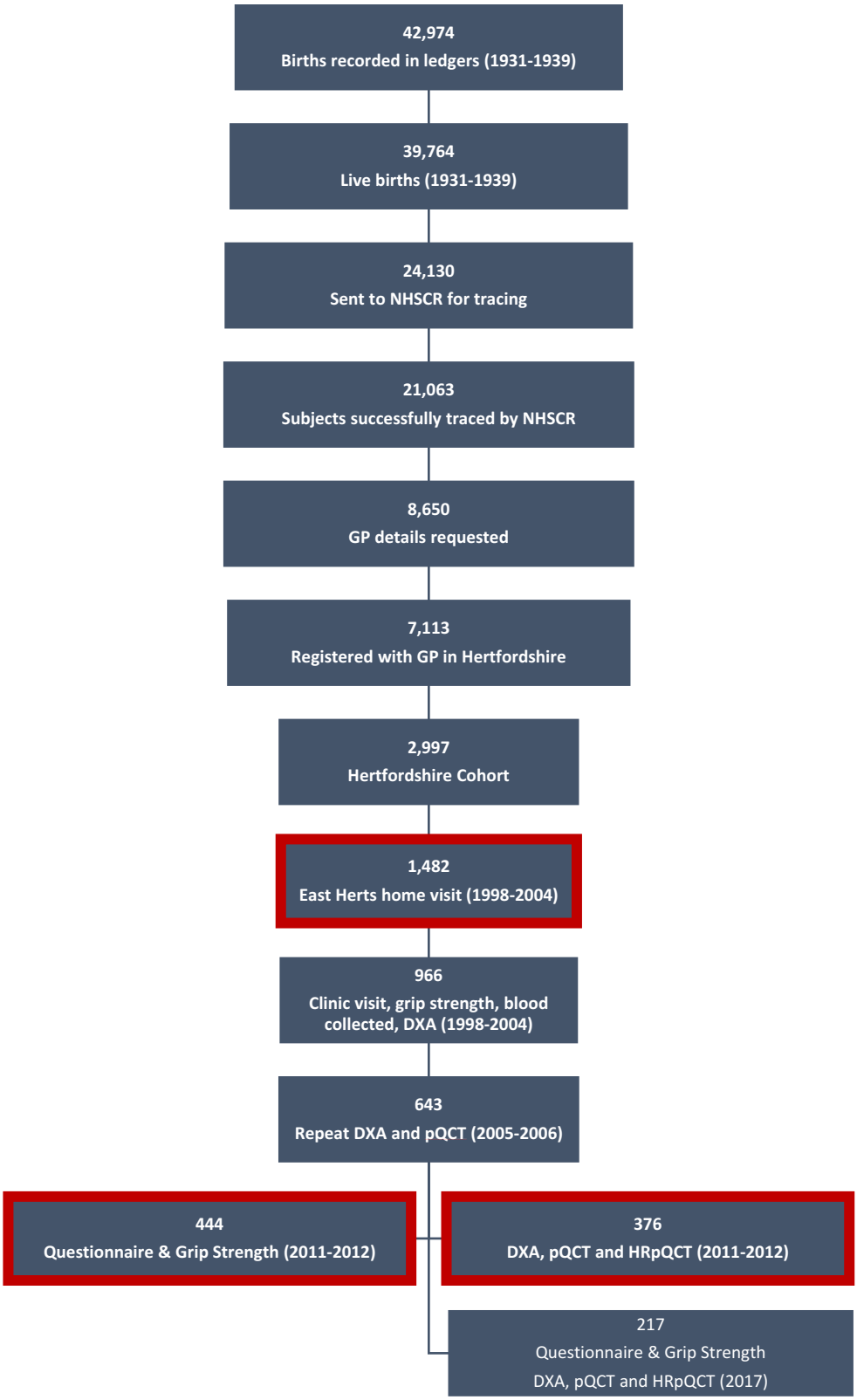


Figure 2-1: Flow diagram of study participant structure of the Hertfordshire Cohort Study. Data collected in 1998-2004 and 2011-2012 cohort were used as baseline data for this thesis (in red).

2.1.1 Procedures

2.1.1.1 Height and weight measurements

Height was measured using a wall-mounted stadiometer. The subject was asked to remove their shoes and stand on the floor with their back to the wall. They were asked to stand as tall and straight as possible (to avoid lordosis) with their feet together. The wall-mounted head plate was lowered and placed on the top of the subject's scalp with the participant's head in the Frankfurt Plane (a theoretical, horizontal line running from the external auditory meatus to the lower border of the orbit).

When measuring weight, the scales were zeroed and shoes, heavy items in pockets and jewellery were removed prior to weighing.

2.1.1.2 Dual X-ray absorptiometry

The procedure was explained prior to the commencement of scanning and communication continued during the scan. The participants were asked to keep still and not to talk during the scan to minimize movement artefact (Figure 2-2).

A dressing gown was provided and any clothing with metal fasteners removed together with metal jewellery, glasses or any object which could attenuate the x-ray beam and cause artefact. The participant was asked to lie on the scanner bed aligned within a white rectangle marked on the mattress. Bone mineral density (BMD) of the total hip was assessed using DXA in 2004 (East Hertfordshire cohort) and of femoral neck in 2011 (EPOSA study).

Figure 2-2: HCS participant undertaking DXA scan.

2.1.1.3 Vertebral fracture assessment

In addition to the assessment of bone health in terms of bone mineral density, DXA scanners can also be used to evaluate for vertebral fractures. This is known as vertebral fracture assessment (VFA). The Genant method is based on evaluation by radiologists or experienced clinicians to correctly identify and then classify vertebral fractures. Normal vertebrae are grade 0; mild but definite fractures (20-25% reduction in anterior, middle, and/or posterior height, and 10-20% reduction in area) are grade 1; moderate fractures (25-40% reduction in any height and 20-40% reduction in area) are grade 2; and severe fractures (40% or greater reduction in any height and area) are grade 3 (Figure 2-3). Morphometric vertebral fractures were diagnosed from a lateral spine view imaged using the same DXA scanner and graded based on the Genant semi-quantitative method of vertebral fracture assessment in our cohort [145].

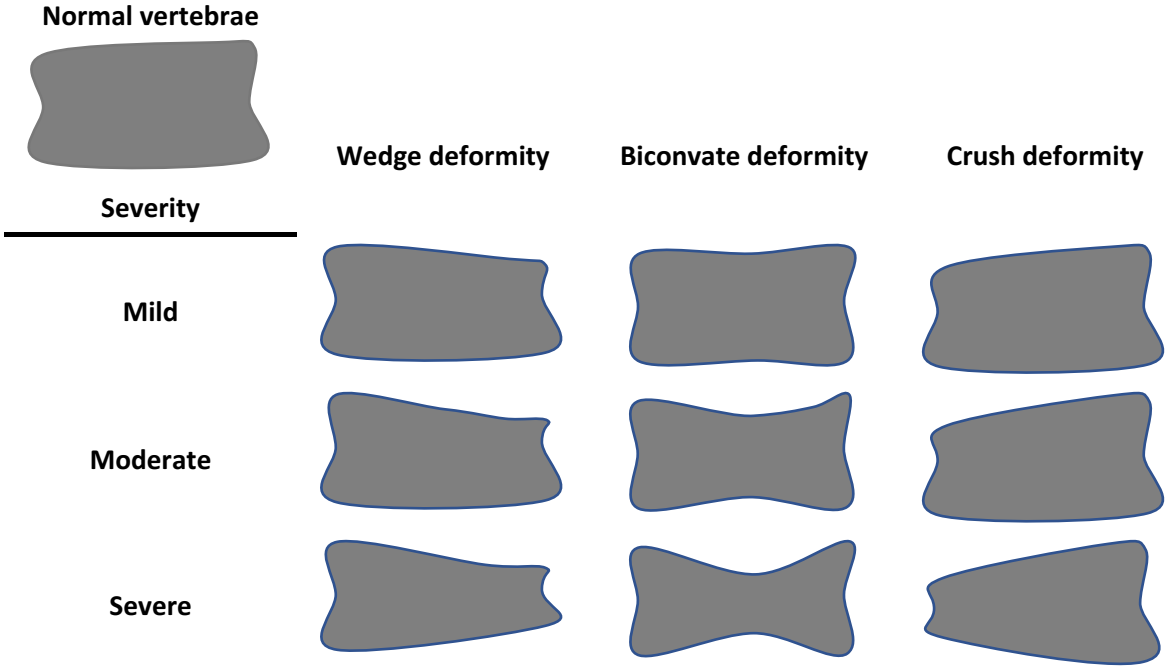


Figure 2-3: Semiquantitative grading of vertebral deformities, Reproduced from Genant et.al., Vertebral fracture assessment using a semiquantitative technique [145].

2.1.1.4 Peripheral quantitative computed tomography (pQCT)

Estimates of bone strength (including strength strain index (SSI)), cortical bone and trabecular bone obtained by peripheral Quantitative Computed Tomography (pQCT). Peripheral quantitative computed tomography (pQCT) provides a non-invasive assessment of bone strength and a volumetric assessment of bone density.

Scanning at the radius and tibia (non-dominant side) using a Stratec 2000XL pQCT scanner running software version 6.00 were used [146] (Figure 2-4).

Figure 2-4: HCS cohort participants undertaking pQCT of the radius.

The radial length was measured from the distal end of the ulna styloid to the tip of the olecranon in millimetres (mm). The tibial length was measured from the prominence of the medial malleolus to the tibial plate (mm). Forearm and lower leg scout views identified measurement reference lines at the cortical end plates. Two slices were taken in the forearm scan: 4% distal radius and 66% radial mid-shaft and forearm cross-sectional area (CSA) of muscle. Three slices were taken for the lower leg scan: 4% distal tibia, 38% tibial midshaft and 66% calf CSA. Assessment of muscle size by pQCT has been found to be valid and reliable. Trabecular parameters were measured distally, and cortical parameters were measured in the mid-shaft (radius, 66%; tibia, 38%). Measurements were taken from both the radius and tibia of distal total bone area (dTBA), trabecular bone mineral density (tBMD), cortical bone mineral density (cBMD), cortical bone area (cBA), and polar strength strain index (SSI). Mid-shaft periosteal circumference (PC) and mid-shaft endosteal circumference (EC) where then calculated assuming that the bone had a circular cross-section. Measurement precision error, expressed as a coefficient of variation, ranged from 0.88% (tibial total density, 4% slice) to 8.8% (total radial area, 66% slice), but was typically around 1-3%.

These figures were obtained by 20 volunteers who were part of the study undergoing 2 scans on the same day, with limb repositioning between examinations.

For all scans a threshold of 280 mg/cm^3 was used to separate the bone from the soft tissue background. Once separated, the default peeling algorithm was applied to the distal 4% scans to separate trabecular bone. With this peeling, 55% of the outer bone area was concentrically separated and defined as cortical and subcortical; the remaining 45% was defined as trabecular bone. For proximal scan locations the default threshold of 710 mg/cm^3 was used to separate cortical bone. Muscle CSA at the forearm and calf was derived using the default analysis steps that utilize various threshold and edge tracking settings to segment muscle from subcutaneous fat. We chose to adopt this algorithm as it allowed better comparability for our work with other studies and as we hope to perform follow-up scans on this group, it will allow consistency in our approach. Those with significant movement artefact were excluded from analyses. The same approach was followed in 2004 and in 2011-2012 cohorts.

2.1.1.5 Gait speed

An 8-foot walking course was marked out using a tape measure. Participants were asked to "Walk to the other line at the end, at your usual walking pace, as if you were walking to the shops.". Participants were allowed to use assistive devices if required. The timer was started after the prompt of "One, two, three, Go" and stopped as the participant passed through the finish line. Gait speed was quantified from the time taken to complete an 8-foot walk test.

2.1.1.6 JAMAR Grip Strength Dynamometry

Whilst seated in a chair the participants were asked to position their elbows at right angles and their wrists in a neutral position with their hands gripping the dynamometer comfortably. The dynamometer was adjusted for size if necessary and the participant was encouraged to squeeze the instrument "as hard as possible", and the result recorded to the nearest 1kg. Grip strength was measured three times in each hand using a Jamar hand-held isokinetic dynamometer using a standardised protocol [147]. The maximum value was used in analyses.

2.1.1.7 Questionnaires

A detailed questionnaire was administered at each time point to obtain information on lifestyle, medical history, falls risks and history, fracture history, cigarette smoking and alcohol consumption. Details regarding physical activity, dietary calcium intake, socioeconomic status, quality of life parameters and, in women, years since menopause and use of oestrogen replacement therapy had already been obtained from a questionnaire which was administered by trained nurses when the participants were initially recruited into the HCS (1998-2003). Physical activity was calculated as a standardised score ranging from 0–100 derived from frequency of gardening, housework, climbing stairs and carrying loads in a typical week. Higher scores indicated greater levels of activity [148]. Dietary calcium intake was assessed using a food frequency questionnaire [149]. Socioeconomic status was determined using own current or most recent occupation of the participant in men and single women, and of the husband in ever-married women based on the OPCS Standard Occupational Classification scheme for occupation and social class [150]. The questionnaire was completed by the researcher using the answers provided by the participant.

2.2 Establishing a Resource to Assess Musculoskeletal Health in Older Adults: The Southampton Longitudinal Study of Ageing (SaLSA) (Appendix J)

2.2.1 Introduction

As discussed, we sought to establish a new resource to study further the muscle-bone relationships in older adults. The establishment of the study was published in Osteology, and it will be described in detail below. The introduction to his publication was presented at Chapter 1.

The COVID19 pandemic has led to widespread change in lifestyle globally, as ‘stay at home’ guidance was widely invoked. Older adults, the group most vulnerable to severe disease, were commonly asked to shield, or voluntarily severely restricted activities. In recent work, we evaluated how wave one of pandemic affected older adults in a pilot study [Nutrition and Physical

activity Study (NAPA)] conducted in the Hertfordshire Cohort Study (HCS) [151]. 71 eligible Caucasian, community dwelling participants, 39 male and 32 female mean age (SD) 83.6 (2.5) years were surveyed. In this modest sample more than half (52%) of respondents reported being less physically active than before the pandemic. A number of variants of the COVID19 virus have been identified, with rolling restrictions remaining in many countries. Widespread vaccination has provided reassurance to many older adults, but many are still fearful of engaging in activities they previously would have enjoyed [152]. Changes in lifestyle might be expected to have effects on both muscle and bone health, with studies of older adults now required to study these in depth. Given the burden of musculoskeletal disease in late adulthood, research in this group is key. Although the rationale for studying this age group is hence clear, the feasibility of establishing a cohort of octogenarians living in their own homes in a global pandemic is untested. We have provided our own experience of recruitment to a) highlight the need to consider these issues in older adults b) advertise the study to invite collaboration early in the study process. Specifically, this study represents a research partnership across the primary-secondary care interface that is unusual in the UK and might be replicated elsewhere. Here we report our experience of this, before describing the methodology of the study that is planned.

2.2.2 Materials and Methods

2.2.2.1 Study Design

Ethics approval was obtained for the first phase of the MSK Southampton study in March 2021 (Appendix A). In July 2021 we identified all patients over the age of 75 who were registered at a large GP partnership in Southampton, UK (Living Well Partnership (LWP), https://livingwellpartnership.nhs.uk). Eligibility to participate in the study was decided by their primary care physician. Our sole inclusion criterion was the age of participants (> 75 years of age) at the time of recruitment, as we aim to consider musculoskeletal health in this specific age group. Our exclusion criteria included the following:

- Patients with safeguarding issues.
- Patients with mental health and capacity issues.

- Patients with dementia or who were unable to provide consent.
- Patients with learning disabilities.
- Patients in end-of-life care.
- Patients who are permanently bedbound.
- Patients in residential or nursing homes.

All eligible participants were sent a study pack from LWP, consisting of a participant information sheet (PIS), two copies of a consent form, a questionnaire, and the contact details form.

Initial searches of the Egton Medical Information Systems (EMIS) database identified 2523 registered patients over the age of 75 years from any sex and ethnic group. Of those 2523 patients, 1993 (78%) were deemed eligible to participate in the study by their primary care physician (Figure 2-5).

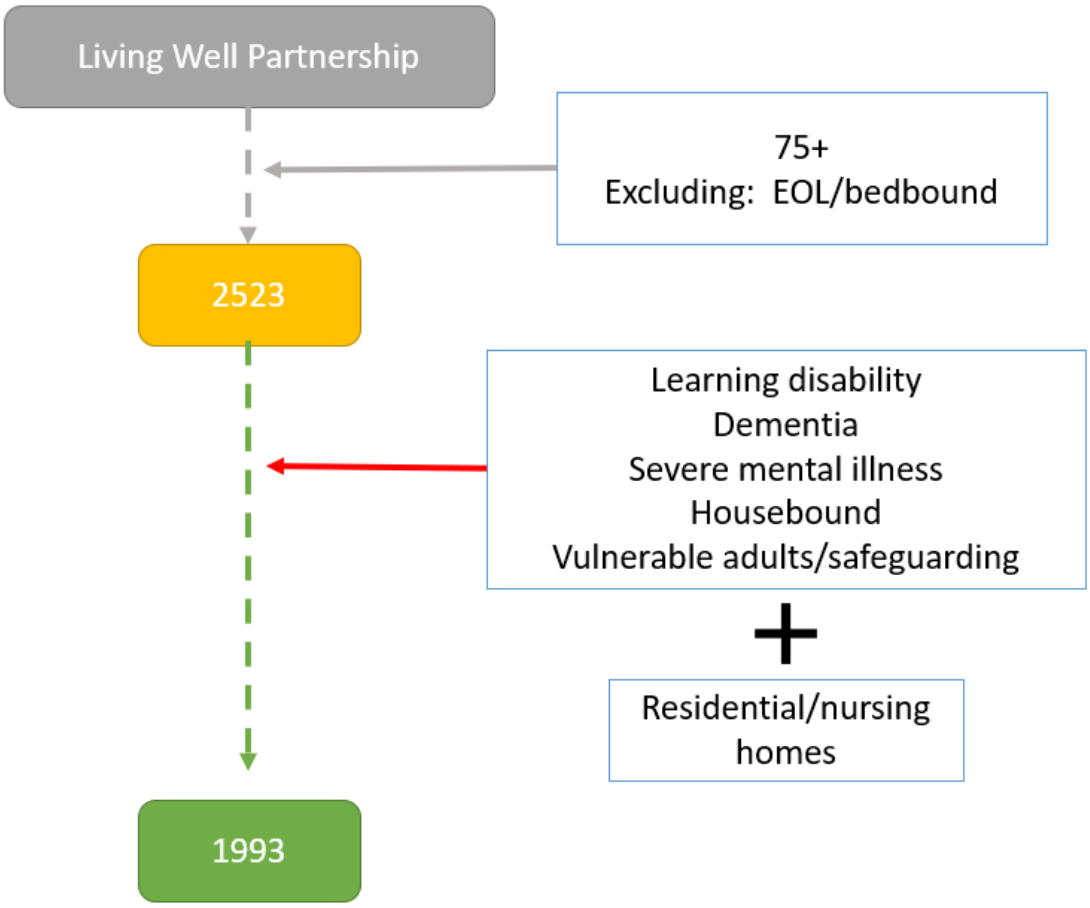


Figure 2-5: Flowchart of selection of eligible participants.

1993 participants were invited to participate in the study by postal invitation only. Participants indicated their willingness to be involved in the study and returned the copy of the signed consent

form along with the completed questionnaire and the contact details form to the research team at the MRC Lifecourse Epidemiology Centre (MRC LEC) Southampton using a pre-paid envelope. Participants had the opportunity to contact the research team using a dedicated research mobile phone and/or email that was provided for further queries. The returned documents were reviewed by a research team member to ensure the validity of those documents and to identify any missing information. An anonymised ID number was allocated to each participant after ensuring that consent was obtained. A research team member contacted those participants who did not fully complete the consent or contact details form via email, phone or in writing.

Invitations were sent out in batches to manage workflow as researchers were still largely working from home. Phase 1 led to the return of 175 complete questionnaires (Table 2-1).

Table 2-1: Preliminary baseline characteristics of participants in SaLSA (Southampton Longitudinal Study of Ageing).

Characteristic	Female				Male			
	N	Median	IQR	%	N	Median	IQR	%
Age	53	80.53	77–84		119	80.4	77–83	
Number of medications	53	5	3–7.75		117	4	3–7	
Polypharmacy (>=5)	33			62.2	22			18.8
Number of comorbidities	53	3	2–4		119	3	1–3	
Multimorbidity (>=2)	22			82	86			71
	N	**N**		**%**	**N**	**N**		**%**
Ethnic group	53				118			
White		50		94		118		100
Indian		2		4		0		0
Black Caribbean		1		2		0		0
Marital status	53				119			
Alone		36		68		38		32
Not alone (lives with friend/partner/family)		17		32		81		68
Age leaving school	52				119			
<=14		2		4		17		14
> 14		50		96		102		86
Education after school	52				119			
None		24		46.1		33		27.7

Apprenticeship	7	13.4	47	39.4
Part-time college	8	15.3	45	37.8
Full-time college	8	15.3	15	12.6
Other	9	17.3	12	10
Higher qualifications				
None	22	40	41	34
O levels	23	42	48	40
A levels	10	18	20	17
Vocational training certificate	12	22	42	35
University degree	1	2	20	17
Higher professional qualifications	7	13	13	11
Smoking status	53		118	
Ex-smoker	20	71.6	78	66
Current smoker	0	0	5	3.38
Alcohol	54		121	
More than recommended units/week (14)	1	1.85	25	20.6
COVID-19 infection	50		117	
Yes	0	0	4	3.41
No	48	96	111	95
Suspected but not confirmed	2	4	2	1.7
Self-reported walking speed	54		121	
Fast	2	4	1	1

Fairly brisk		8	15		22	18
Normal speed		13	24		40	33
Stroll at an easy pace		15	28		34	28
Very slow		15	28		23	19
Unable to walk		1	2		1	1
	N	**N**	**%**	**N**	**N**	**%**
Falls past year	52			114		
>=1	17		32.6	28		24.5
Fracture since age 45	52			112		
Yes		19	36.5		15	31.25
No		33	67		97	87
Self-rated health (SF-36)	53			120		
Excellent		3	5.66		4	3.33
Very good		13	24.5		27	22.5
Good		19	35.8		51	42.5
Fair		17	32		32	26.6
Poor		1	1.88		6	5

The questionnaire participants completed, included information on household, lifestyle factors, comorbidities, medical history, physical activity and capability, level of frailty, nutrition, self-reported walking speed, quality of life, and wellbeing. Where available, questions were sourced from validated questionnaires [153–158] (Table 2-2). Self-reported walking speed has been shown to be a good marker of measured walking speed, and has previously been validated in the Hertfordshire Cohort Study [154]. The remaining questionnaires used in the study have previously been used in the HCS, which was also conducted by the MRC LEC Southampton [143].

Table 2-2: List of subsections of questionnaires and data collected during the 1st phase of SaLSA

Questionnaires
Living circumstances and lifestyle factors
COVID-19 questionnaire
Medical conditions and medication history
Physical activity scale for the elderly (PASE)
Self-reported walking speed
Bone health questionnaire
Fried frailty questionnaire
Sarcopenia questionnaire (SARC-F)
Quality of life questionnaire (SF-36)
DETERMINE checklist
Food frequency questionnaire (FFQ)

In the planned next phases of the study, participants will be invited to attend a face-to-face clinic visit, where anthropometry, grip strength, gait speed, appendicular lean mass, and bone mineral density will be measured. Ultrasound scans, as a new screening method to diagnose sarcopenia, will also be performed [54]. Standardised effect sizes for objectively measured physical activity in relation to grip strength, walking speed, and appendicular mass index were estimated as 0.11, 0.26, and 0.15, respectively, in a cohort of a similar age [159]. The sample sizes required to detect these effect sizes with 80% power and a 5% significance level are 651 for grip strength, 119 for walking speed, and 351 for appendicular lean mass index; Statistics Kingdom was used for these calculations [160]. A subset of patients who are willing and have given consent will also undergo a high-resolution pQCT scan, before undergoing a percutaneous muscle biopsy of the vastus lateralis [161]. Outcome measures for SaLSA are summarised in Table 2-3.

Table 2-3:Overview of the measures to be collected during the 1st and 2nd phases of the study

Variables	Instrument/Scale	Type of Assessment	1st Phase	2nd Phase
Age	Calculated based on the date of birth given	Questionnaire	√	
Sex	Female or male stated	Questionnaire	√	
Ethnicity	As self-reported	Questionnaire	√	
Marital status	Self-reported marital status	Questionnaire	√	
Education	Age of leaving school	Questionnaire	√	
	Self-reported education after school and/or higher qualifications	Questionnaire		
Living arrangements	Self-reported: own property/rented accommodation/residential home/nursing home/other	Questionnaire	√	
Smoking history	Self-reported as current or ex-smoker/packs/year	Questionnaire	√	
Alcohol consumption	Self-reported as drinking or not alcohol and units/week	Questionnaire	√	
Social status	Maastricht Social Participation Profile (MSSP), Hospital Anxiety and Depression Scale (HADS)	Questionnaire		√
Social isolation/loneliness	Six-item Lubben Social Network Scale (LSNS-6), De Jong Gierveld Short Loneliness Scale	Questionnaire		√
Occupation history	Self-reported current or previous employments	Questionnaire		√
Medical history/comorbidities	Self-recorded list of current regular medications including anti-osteoporosis medications	Questionnaire	√	
Number of medications	List of medical conditions provided used previously in HCS study	Questionnaire	√	
COVID-19 status	COVID-19 questionnaire developed during the pandemic and used previously in the HCS study. Assess COVID-19 infection status and symptomatology/long-term consequences;	Questionnaire	√	

	COVID-19 vaccination status			
Physical activity	Physical Activity Scale for the Elderly (PASE)	Questionnaire	√	
Physical capability	Self-reported walking speed	Questionnaire	√	
Frailty	Fried frailty criteria	Questionnaire and research visit	√	√
	Clinical frailty scale	Research visit		√
	Frailty index (eFI)	Research visit		√
Fractures/falls	Self-reported number of fractures since the age of 45 and in the past year X-rays and vertebral fracture assessment	Questionnaire	√	
	Self-reported number of falls since the age of 45 and in the past year	Questionnaire	√	
Muscle health	Strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) Sarcopenia status (EWGSOP2)	Questionnaire	√	
Bone, muscle, fat: density/microarchitecture/morphology	DXA scan of lumbar spine and femoral neck	Research visit		√
	High-resolution peripheral quantitative computed tomography (HRpQCT)	Research visit		√
	Percutaneous muscle biopsy of vastus lateralis	Research visit		√
	Muscle ultrasound	Research visit		√
Perceived health state	SF-36 SarQoL (sarcopenia and quality of life)	Questionnaire	√	
Nutrition	DETERMINE checklist—identifying malnutrition	Questionnaire	√	
	Food frequency questionnaire—assessing habitual diet	Questionnaire	√	
Anthropometric measurements	Weight, height, BMI, waist, hip, mid–upper arm, and thigh circumferences	Research visit		√
	Triceps, biceps, subscapular, and supra-iliac skinfold thicknesses	Research visit		√

	Blood pressure, pulse rate	Research visit	√
Cardiovascular assessment	Standard 12-lead electrocardiograph	Research visit	√
Blood profile	Fasting blood samples to be taken from the anterior cubital fossa for subsequent glucose, insulin, HbA1c, bone profile, albumin, lipid profile, vitamin D, vitamin C, hormonal, inflammatory, and DNA analyses, for posterity and further assays;	Research visit	√
Physical performance	Grip strength (Jamar hand-grip dynamometer) Quadriceps strength Timed 6 m up-and-go test and 3 m walk Chair rises Timed one-legged stand	Research visit	√
Cognitive function	AMTS [1]/MoCA [2 9]	Research visit	√

[9 1] Abbreviated mental test score; [2] Montreal Cognitive Assessment.

2.2.2.2 Patient and Public Involvement (PPI)

Key to the success of SaLSA will be PPI. A research team member attended a virtual patient and public coffee morning meeting organised by the Patient and Public Group (PPG) of LWP. PPG representatives highlighted the importance of making sure that we ask the potential participants about their willingness to attend a future clinic and advised that patients need to be seen in a "COVID-19-safe environment". We are continuing our engagement with the PPG group during the next phases of the study, in order to understand what COVID-19 mitigations would be required for participants to feel safe.

2.2.2.3 Data Access

A steering committee will be established to review all data access requests in due course. It will not be possible for participants to be identified from any of the statistical analysis outputs/results.

2.2.3 Results

2.2.3.1 Preliminary Sample

1993 participants were invited to participate by post only. 450 (22.5%) participants returned a questionnaire. 353 (79%) questionnaires were complete. 295 participants (84%) said they are happy to be contacted again to participate in future studies and 35 (10%) were not sure.

The summarised demographics of participants who returned the first 175 questionnaires are presented in Table 2-1. The median age of participants was 80.4 (77–83) years in both sexes (80.5 years (77.9–84) in females and 80.4 years in males (77.3–83.6)). The majority (N = 168/171, 98%) of participants were of white ethnic background. Two (2) females of Indian origin and one (1) female of Black Caribbean origin were included. In total, 36/53 (68%) female participants and 38/119 (32%) male participants live alone; 152/171 participants left school over the age of 14 (50/52 females and 102/119 males). Over half of female participants (28/52 (53%)), and 86/119 (72%) male participants continued with education after school; 29/54 female and 78/121 male participants obtained a higher qualification degree; 58% (98/171) of participants are ex-smokers, and only 5/171 still smoke, all of whom are males (3%). Only 1/54 of females and 25/121 of male

participants who drink alcohol consumed more than the recommended units/week (14 UI/week). Only 2/50 (4%) females suspect that they have had COVID-19, and 4/117 (2%) male participants had confirmed COVID-19 infection.

Over 70% of female and male participants (n = 149/175) reported having >=2 comorbidities, and so would fulfil the definition of multimorbidity. Over 60% of female participants (33/53) reported polypharmacy, defined as >=5 regular medications, compared to 18% (22/117) of male participants. Walking speed was self-reported by all participants. Around one-third of participants self-reported walking at a normal speed (13/54 (24%) females and 40/121 (33%) males) and strolling at an easy pace (15/54 (28%) females and 34/121 (28%)) in both sexes.

One-third of female participants (17/52) and one-quarter of male participants (28/114) reported at least one fall in the past year. One-third of all participants (19/52 and 15/112 female and male participants, respectively) reported a fracture since the age of 45.

Most participants rated their health to be “good” (70/175 (40%)). Their health was rated as “fair” in 28% (49/175) and “very good” in 23% of participants in both sexes (40/175). Only 4% self-rated their health as “excellent” (7/175) or “poor” (7/175) in this cohort.

We have previously studied the impact of the COVID-19 pandemic on participants in the HCS. We were therefore interested to understand how comparable the two cohorts were. Participants recruited in the SaLSA and NAPA (Nutrition and Physical Activity Study) studies were septuagenarians and octogenarians (Median age (IQR) in females: 80.5 (77–84)) and 83.8 (81.5–85.9) years, respectively; and in males: 80.4 (77–83) and 83.1 (81.5–85.5) years, respectively). Polypharmacy was common in both cohorts (the median number of medications used was 5 in females in both the NAPA and SaLSA studies, and in males in the NAPA study). Most female participants in SaLSA live alone (68%), whereas in NAPA less than half of female participants reported living alone (45.1%).

2.2.4 Discussion

Musculoskeletal conditions such as osteoporosis and sarcopenia are a public health burden, and treatment strategies, including a need to develop novel therapeutic targets are urgently required. This manuscript reports the first stages in establishing a new resource for the study of musculoskeletal health. which began at the time of a global pandemic, when many older adults experienced significant disruptions to their lifestyle, through public health messages designed to protect them from the risk of COVID19 infection. The work is indicated now as there is an even greater need to consider musculoskeletal health in this group. Currently, it is uncertain whether these lifestyle changes will be reversible, in context of widespread vaccination. Previous research in HCS and elsewhere has shown that lifestyle risk factors cluster together to impact on physical function in later life and contribute to the progression of sarcopenia, osteoporosis and/or osteoarthritis, so information on this topic is urgently required [143].

A particular challenge of this work has been its initiation while the pandemic is continuing. Recruitment of community participants for clinical research studies is often a challenging task. SaLSA is unique as will allow the assessment of the feasibility and practicality of recruiting older adults from the community who are likely research naïve. It will establish a platform for future observational and interventional studies to identify at risk groups or normal ageing participants. The cohort data will enable the development and evaluation of interventions targeted at improving health care outcomes for older adults. Specifically, data will be used to identify at-risk groups such as osteoporosis, sarcopenia, osteosarcopenia and/or frailty.

There has been growing interest recently in the coexistence of osteoporosis and sarcopenia in some individuals, often termed osteosarcopenia. There appears to be higher morbidity from falls, fracture, disability as well as mortality in individuals diagnosed with osteosarcopenia [42,43]. However, there are limited epidemiological data on the subject and more work is needed to understand the inter-relationships between the two conditions. Specifically, knowledge of the overlap in the pathophysiology of osteoporosis and sarcopenia might inform the development of potential treatments for osteosarcopenia [27]. A variety of physical assessments are at the

clinician's disposal when assessing for osteosarcopenia and will be assessed in this study. The choice of physical assessment(s) is largely dependent on the clinician's preferred definition of sarcopenia. The two most useful physical assessments are the measurement of hand grip strength (kg) using a hand‐held dynamometer, and calculation of walking speed (m/s) over 4 m as per the European Working Group on Sarcopenia in Older Adults (EWSGOP2) [35].

An exciting area of sub-study is in depth muscle and bone phenotyping. We have previously studied muscle-bone interrelationships in HCS [9,162] but SaLSA provides an opportunity to perform detailed investigation of bone trabecular and cortical microarchitecture using HRpQCT [163–167], muscle ultrasound [54] and muscle biopsy, a technique which we have previously shown to be acceptable to older adults [161]. These studies are critical, as muscle-bone crosstalk is an important and emerging area of research. Genetic, mechanical, and endocrine factors may, explain the age-related association between muscle and bone loss[168]. There is accumulating evidence that other localized and systemic factors are involved included mesenchymal stem cells residing in connective tissue (muscle, bone, and fat), myokines and osteokines (molecules released from muscle and bone cells respectively), inflammageing and fat infiltration [169]. These pathophysiological findings are common to both sarcopenia and osteoporosis, thus suggesting that are closely linked [170].

There are of course limitations to our study, including the low number of non-Caucasian participants currently recruited, and our decision to exclude residential and nursing home residents, which might affect the implementation of our results to this group of older adults. We will consider the characteristics of our study population against national census data at the conclusion of phase 1 of this study. However, the strengths of the study include a strong collaboration with LWP and their PPG group, supported by an experienced team of multidisciplinary team of researchers from the MRC LEC.

2.2.5 Conclusions

We have demonstrated that recruitment of participants from primary care is feasible with high levels of consent to contact for future study to establish a longitudinal study of ageing. Through SaLSA, we aim to study bone/ muscle interrelationships in depth and provide an opportunity to collaborate with other researchers working in similar cohorts globally. Other future sub studies could also explore determinants related to healthy ageing including relevant psychosocial factors such as isolation, attitudes to ageing, social networks, satisfaction with life and many more. In addition, having an interdisciplinary team of investigators encourages collaboration, enables the introduction of in-depth and novel health assessments contributing to generating novel ideas for future research allowing comparison with other cohorts such as HCS. SaLSA will also promote training opportunities for both quantitative and qualitative early career researchers. Adopting a community-based recruitment strategy will allow efficient coordination of activities between researchers in university, secondary care establishments and the community. SaLSA will set an example and will allow the establishment of a unique community dwelling cohort and in time we hope it will provide clinicians, researchers, and policymakers with a rich resource for further collaborative study with the ultimate aim of improving health care of our local community dwelling older people.

Chapter 3. Associations of sarcopenia and osteoporosis with frailty and multimorbidity (Appendix K)

3.1 Introduction

Sarcopenia, osteoporosis, and frailty are highly prevalent in older adults but are frequently under-recognised. They have all been shown to have an adverse impact on quality of life and are associated with disability and mortality [171]. United Nations estimations showed that in 2010 there were 524 million people in the world aged 65 years old and over, with projections indicating that this number will increase to 1.5 billion by 2050 (a threefold increase) [172]. Hence, identification of individuals who might be particularly vulnerable to the adverse outcomes of musculoskeletal ageing is of clinical and public health concern.

Sarcopenia is characterised by progressive and generalised decline in muscle strength, function, and muscle mass with increasing age or secondary to a disease process. Sarcopenia increases the likelihood of falls and adversely impacts on functional independence and quality of life [173,174]. Osteoporosis is the commonest metabolic bone disease in older people, is characterised by both low bone mass and microarchitectural deterioration that predisposes to low-energy transfer fragility fractures. These are associated with chronic pain, impaired physical function, loss of independence and a higher risk of short-and longer-term institutionalisation [175]. Consequently, both these conditions confer a high health burden for the individual as well as health care systems. 'Osteosarcopenia' is the term given when osteoporosis and sarcopenia occur in consort and recent intense focus has been on their combined effects on current and future health.

The syndrome of frailty is associated with, but not an inevitable consequence of ageing and is characterised by a vulnerability to stressor events that can be both internal and external [176]. Both frailty and pre-frailty, the prodromal state before the onset of clinically identifiable frailty, are associated with adverse outcomes [177]. The most widely used definitions of physical frailty are the phenotype model described by Fried, where frailty is identified by the presence of at least

three out of five physical characteristics: weight loss, exhaustion, low energy expenditure, slow walking speed and low handgrip strength [4]. The cumulative deficit model of frailty described by Rockwood et al also predicts adverse health outcomes and comprises age associated accumulation of deficits that range from symptoms, sensory deficits, clinical signs, diseases, disabilities and abnormal laboratory test results [178].

Few other studies have considered interrelationships between sarcopenia, osteoporosis, and frailty. For example, participants with sarcopenia were reported to have a high incidence of osteoporosis, a higher incidence of falls and fractures [50,179–187], but in these analyses frailty was not considered the outcome. For instance, patients with sarcopenia had 12.9 times higher odds of having osteoporosis and 2.7 times higher odds of having fractures than the non-sarcopenic ones in a population based Finnish study [64]. Similarly BMD was found to be lower in sarcopenic individuals in the Copenhagen Sarcopenia study, increasing the risk of having osteoporosis [49]. Older males with a diagnosis of probable and definite sarcopenia were 8 times more likely to have a diagnosis of osteopenia or osteoporosis [65], where in postmenopausal Brazilian women, sarcopenia and severe sarcopenia was shown to impose a higher risk for osteoporosis adding to the growing evidence that sarcopenia and osteoporosis frequently co-occur [63].

However, studies that have considered frailty as an outcome suggest the risks of serious morbidity are notably higher when osteoporosis and sarcopenia co-exist [60,188,189]. Individuals with osteosarcopenia have also increasingly higher risk of mortality compared to those with sarcopenia or osteoporosis alone [190].

Given that ageing is commonly associated with sarcopenia and osteoporosis, the aims of this study were 1. to explore associations between sarcopenia and osteoporosis, individually or in combination, with frailty in community dwelling older adults participating in the Hertfordshire Cohort Study (HCS), and 2. to determine if coexistence of both sarcopenia and osteoporosis (osteosarcopenia) carries a higher likelihood of being frail. Given the importance of multimorbidity on health outcomes [191], and the association that previously has been described

between osteosarcopenia and chronic diseases [192] we also considered 3. whether the coexistence of sarcopenia and osteoporosis was associated with a significantly heavier health burden, as assessed by the number of concurrent long-term conditions. The wealth of phenotypic information collected in the HCS, a cohort study of community-dwelling older adults has allowed us to describe the prevalence and pre-frailty in this group and to consider whether the coexistence of sarcopenia and osteoporosis in individuals interacted to amplitude risk of frailty. This is of high clinical relevance as the identification of coexistent sarcopenia and osteoporosis not only allows early treatment and the development of management strategies, but might also offer an opportunity to mitigate frailty risk [175,176].

3.2 Methods

The Hertfordshire Cohort Study (HCS) was designed to examine the relationship between growth in infancy and the subsequent risk of common adult diseases, including OP and SP and has been described in detail elsewhere [143]. Participants have been followed up at a number of timepoints since its inception. The present study was performed using baseline data collected in 2011. All study participants provided written informed consent and ethical approval was obtained from the Hertfordshire Research Ethics Committee. All participants gave written informed consent.

3.2.1 Data collection

3.2.1.1 Questionnaire and anthropometry

Participants completed questionnaires that comprised questions related to lifestyle including smoking habits, alcohol consumption, physical activity (LASA Physical activity Questionnaire - LAPAQ), and nutrition (Short food frequency questionnaire - FFQ). Anthropometric measurements including height and weight were measured to calculate body mass index (BMI).

3.2.2 Physical performance and muscle mass

Grip strength was measured three times in each hand using a Jamar hand-held isokinetic dynamometer using a standardised protocol [147]. The maximum value was used in analyses. Gait

speed (metres/second) determined after timed 8-foot walk test. The use of assistive devices was permitted, if required. For chair rises (also used to assess for physical function), the time taken for participants to stand up and sit down again (with their arms crossed across their chest) a total of five times was recorded.

Skeletal muscle mass was measured with a body composition dual-energy X-ray absorptiometry (DXA) scan (Lunar Prodigy Advanced) to quantify regional as well as total lean mass, fat mass and bone mineral content. Proximal femur BMD values were determined using standard DXA.

Skeletal muscle mass was measured with a body composition dual-energy X-ray absorptiometry (DXA) scan (Lunar Prodigy Advanced) to quantify regional as well as total lean mass, fat mass and bone mineral content. Proximal femur BMD values were determined using standard DXA. Spine BMD were not available for analysis in this cohort. All measures were taken in 2011.

3.2.3 **Definitions**

3.2.3.1 Sarcopenia

Sarcopenia was defined using the revised EWSGOP2 criteria for low muscle strength measured by hand grip strength (<27kg in men and <16kg in women) or slow chair rise time (>15s for 5 rises) and low muscle quantity (appendicular skeletal mass [ASM] index [ASM/height2] <7.0 kg/m2 in men and <5.5 kg/m2 in women) [193].

3.2.3.2 Osteoporosis

Osteoporosis was defined according to the World Health Organization criteria and diagnosed when BMD T- scores were lower than the peak bone mass by 2.5 SD at the femoral neck or the use of osteoporotic treatment including hormone replacement therapy (HRT), Bisphosphonates, or Raloxifene was reported.

3.2.3.3 Frailty

Frailty was defined using the standard Fried definition using similar cut offs for muscle strength that were used to define sarcopenia (grip strength <27kg men, <16kg women) in addition to the

presence of unintentional weight loss, self-reported exhaustion and lowest sex-specific fifth of activity time: 0 out of 5 domains = non-frail, 1 or 2 domains = pre-frail, ≥3 domains = frail. The presence of unintentional weight loss was defined as a positive answer to the question: "In the last year, have you lost more than 10 pounds (4.5Kg) unintentionally (i.e., not due to dieting or exercise)?". The presence of self-reported exhaustion was defined as an answer of a moderate amount of time or most of the time (i.e., ≥3 days) to the question: How often in the last week did you feel "everything I did was an effort" or I could not get going".

3.2.3.4 Comorbidity

Participants were asked to self-report their comorbidities with the use of a questionnaire; An existing list of common comorbidities was given to participants with a Yes/No option and participants were also able to provide their comorbidities as a free text, if those were not listed. We then categorized the number as none, one, two, and three or more. Multimorbidity was defined when participants self-reported 3 or more comorbidities.

3.2.4 Statistical analysis

Descriptive statistics for continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables were expressed as frequency (N) and percentage (%). Differences between groups (such as frailty status) were assessed using analysis of variance (ANOVA), Kruskal-Wallis tests, Pearson's χ^2 tests or Fisher's exact tests as appropriate. Logistic regressions were performed to analyse associations of osteoporosis at femoral neck, sarcopenia and co-existence of osteoporosis and sarcopenia as explanatory variables for frailty adjusting for sex only initially, then further adjusting for age, BMI, current smoker, and alcohol consumption.

3.3 Results

Complete baseline data were available for 405 participants (199 men and 206 women). The median (SD) age of participants at baseline was 75.5 (73.4 - 77.92) years. The characteristics of

this population are shown in Table 3-1. One fifth of participants had evidence of osteoporosis and 8% had evidence of sarcopenia. 20.5% (83/405) self-reported 3 or more comorbidities. 4.5% of men and 2.9% of women were current smokers with no sex difference (p = 0.391). There was a significant difference between women and men at baseline in the median (IQR) alcohol consumption [(men: 6.2 (1.0 - 12.3) units per week; women: 0.3 (0.0 - 3.1) units per week; p<0.001)]. Over half of participants reported to have low walking speed (≤0.8m/s) (55.2%, 217/393) and one fifth of them had low physical activity (80/394). One fifth of participants had evidence of osteoporosis and 8% had evidence of sarcopenia. 20.5% (83/405) self-reported 3 or more comorbidities.

There were significant differences between non-frail, pre-frail, and frail participants with respect to age (p=0.002), height (p=0.035), BMI(kg/m^2) (p<0.001), alcohol consumption (p=0.027), physical activity in the last 2 weeks (p<0.001), walking speed (p<0.001) and grip strength (p<0.001) as shown in Table 3-2. Of the five Fried frailty components, low walking speed and low physical activity followed by self-reported exhaustion were the most prevalent (96.6%, 87.5% and 75.8% respectively) among frail participants.

Participants for whom data were available at follow up and developed frailty, were overall healthier (Table 3-3). They were younger (p<0.001), heavier (p=0.045), taller (p=0.043), stronger (p=0.003), faster walkers (p=0.002) and had better physical activity (p=0.014) compared to those for whom data were not available on incidence frailty.

Table 3-1: Baseline characteristics of all participants[10].

	All participants		
	N	Median	IQR
Age (years)	405	75.5	73.4 - 77.9
Weight (kg)	405	76.0	68.2 - 85.8
BMI (kg/m2)	402	27.4	25.1 - 30.9
Alcohol consumption (units per week)	405	2.0	0.1 - 8.3
Activity time in last 2 weeks (min/day)	394	190	124 - 283
	N	Mean	SD
Height (cm)	402	165.7	9.3
Maximum grip (kg)	405	28.7	10
Gait speed (m/s)	393	0.75	0.18
ALM index (kg/m2)1	295	7.27	1.08
Femoral neck BMD (g/cm2)2	306	0.889	0.139
	Total N	N	%
Female sex	405	206	50.9
Unintentional weight lost	404	16	4.0
Self-reported exhaustion	405	48	11.9
Low grip strength (<27kg men; <16kg women)	405	47	11.6
Low walking speed (≤0.8 m/s)	393	217	55.2
Low physical activity3	394	80	20.3
Emaciated (BMI <18.5kg/m2)	402	2	0.5
Current smoker	405	15	3.7
Osteoporosis4	308	66	21.4
Sarcopenia	323	26	8.0
Having 3 or more comorbidities	405	83	20.5

[10] 1 ALM = Appendicular lean mass, 2 Minimum of left and right femoral neck BMD, 3 Low physical activity = lowest 20% of activity time, 4 Osteoporosis = femoral neck t-score <-2.5 or taking HRT, bisphosphonates or raloxifene

Table 3-2: Characteristics of individuals by frailty category; frailty components and association with sarcopenia and osteoporosis. categories[11].

	Non-frail			Pre-frail			Frail			
	N	**Median**	**IQR**	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	**p-value[1]**
Age (years)	139	74.7	73.1 - 76.8	233	75.7	73.7 - 78.5	33	77.0	74.7 - 78.9	***0.002****
Weight (kg)	139	74.3	68.2 - 81.9	233	76.6	68.2 - 88.0	33	78.5	70.6 - 88.7	0.143
BMI (kg/m^2)	139	26.5	24.4 - 29.2	230	28.4	25.6 - 31.2	33	29.4	25.4 - 32.8	***<0.001****
Alcohol consumption (units per week)	139	3.3	0.3 - 10.0	233	2.0	0.1 - 7.5	33	0.5	0.0 - 5.0	***0.027****
Activity time in last 2 weeks (min/day)	139	231	178 - 327	223	176	107 - 240	32	63	42 - 91	***<0.001****
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**p-value[1]**
Height (cm)	139	167.3	9.1	230	165.0	9.3	33	163.9	9.9	***0.035****
Maximum grip (kg)	139	32.4	9.3	233	27.7	9.5	33	20.6	10.1	*<0.001**
Gait speed (m/s)	139	0.90	0.1	225	0.69	0.15	29	0.53	0.14	***<0.001****
ALM index (kg/m^2)[2]	110	7.28	1.08	168	7.28	1.08	17	7.08	1.10	0.745
Femoral neck BMD (g/cm^2)[3]	115	0.892	0.127	172	0.892	0.148	19	0.853	0.134	0.500
	Total N	**N**	**%**	**Total N**	**N**	**%**	**Total N**	**N**	**%**	**p-value[1]**
Female sex	139	62	44.6	233	125	53.6	33	19	57.6	0.174
Unintentional weight lost	139	0	0	232	8	3.4	33	8	24.2	***<0.001****
Self-reported exhaustion	139	0	0	233	23	9.9	33	25	75.8	***<0.001****
Low grip strength (<27kg men; <16kg women)	139	0	0	233	27	11.6	33	20	60.6	***<0.001****

[11] 1 p-value for the difference between the frailty categories, 2 ALM = Appendicular lean mass, 3 Minimum of left and right femoral neck BMD,4 Low physical activity = lowest 20% of activity time as measured by LAPAQ, 5 Osteoporosis = femoral neck t-score <-2.5 or taking HRT, bisphosphonates or raloxifene, N= number of participants, IQR=Interquartile range * p-value <0.05. P values are reported for the difference between the frailty categories.

Low walking speed (≤0.8 m/s)	139	0	0	225	189	84.0	29	28	96.6	***<0.001****
Low physical activity[4]	139	0	0	223	52	23.3	32	28	87.5	***<0.001****
Emaciated (BMI <18.5kg/m^2)	139	2	1.4	230	0	0	33	0	0	0.277
Current smoker	139	2	1.4	233	12	5.2	33	1	3.0	0.169
Osteoporosis[5]	118	24	20.3	173	36	20.8	17	6	35.3	0.375
Sarcopenia	126	5	4.0	179	16	8.9	18	5	27.8	***0.005****
Having 3 or more comorbidities	139	19	13.7	233	48	20.6	33	16	48.5	***<0.001****

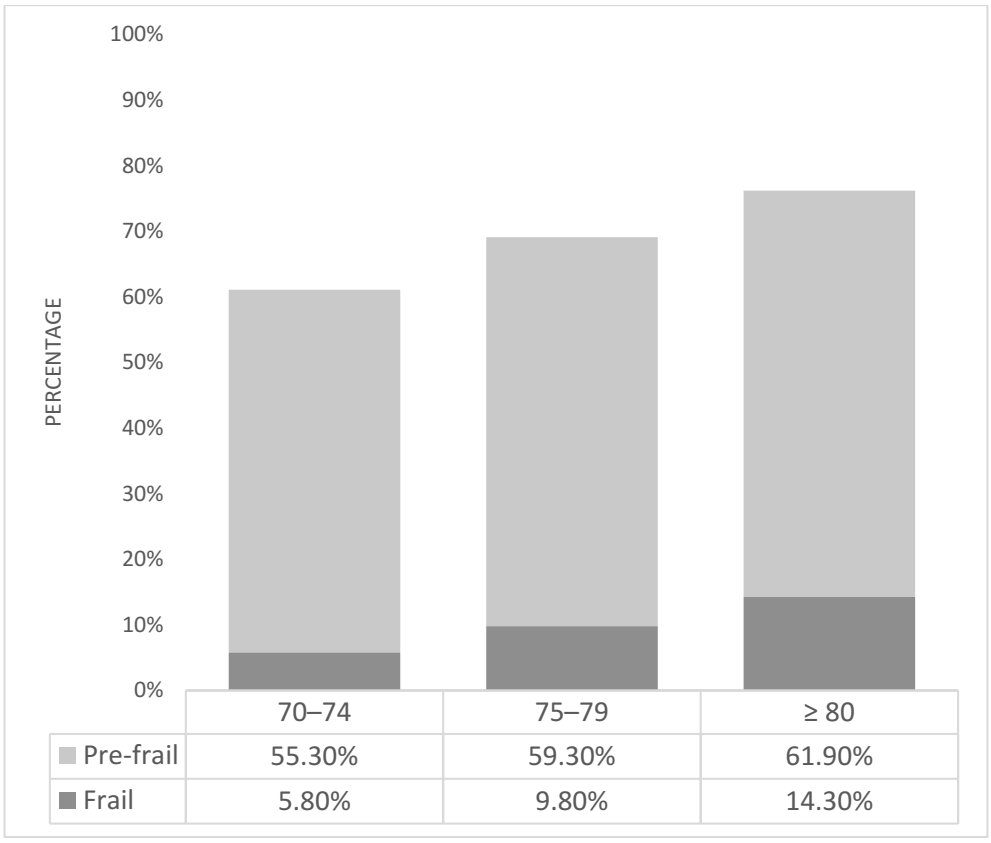
Table 3-3: Baseline (EPOSA) characteristics for those who do / do not have data on incident frailty [12]

	No data on incident frailty			Data on incident frailty			
	N	**Median**	**IQR**	**N**	**Median**	**IQR**	**p-value**
Age (years)	218	76.1	73.8 - 78.5	187	74.7	73.0 - 77.2	***<0.001***
Weight (kg)	218	74.8	67.3 - 84.0	187	77.5	70.0 - 88.1	***0.045***
BMI (kg/m^2)	216	26.8	24.8 - 31.0	186	28.1	25.3 - 30.6	0.314
Alcohol consumption (units per week)	218	1.6	0.1 - 7.5	187	2.9	0.3 - 9.0	0.056
Activity time in last 2 weeks (min/day)	214	185	95 - 249	180	201	137 - 289	***0.014***
Age (years)	218	76.1	73.8 - 78.5	187	74.7	73.0 - 77.2	***<0.001***
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**p-value**
Height (cm)	216	164.8	9.7	186	166.7	8.8	***0.043***
Maximum grip (kg)	218	27.3	9.5	187	30.3	10.4	***0.003***
Gait speed (m/s)	210	0.73	0.19	183	0.78	0.16	***0.002***
ALM index (kg/m^2)[1]	121	7.15	1.02	174	7.36	1.11	0.095
Femoral neck BMD (g/cm^2)[2]	126	0.879	0.142	180	0.897	0.137	0.278
	Total N	**N**	**%**	**Total N**	**N**	**%**	**p-value**
Female sex	218	117	53.7	187	89	47.6	0.223
Unintentional weight lost	217	14	6.5	187	2	1.1	***0.008***

[12] 1 ALM = Appendicular lean mass, 2 Minimum of left and right femoral neck BMD, 3 Low physical activity = lowest 20% of activity time, 4 Osteoporosis = femoral neck t-score <-2.5 or taking HRT, bisphosphonates or raloxifene, 5 Out of high blood pressure, diabetes, lung disease (eg asthma, chronic bronchitis, emphysema or COPD), rheumatoid arthritis, multiple sclerosis, thyroid disease, vitiligo, depression, Parkinson's disease, heart disease (eg heart attack, angina or heart failure), peripheral arterial disease (eg claudication), stroke and cancer.

Self-reported exhaustion	218	32	14.7	187	16	8.6	0.057
Low grip strength (<27kg men; <16kg women)	218	30	13.8	187	17	9.1	0.143
Low walking speed (≤0.8 m/s)	210	128	61.0	183	89	48.6	***0.014***
Low physical activity[3]	214	55	25.7	180	25	13.9	***0.004***
Emaciated (BMI <18.5kg/m^2)	216	1	0.5	186	1	0.5	1.000
Current smoker	218	9	4.1	187	6	3.2	0.625
Osteoporosis[4]	130	32	24.6	178	34	19.1	0.244
Sarcopenia	145	15	10.3	178	11	6.2	0.171
Having 3 or more comorbidities[5]	218	41	18.8	187	27	14.4	0.241

In our sample, the prevalence of frailty and pre-frailty at baseline was 8.1% (men, 7.0%, women, 9.2%) and 57.5% (men, 54.3%; women, 60.7%), respectively. Figure 3-1 illustrates the prevalence of frailty in the 70–74-, 75–79-, and ≥ 80-year age groups. These were 5.8%, 9.8%, and 14.3% respectively, and that of pre-frailty was 55.3%, 59.3% and 61.9% respectively. Figure 3-2 also shows the age- and gender- stratified prevalence of frailty and pre-frailty. There were no significant differences in frailty status between men and women nor between the age groups in both sexes.



	70–74	75–79	≥ 80
Pre-frail	55.30%	59.30%	61.90%
Frail	5.80%	9.80%	14.30%

Figure 3-1: Pooled prevalence of frailty and pre-frailty at baseline

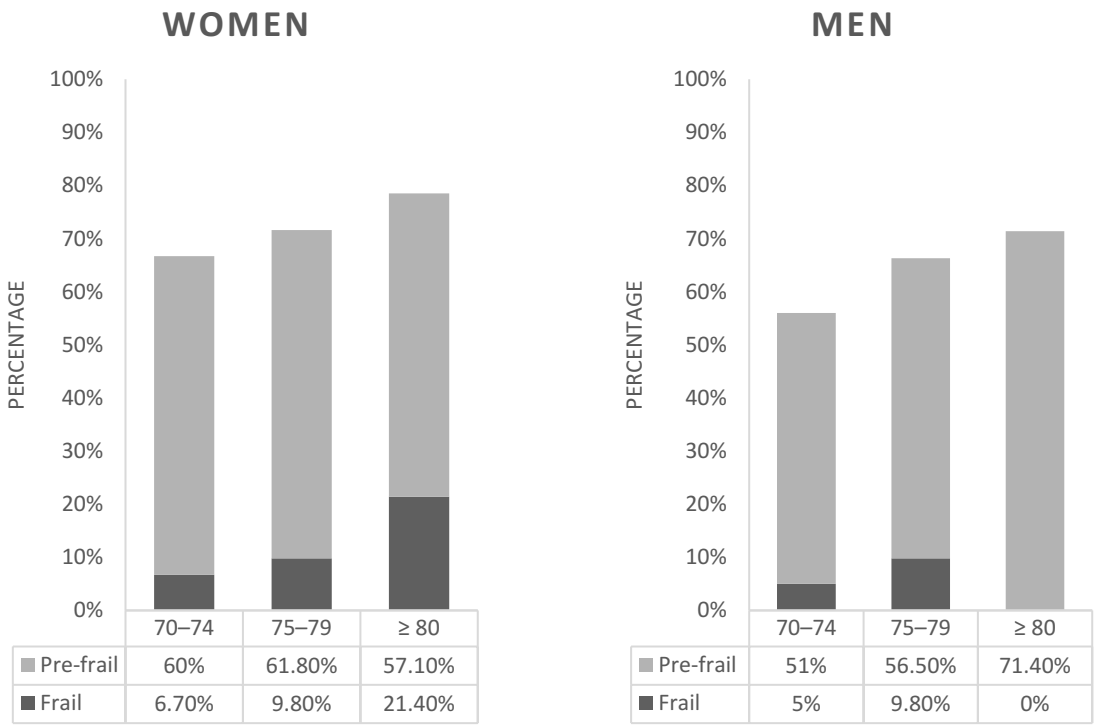


Figure 3-2: Age and gender stratified prevalence of frailty and pre frailty at baseline.

We next considered interrelationships between sarcopenia, osteoporosis, or both with frailty. Co-existence of sarcopenia, osteoporosis and frailty was observed in 1% of this population. 2% of the study sample had sarcopenia and osteoporosis. 73% had no evidence of sarcopenia, osteoporosis, or frailty (Figure 3-3). Amongst the participants with frailty, 27.8% had a concomitant diagnosis of sarcopenia, compared with 8.9% in the pre-frail and 4.0% in the non-frail categories (p=0.005).

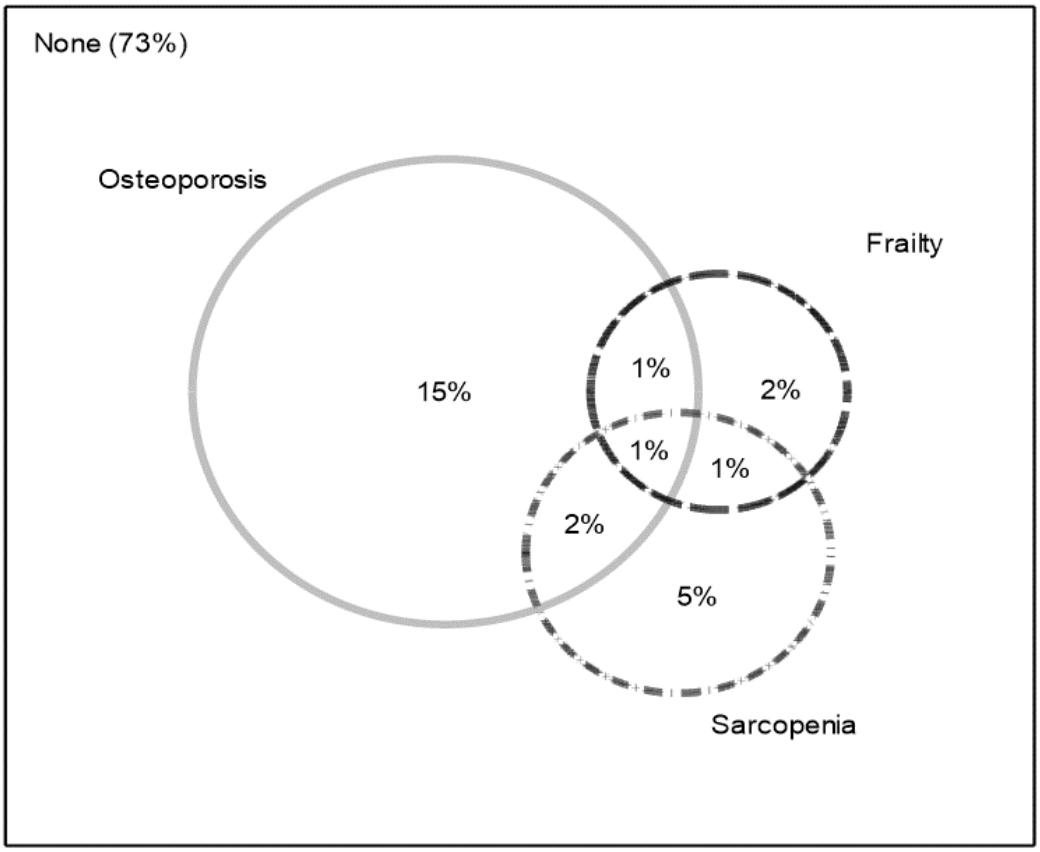


Figure 3-3: Venn diagram illustrating the relationships of osteoporosis, sarcopenia, and frailty at baseline

In a model of sarcopenia/osteoporosis status, having sarcopenia only was strongly associated with frailty (OR 8.28, 95% CI 1.27, 54.03; p=0.027), while the association between having osteoporosis alone and frailty was weaker (OR 2.57, 95% CI 0.61,10.78; p=0.196) (Table 3-4). The likelihood of being frail was substantially higher in the presence of co-existing sarcopenia and osteoporosis (OR 26.15, 95% CI 3.13,218.76; p=0.003) (Table 3-4).

Having sarcopenia alone and osteoporosis alone were both associated with having 3 or more comorbidities (OR 4.71, 95% CI 1.50, 14.76, p=0.008 and OR 2.86, 95% CI 1.32, 6.22; p=0.008 respectively) though this relationship was not stronger with co-existing sarcopenia and osteoporosis (OR. 3.45, 95% CI 0.59, 20.26; p=0.171) (Table 3-5).

Table 3-4: Relationship of sarcopenia, osteoporosis, and frailty at baseline[13].

	Adjusted for sex only				Fully adjusted[1]			
	N	OR	95% CI	p-value	N	OR	95% CI	p-value
OP & SP status	293				284			
Neither OP nor SP (reference)								
OP only		2.24	0.53, 9.56	0.274		2.57	0.61, 10.78	0.196
SP only		3.77	0.68, 20.90	0.129		8.28	1.27, 54.03	***0.027****
Both OP & SP		***9.98***	***1.60, 62.22***	***0.014****		***26.15***	***3.13,218.76***	***0.003****

N= number of participants, OR= Odds ratio, CI= Confidence interval, OP=Osteoporosis, SP=Sarcopenia, ** p-value <0.05*

Table 3-5: Relationship of sarcopenia, osteoporosis, and multimorbidity (≥3 comorbidities) at baseline.[14]

	Adjusted for sex only				Fully adjusted[1]			
	N	OR	95% CI	p-value	N	OR	95% CI	p-valu
OP & SP status	288				286			
Neither OP nor SP (reference)								
OP only		***2.76***	***1.35, 5.67***	***0.006****		2.86	1.32, 6.22	***0.008****
SP only		***2.98***	***1.02, 8.74***	***0.047****		4.71	1.50, 14.76	***0.008****
Both OP & SP		2.12	0.39, 11.64	0.385		3.45	0.59, 20.26	0.171

N= number of participants, OR= Odds ratio, CI= Confidence interval, OP=Osteoporosis, SP=Sarcopenia, ** p-value <0.05*

13 Values in the fully adjusted categories are adjusted for sex, age, BMI, current smoking history, and alcohol consumption. OP values refer to a femoral neck T-score of less than -2.5 or taking HRT, bisphosphonates, or raloxifene. SP was defined using the EWSGOP2 criteria

14 Values in the fully adjusted categories are adjusted for sex, age, BMI, current smoking history, and alcohol consumption. OP values refer to a femoral neck T-score of less than -2.5 or taking HRT, bisphosphonates, or raloxifene. Comorbidities self-reported by participants. SP was defined using the EWSGOP2 criteria.

3.4 Discussion

In this study, we examined the association between SP, OP or co-existence of sarcopenia and osteoporosis, with frailty and multimorbidity in 405 community dwelling older men and women. We also report prevalence and incidence of frailty in the same group of community dwelling older adults. As might be anticipated, SP was associated with frailty but the association of OP with frailty was weaker. However, we also reported that the likelihood of being frail was markedly higher in the presence of co-existing sarcopenia and osteoporosis than with SP alone. We had anticipated relationships between SP and frailty because of the diagnostic criteria for the two conditions [194]. For this reason, we also considered the relationship with multimorbidity as a proxy marker for frailty. Both SP and OP were associated with multimorbidity, but in this case there did not appear to be an interaction between the two conditions.

The concept of osteosarcopenia is relatively new, but in previous work co-existence of sarcopenia and osteoporosis has been associated cross-sectionally with depression, malnutrition, peptic ulcer disease, inflammatory arthritis and reduced mobility [42]. Studies from Australia and China have demonstrated that individuals with both osteoporosis and sarcopenia are at higher risk of falls and fractures than those with osteoporosis or sarcopenia alone [42,60]. Only a few studies have examined the association between both osteoporosis and sarcopenia with frailty in community dwelling older adults. In the Women's Health and Aging Studies II, the likelihood of being frail was higher in the presence of these two conditions, but the association was not statistically significant. The criteria used in this study to assess sarcopenia was appendicular lean mass by height^2 without taking into account muscle strength, possibly leading to an under recognition of sarcopenic participants [195]. In the SARCOS-study, low lean mass together with osteoporosis showed an association with frailty; cut-offs for lean mass were based on FNIH criteria and the authors aimed to characterize the phenotype of sarcopenic older adults only based on lean mass [196]. In a study of octogenarians in China, women were more likely to have osteosarcopenia compared to men; sarcopenia and osteoporosis alone or in combination were associated with frailty [60]. Osteoporosis, risk of falls and sarcopenia were reported in the I-Lan Longitudinal Aging Study to

be associated with frailty independently [197] In a hospital based study, sarcopenia was strongly associated with frailty ($p<0.001$) while relationships with osteoporosis were weaker ($p=0.055$) [198]. Finally, in a retrospective study among postmenopausal patients with known osteoporosis attending a hospital bone clinic, those with a diagnosis of osteosarcopenia were more likely to be frail than those with osteoporosis alone [188].

The prevalence of frailty and pre-frailty in community dwelling older adults is also reported. As expected, frailty and pre-frailty were more prevalent in individuals over the age of 80 in both sexes. Both the prevalence of frailty and pre-frailty increased with age in women, but only pre-frailty was increased with age in men, however the number of men aged over 80 in our study was low. Previous UK based studies report similar prevalence of frailty that is found in our study but sex difference were noted [199]. Weighted prevalence in the English Longitudinal Study of Ageing (ELSA) was 14% among participants age 60-90 years [200]; prevalence did increase with age, was more common in women, and was associated with a burden in regard to mobility, and everyday activities.

Other groups studying an older population have found the prevalence of frailty and pre-frailty to be similar to our study [197,201–203], although different population sampling and definitional approaches may lead to differences in study findings. For example in a community dwelling cohort of men and women in Japan with mean age of 70.3 (SD 11.0) years, the prevalence of frailty was estimated to be 5.6% in both sexes (in the same cohort frailty was more common in the presence of both sarcopenia and osteoporosis) [204]. In a recent systematic review and meta-analysis, the pooled prevalence of frailty for community dwellers aged ≥50 years, using full and recognised modifications of Fried's, was 12% across 62 counties worldwide compared to 24% when other measures of frailty were used, highlighting that instrument selection influences prevalence proportions [205]. In Europe specifically the prevalence of frailty was 8%, a percentage close to our calculated prevalence, when using physical frailty measures and that of pre-frailty was 42% [205]. Far fewer data are available regarding the prevalence of pre-frailty in community dwelling populations. The Survey of Health, Aging and Retirement in Europe (SHARE) was one of

the few studies assessing pre-frailty and found that the prevalence of pre-frailty in individuals over the age of 50 in ten European countries ranged between 34.6% and 50.9% [206]. In our study, the prevalence of pre-frailty was higher, ranging from 55.3% to 61.9%. Approximately 43.4 and 150.6 per 1000 person-years was the estimated incidence of frailty and pre-frailty respectively in a recent systematic review and meta-analysis [207]; a higher incidence compared to our study although there is likely to be substantial geographic variation when measuring incidence [208].

This study has some limitations. Participants in the HCS cohort study are all community living, and therefore might be expected to show a healthy cohort bias, limiting our ability to discern some relationships. This is reflected by the relatively low number of sarcopenic and frail individuals and by the fact that participants for whom data were available at follow up and developed frailty, were overall healthier. They were younger, heavier, taller, stronger, faster walkers and had better physical activity compared to those for whom data were not available on incidence frailty. However, this study has been able to draw on the detailed phenotypic information available in the HCS to report the epidemiology of coexisting osteoporosis and sarcopenia, and its association with multimorbidity and frailty. Furthermore HCS participants have been compared with those in the nationally representative Health Survey for England and have been found to be broadly comparable in terms of their health and lifestyle [209]. We therefore suggest that the results from the current study could be reasonably generalised to the wider population of older men and women.

Our study suggests that the likelihood of being frail was markedly higher when sarcopenia and osteoporosis were co-existent. However, the relationship may be bidirectional given the risk factors and pathophysiological pathways that drive individual conditions. Future longitudinal cohort studies of older people who are diverse in both ethnicity and socio-economic status may provide a more comprehensive understanding to the relationship between osteosarcopenia and frailty.

3.5 **Conclusion**

We have shown an overall prevalence of frailty in community dwelling older UK adults of 8.1% with the risk increasing with age. Corresponding figures for pre-frailty were 57.5% with the risk increasing with age only in females. We found that the presence of baseline sarcopenia and osteoporosis together are associated with a much higher risk of frailty cross-sectionally than either condition alone, and that sarcopenia and osteoporosis are both closely linked with multimorbidity.

As the presence of co-existing SP and OP were highly associated with frailty, appropriate treatment and early intervention of these conditions can have a clinical benefit to reduce the progression to frailty. Furthermore, identifying and treating individuals with pre-frailty and probable SP as early and reversible risk states may be associated with better healthcare outcomes and lower risk of developing frailty. Muscle and bone inter-relationships need to be further studied in large prospective longitudinal cohorts as better understanding of the epidemiology of osteosarcopenia is extremely relevant to inform the development of future interventions and therapeutics to maintain older people's independence.

Chapter 4. Determinants of muscle density and clinical outcomes: findings from the Hertfordshire Cohort Study (Appendix L)

4.1 Introduction

Sarcopenia is associated with a number of adverse health outcomes, including decreased quality of life, functional impairment, disability, increased risk of falls, hospitalisation, and increased mortality [210–216]. Muscle health can be assessed in many ways, and researchers have sought to identify muscle parameters, including muscle quality [217], which has been linked to muscle density [218,219]. Few studies have considered the demographic and lifestyle determinants of muscle density, which has been shown to decrease with age [220]. Furthermore lower muscle density may imply greater fatty infiltration within skeletal muscle and so might link to adiposity [170,216].

Muscle density represents an interesting muscle variable to study further as reduced leg muscle density increases the risk of mobility loss and has been associated with falls [221,222], which may increase future fracture risk. Muscle density has been shown to perform better than bone mineral density or muscle size in discriminating individuals with a history of hip fracture, and has been associated with an increased risk of hospitalisation [221,223–228].

Muscle density can be assessed by peripheral Quantitative Computed Tomography (pQCT), a technique that was developed for bone density and bone strength estimation. This technique produces a cross-sectional image that permits quantification of three-dimensional tissue structure properties of a limb segment, enabling the cross-sectional area (CSA) of soft tissue and muscle density to be estimated. Since fat is calibrated to zero with pQCT, typical muscle density values range from 65 to 90 mg/cm^3 [229]. Recent studies have highlighted the link between muscle density assessed by pQCT, and fracture risk [230], but these data were collected in a large US study of older males only.

Assessment of muscle-bone relationships using pQCT-derived variables has been undertaken previously in the Hertfordshire Cohort Study; muscle size and grip strength were associated with bone size and strength, but relationships between gait speed and bone structure and strength were not apparent in this cohort, supporting a role for the muscle-bone unit [9]; in other work in Hertfordshire, we have shown positive associations between changes in muscle area and cortical area in both men and women [231].

Given the relative paucity of available research on muscle density, our aims were to use a prospective study of community-dwelling adults to: (1) identify determinants of peripheral muscle density (lifestyle and anthropometric characteristics); and (2) to relate peripheral muscle density measures to history of falls and prevalent fractures. In our study, participants had a mean age at baseline of 64.7 years. This is a stage in the lifecourse when identification of individuals at high risk of poor musculoskeletal outcomes later in life might be possible, and if evidence exists that lifestyle modification might be beneficial, this may result in substantial personal and societal benefit.

4.2 Methods

4.2.1 The Hertfordshire cohort study:

The Hertfordshire Cohort Study (HCS) is a population-based cohort of older adults, consisting of 1579 males and 1418 females, born in Hertfordshire, UK, between 1931 and 1939 and still living in the county in 1998–2004. All participants were Caucasian. Following our initial contact in 1998–2004, participants completed a baseline home interview and attended a research clinic for detailed assessment of their socio-demographic, lifestyle and clinical characteristics; the study has previously been described in detail [143,144]. In 2004, of the 966 participants from East Hertfordshire who had a dual-energy X-ray absorptiometry (DXA) scan at the start of the study, 642 were recruited for a musculoskeletal follow-up study (8/966 had died, 74/966 could not be located and 242/966 declined to participate). In 2011-2012, 570/642 participants from East Hertfordshire were invited to take part in a further bone follow-up study which involved

measurement of muscle density by peripheral quantitative computed tomography (pQCT); 376/570 agreed to participate.

4.2.2 Ascertainment of participant characteristics in 1998-2004

A lifestyle questionnaire was administered at the home interview to collect information on physical activity (Dallosso questionnaire [148]), smoking, and alcohol consumption. Participants completed a food-frequency questionnaire from which protein intake was ascertained, and a 'prudent diet' score was derived using principal components analysis; higher scores reflected healthier diets [149]. Current or most recent full-time occupation (husband's for ever-married females) was ascertained; social class was coded from the 1990 OPCS Standard Occupational Classification (SOC90) unit group for occupation [232]. Social class was coded from current or most recent full-time occupation for all men and also among women who never married, and only from husband's occupation for ever-married women. Details of all prescription and over-the-counter medications currently taken were coded according to the British National Formulary; the number of systems medicated was derived as a marker of comorbidity.

Investigations conducted at the baseline clinic included measurement of standing height (Harpenden pocket stadiometer, Chasmors Ltd, London, UK) and weight (SECA floor scale, Chasmors Ltd, London, UK) which were used to derive body mass index (BMI).

4.2.3 Ascertainment of characteristics at the 2011-2012 follow-up

Bone density measurements have been described in detail previously [233]. pQCT was performed using a Stratec XCT2000 instrument (software version 6.20, Stratec Medizintechnik, Pfrozheim, Germany); scans were acquired at the 4 and 66% sites of the radius, and at the 4 and 38% sites of the tibia. Muscle density was derived at the 66% site on the non-dominant side using standard thresholds and calculated by dividing mass by area; muscle mass was obtained by calculating total area at C1P2, threshold -50, 41 mg/cm^3 and muscle mass at a threshold of 100 mg/cm^3, filer F03F05. All scans were checked for motion artefact by a trained observer. Additionally, scans were excluded if extreme outliers were observed. Bone mineral density (BMD) of the total hip

was assessed using DXA (Lunar Prodigy Advance DXA scanner GE Medical Systems, Waltham MA); the lowest value from the left and right side was used for analysis. Appendicular lean mass (ALM) was derived using the same DXA scanner and height was measured using a wall mounted SECA stadiometer; these measures were used to derive appendicular lean mass index (ALMi) as ALM (kg) divided by the square of height (m).

Grip strength (kg) was measured three times for each hand using a Jamar dynamometer (Promedics, Blackburn); the highest measurement was used for analysis. Mean customary gait speed in metres per second was calculated after two 8ft walking exercises.

Participants were asked the following through nurse-administered questionnaires: 'Have you had any falls since the age of 45 years?' and 'Have you broken any bones since the age of 45 years?'. Morphometric vertebral fractures were diagnosed from a lateral spine view imaged using the Prodigy DXA scanner and graded based on the Genant semi-quantitative method of vertebral fracture assessment by two trained independent observers [145]. Participants with a vertebral fracture or a self-reported fracture since age 45 years were regarded as having had a previous fracture.

4.2.4 **Statistical analysis**

Participant characteristics were described using summary statistics. Standard deviation (SD) scores were derived for continuous baseline characteristics and the muscle density outcomes to enable comparison of effect sizes. For each participant, follow-up time was calculated as the duration from the study baseline (1998-2004) to when the muscle density measures were ascertained at the 2011-2012 follow-up.

Baseline characteristics in relation to muscle density outcomes at follow up were examined separately using linear regression. Sex, baseline age and follow-up time were included as covariates in all models.

Pearson correlations were used to examine muscle density measures in relation to ALM index, grip strength, gait speed and total hip BMD.

Muscle density measures in relation to falls and fractures since age 45 years were examined using logistic regression with adjustment for sex and age and then additionally for total hip BMD.

Analyses were conducted using Stata, release 16.1 (StataCorp, College Station, Texas, USA). The analysis sample comprised the 375 participants who had values for forearm or calf muscle density. To maintain sample size, males and females were pooled for analyses (sex-interaction effects were examined) and analyses were adjusted for sex; $p<0.05$ was regarded as statistically significant.

4.3 **Results**

4.3.1 **Participant's characteristics**

Characteristics of the 375 participants (197 males, 178 females) who were included in the analysis are presented in Table 4-1. Mean (SD) age at baseline was 64.7 (2.7) years and median (lower quartile, upper quartile) follow-up was 11.5 (10.9, 12.3) years. Mean (SD) muscle density values (mg/cm^3) were as follows: forearm [males 79.9 (3.1), females 77.2 (3.2)], calf [males 80.7 (2.6), females 78.5 (2.6)]. Pearson correlations between calf and forearm muscle density were 0.13 (p=0.070) among men and 0.23 (p=0.002) among women (data not shown).

Males, as expected, were taller at baseline (mean [SD] height: males 174.6 [6.7] cm, females 161.9 [5.4] cm) and heavier (mean [SD] weight was 79.9 [10.1] kg among males, 69.6 [12.2] kg among females). Over half of males (n=115, 58.4%) and a third of females (n=62, 34.8%) were identified as current or previous smokers. Only 48 (24.4%) males and 3 (1.7%) females had high alcohol consumption (>21 units per week for males or >14 units per week for females). 55.6% (n=105) of males and 56.7% (n=101) of females were of manual social class. On average, females had higher diet quality scores compared with males (mean prudent diet score 1.0 vs -0.6) and lower physical activity levels (mean Dallosso activity score was 65.6 in males and 62.1 in females). Overall, 117 (59.4%) males and 83 (46.6%) females had less than the recommended protein intake of 1.2 g/kg/day at the HCS baseline stage (1998-2004). This reflects dietary protein intake from food only.

46 (25.7%) males and 51 (30.9%) females self-reported fractures since the age of 45 years or had documented vertebral fractures. 103 (56.6%) males and 119 (72.1%) females self-reported falls since the age of 45 years.

Sex-interaction effects were not statistically significant in any of the regression models fitted; sex-adjusted analyses were therefore performed among the pooled sample of men and women.

Table 4-1: Characteristics of the 375 participants who were included in the analysis sample[15].

Participant characteristic	Mean (SD); median (lower quartile, upper quartile); or n (%)	
	Males (n=197)	Females (n=178)
Baseline (1998-2004)		
Age (years)	63.9 (2.5)	65.6 (2.6)
Height (cm)	174.6 (6.7)	161.9 (5.4)
Weight (kg)	79.9 (10.1)	69.6 (12.2)
BMI (kg/m^2)	26.2 (3.1)	26.5 (4.3)
Ever smoked	115 (58.4%)	62 (34.8%)
Weekly alcohol units (M: Males; F: Females)		
Very low (<1 M&F)	21 (10.7%)	74 (41.6%)
Low (1-10M, 1-7F)	78 (39.6%)	81 (45.5%)
Moderate (11-21M, 8-14F)	50 (25.4%)	20 (11.2%)
High (>21M, >14F)	48 (24.4%)	3 (1.7%)
Dallosso activity score	65.6 (13.6)	62.1 (13.7)
Prudent diet score	-0.6 (2.0)	1.0 (1.7)
Protein intake (g/day)	93.2 (16.6)	84.3 (19.5)
Occupational social class (manual)	105 (55.6%)	101 (56.7%)
Number of systems medicated	1.0 (0.0, 1.0)	1.0 (0.0, 2.0)
Follow-up (2011-2012)		
Age (years)	76.1 (2.5)	76.5 (2.6)
Follow-up time (years)	12.3 (11.8, 12.7)	10.8 (10.5, 11.2)
Calf muscle density (mg/cm^3)	80.7 (2.6)	78.5 (2.6)
Forearm muscle density (mg/cm^3)	79.9 (3.1)	77.2 (3.2)
Appendicular lean mass index (kg/m^2)	8.0 (0.7)	6.4 (0.7)
Grip strength (kg)	36.6 (7.5)	21.8 (6.2)
Gait speed (m/s)	0.79 (0.17)	0.74 (0.18)
Total hip BMD (g/cm^2)	1.03 (0.15)	0.88 (0.14)
Previous fall since age 45 years	103 (56.6%)	119 (72.1%)
Self-reported fracture since age 45 years	40 (22.3%)	45 (27.1%)
Vertebral fracture	11 (5.6%)	14 (8.0%)
Previous fracture since age 45 years	46 (25.7%)	51 (30.9%)

[15] Previous fractures included self-reported and vertebral fractures

4.3.2 Associations between baseline characteristics and muscle density

Associations between baseline characteristics and muscle density measures at follow-up are presented in Table 4-2. Sex, baseline age and follow-up time were included as covariates in all models. Female sex, lower weight, and lower BMI were associated with both lower forearm and calf muscle density. SD differences in calf muscle density for females compared to males, and per SD lower weight and BMI were -0.84 [95%CI: -1.13, -0.54]), -0.37 [-0.46, -0.27] and -0.31 [-0.40, -0.23] respectively. Additional correlates of lower calf muscle density included older age (SD difference per SD lower age: 0.20 [0.10,0.30], p<0.001) and shorter stature (SD difference per SD shorter height: -0.16 [-0.30, -0.03], p=0.018). Lifestyle factors, social class and comorbidity were not associated with either of the muscle density measures.

4.3.3 Muscle density in relation to musculoskeletal parameters and clinical outcomes

Forearm and calf muscle density were weakly correlated with total hip BMD (males: r=0.13 (p=0.089) and r=0.20 (p=0.006), females: r=0.19 (p=0.011) and r=0.29 (p<0.001) respectively) (Table 4-3). Calf muscle density was moderately correlated with ALM index among both males (r=0.41, p<0.001) and females (r=0.38, p<0.001); calf muscle density was also correlated with grip strength among males (r=0.23, p=0.002). In general, correlations between musculoskeletal parameters and forearm muscle density were weaker than the correlations with calf muscle density (Table 4-3).

After adjustment for sex and age, lower forearm muscle density was related to increased risk of previous fracture (odds ratio (95% CI) per SD lower forearm muscle density: 1.42 (1.07,1.89), p=0.015) (Table 4-4). This association was attenuated after adjustment for total hip BMD (p>0.08). By contrast, no significant relationships were seen between calf or forearm muscle density and previous falls. However, a trend was observed between lower calf muscle density and increased risk of previous fracture after adjustment for sex and age (odds ratio (95% CI) per SD lower calf muscle density: 1.23 (0.94,1.62), p=0.131). Similarly, lower values of each muscle density measure were associated with greater risk of vertebral fracture after adjustment for sex and age, but these associations were not statistically significant

Table 4-2: SD difference in forearm and calf muscle density (2011/2012) per SD lower level of characteristic at HCS baseline (1998-2004).[16]

Participant characteristic	Forearm muscle density		Calf muscle density	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Age	0.09 (-0.01,0.19)	0.082	***0.20 (0.10,0.30)***	***<0.001***
Sex (female vs male)	***-1.04 (-1.33,-0.74)***	***<0.001***	***-0.84 (-1.13,-0.54)***	***<0.001***
Height	-0.11 (-0.24,0.02)	0.109	*-0.16 (-0.30,-0.03)*	*0.018*
Weight	***-0.16 (-0.26,-0.06)***	***0.002***	***-0.37 (-0.46,-0.27)***	***<0.001***
BMI	***-0.12 (-0.21,-0.03)***	***0.012***	***-0.31 (-0.40,-0.23)***	***<0.001***
Smoking (ever vs never)	0.01 (-0.18,0.20)	0.908	0.00 (-0.19,0.19)	0.997
Alcohol consumption (per lower band)	0.05 (-0.06,0.15)	0.374	0.04 (-0.07,0.14)	0.507
Dallosso activity score	0.05 (-0.04,0.14)	0.284	-0.04 (-0.13,0.06)	0.469
Prudent diet score	0.03 (-0.07,0.13)	0.612	-0.10 (-0.20,0.00)	0.052
Protein intake	0.04 (-0.05,0.14)	0.398	0.04 (-0.06,0.13)	0.422
Social class (manual vs non-manual)	0.10 (-0.08,0.28)	0.278	-0.03 (-0.22,0.16)	0.743
Comorbidity (per fewer system medicated)	-0.00 (-0.08,0.08)	0.983	0.06 (-0.02,0.15)	0.139

[16] SD: Standard deviation, CI: Confidence interval, each regression model included the individual participant characteristic of interest along with sex, baseline age and follow-up time, Significant associations ($p<0.05$) are shown in italic

Table 4-3: Cross-sectional Pearson correlations between musculoskeletal parameters and muscle density at the forearm and calf (2011/2012) stratified by sex. [17]

Parameter	Forearm muscle density	Calf muscle density
Males		
ALM index	r=0.16 (p=0.033)	r=0.41 (p<0.001)
Grip strength	r=0.08 (p=0.262)	r=0.23 (p=0.002)
Gait speed	r=0.00 (p=0.980)	r=0.08 (p=0.331)
Total hip BMD	r=0.13 (p=0.089)	r=0.20 (p=0.006)
Females		
ALM index	r=0.14 (p=0.073)	r=0.38 (p<0.001)
Grip strength	r=-0.02 (p=0.832)	r=0.04 (p=0.603)
Gait speed	r=0.02 (p=0.845)	r=0.07 (p=0.369)
Total hip BMD	r=0.19 (p=0.011)	r=0.29 (p<0.001)

[17] ALM: Appendicular lean mass, BMD: Bone mineral density

Table 4-4: Odds ratios for previous falls and fractures since age 45 years per SD decrease in parameter in 2011/2012.[18]

Parameter	Adjustments	Previous fall		Previous fracture		Previous vertebral fracture	
		Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Forearm muscle density	Sex, age	0.90 (0.70,1.17)	0.439	*1.42 (1.07,1.89)*	*0.015*	1.44 (0.88,2.37)	0.151
	Sex, age, total hip BMD	0.88 (0.67,1.14)	0.330	1.30 (0.97,1.75)	0.081	1.23 (0.73,2.06)	0.431
Calf muscle density	Sex, age	1.01 (0.78,1.30)	0.938	1.23 (0.94,1.62)	0.131	1.53 (0.95,2.44)	0.077
	Sex, age, total hip BMD	0.98 (0.75,1.27)	0.866	1.10 (0.82,1.47)	0.527	1.15 (0.70,1.90)	0.574

[18] Previous fractures include self-reported and vertebral fractures, Significant associations ($p<0.05$) are shown in italic.

4.4 **Discussion**

In this study we reported muscle density values for community-dwelling Caucasian UK males and females in older age, and explored the demographic, anthropometric and lifestyle determinants of muscle density. We also considered the relationships of muscle density measures to the clinical outcomes of falls and fractures. Our study demonstrated that demographic and anthropometric (female sex, older age, and lower adiposity), rather than lifestyle factors examined such as physical activity and diet, were associated with lower muscle density, approximately 11 years later. We have also demonstrated that forearm muscle density was associated with previous fracture, rather than falls history.

These findings complement earlier evidence linking lower muscle density/attenuation with adverse clinical outcomes including falls, fractures, poor physical performance, reduced muscle strength, frailty, and poor prognosis [219,226,241–247,227,234–240]. We found that only forearm, and not calf muscle density, was significantly associated with previous fracture in our cohort; we examined these associations with previous fractures at any site. Additional information on fractures since age 45 years, such as their type, date, and total number, was unavailable. However, it seems likely that a high proportion of fractures were upper limb distal forearm fractures, as the majority occurred in women in midlife. We suspect that the lack of association of calf muscle density with prior fracture reflects a health survivor bias in this cohort making calf muscle density less reflective of functional limitations, whereas forearm muscle density may be more reflective of general fragility contrary to lower limbs which are load bearing sites. In other studies, fat infiltration at mid femur, a measure of reduced muscle quality likely through reduction in force generating capacity through loss of type II fibres, was independently associated with a modest increase risk of incident clinical fracture in the Health, Aging, and Body Composition Study [248]. As lower extremity muscle attenuation and pQCT-derived muscle density is associated with poor physical performance, this might explain the relative higher reported risk of hip fractures in those individuals [228,241,243,249–251].

The lack of association between grip strength and forearm muscle density among both males and females was surprising. However, a possible reason for the lack of association is that muscle density was only assessed on the non-dominant side whereas the highest out of six grip strength measurements (three on each side) was used for analysis. We also report no association between forearm or calf muscle density with falls which is somewhat unexpected. Muscle density has previously been shown to be associated with falls status, and this association is independent of functional mobility [221,243]. Again, this may reflect our use of retrospective questionnaires, which may be limited by recall bias.

Our other findings are certainly consistent with what is currently known. Older age was associated with lower calf muscle density in our cohort after adjustment for sex and follow-up time; this association was also robust when additionally adjusted for weight (data not shown). Skeletal muscle fibre changes have been reported in ageing humans [252], and changes in muscle fibre morphology, infiltration of fat and other non-contractile proteins, altered gene expression, and innervation can all affect muscle quality [162,253,254]. Previous cross sectional and longitudinal cohorts have suggested that muscle density changes over time are also age-related [219,255–257] supporting our findings, while female sex and poor quality of life (according to HAS scores) were associated with declines in muscle density in a study of patients with rheumatoid arthritis [240]. Therefore, changes in muscle density over time might precede adverse outcomes such as falls and fractures and may be a long-term predictor of frailty. It could be also suggested that muscle density could be a more clinically meaningful surrogate of functional decline and disability than muscle size or mass but more studies are needed to support this notion [228,258].

In our cohort, lifestyle factors such as physical activity, diet, smoking, and alcohol consumption were not associated with future muscle density. Previous studies have examined the effect of smoking on muscle mass and strength in older adults, but not muscle density in the general population [83,259], though one study examining factors associated with declines in pQCT derived-muscle density in rheumatoid arthritis patients showed that active smoking was associated with lower muscle density [260]. In addition, the toxic effects of excess alcohol on

skeletal muscle are recognised as important [82,261]; however, a recent meta-analysis did not show alcohol as a risk factor for sarcopenia [84] and studies examining the associations of alcohol specifically with muscle density are absent, so our observations here (where few participants drank to excess, or were current smokers) are perhaps unsurprising. Nutrition intake, specifically dietary protein, alone and/or resistance exercise are recognised as important for muscle health [102,262]. In contrast, dietary protein intake was not related to subsequent muscle density in our cohort possibly because the proportion of adults not consuming recommended levels was lower than in other samples [263]. Information on resistance exercises was not available in our cohort at baseline; however, carrying loads of 10lb more frequently was related ($p=0.038$) to greater subsequent calf muscle density at follow-up after adjustment for sex, age, and follow-up time (data not shown).

There are strengths and limitations of the current study, some of which have been discussed previously. The determinants of future muscle density have not been previously explored in a community or hospital-based cohort. The literature on pQCT analyses in older adults is limited and previous studies have focused on associations between pQCT derived muscle data and outcomes but not determinants of future muscle density [244,264–266]. Peripheral QCT is proving to be a useful tool for the measurement of muscle density and has been found to be highly correlated to MRI-derived measures of muscle cross-sectional area [267]. HCS is a well characterized cohort that has been extensively phenotyped according to strict protocols by highly-trained fieldworkers [143]. Individuals recruited were selected because they had been born in Hertfordshire and continued to live there in 1998-2004, as in previous studies. Although our cohort might be expected to demonstrate a healthy cohort effect (as evidenced by low rates of smoking and high dietary calcium intakes), we have previously demonstrated that the Hertfordshire population studied have similar smoking characteristics and bone density to national figures [144]. This healthy cohort effect might have contributed to the absence of associations between lifestyle factors and future muscle density in our cohort and the fairly high mean values of muscle density observed. Drop out at each stage of the study occurred due to

participants moving away or becoming unwilling to participate in further studies; this has contributed to the relatively small number of participants examined. We also recognise the limitations associated with self-reported information, and the lack of phenotypic data around time spent participating in resistance exercises at baseline. Another limitation is the potential for recall bias from participants self-reporting previous fractures and falls which may have occurred decades ago. Furthermore, additional information on falls and fractures since age 45 years, such as their type, date, and total number, was unavailable. A key limitation is that only falls, and fractures ascertained prior to the muscle density measures were available; determining whether muscle density influences risk of adverse outcomes or vice versa is limited without also having incident outcomes assessed after the muscle density measures. Finally, the narrow age range of the analysis sample prevents a detailed characterisation of how muscle density varies over the lifecourse

4.1 **Conclusion**

This study provides further insights into the determinants of future muscle density and the associations of muscle density with clinical outcomes such as falls and fractures in a well characterised community-dwelling cohort of older adults. pQCT-derived muscle density could provide a biomarker to further complement the musculoskeletal health assessment in older adults and further studies are now warranted.

Chapter 5. Relationships between muscle parameters, and history of falls and fractures in the Hertfordshire Cohort Study: Do all muscle components relate equally to clinical outcomes? (Appendix M)

5.1 Introduction

Falls constitute a major risk factor for fracture and associated morbidity, mortality and economic costs [31]. Sarcopenia is an important contributor to falls risk, and hence fractures [268]. We have previously demonstrated relationships between muscle size and grip strength, and bone size and strength, supporting a role for the muscle-bone unit [9], with stronger relationships in females as it has been observed elsewhere [183,269]. In 2019, the revised European Working Group on Sarcopenia in Older People 2 guidelines were published emphasising muscle strength, relative to muscle mass and function [35]. The aim of this study was to examine the strength of sex-specific associations between each of the key individual sarcopenia components (muscle mass, strength, and function) with the clinically important outcomes of falls and fractures in a population-based cohort of older adults.

5.2 Methods

5.2.1 The Hertfordshire Cohort Study

The Hertfordshire Cohort Study (HCS) comprises 2997 individuals born in Hertfordshire from 1931-1939 who lived there in 1998-2004 where they completed a home interview and clinic visit for a detailed health assessment. In 2004, of the 966 participants from the geographic region of East Hertfordshire who formed the in-depth musculoskeletal subgroup, 642 attended a clinic visit as part of a musculoskeletal follow-up study. The HCS baseline investigations had ethical approval from the Hertfordshire and Bedfordshire Local Research Ethics Committee and all participants

provided written informed consent [143] ; ethical approval was also obtained for all HCS follow-up studies. Further details of HCS have been described previously [143].

5.2.2 Ascertainment of participant information in 1998-2004

Physical activity (Dallosso questionnaire) was ascertained by a nurse-administered questionnaire [148]. Dietary calcium intake was determined using a food-frequency questionnaire [149]. Current or most recent full-time occupation (husband's for ever-married females) was ascertained. Social class was coded from the 1990 OPCS Standard Occupational Classification (SOC90) unit group for occupation [270], using computer-assisted standard occupational coding to generate the following occupational classes: I (Professional); II (Managerial and technical); IIINM (Skilled non-manual); IIIM (Skilled manual); IV (Partly skilled); V (Unskilled) [271]. These were dichotomised as follows: 'Non-manual' (I, II and IIINM) and 'Manual' (IIIM, IV and V). Fractures since age 45 years were self-reported. Among females, information on hormone replacement therapy (HRT) use, the age at which they had their last menstrual cycle and whether they had undergone a hysterectomy was also collected.

5.2.3 Ascertainment of participant information in 2004-2005

Information on fractures since baseline, whether participants had fallen since age 45 years, the number of falls in the last year, smoking status and alcohol consumption was ascertained by a nurse-administered questionnaire. History of fracture since age 45 was determined from questionnaire data here and at baseline. Among females, information on HRT use was updated. Height was measured (Harpenden pocket stadiometer, Chasmors Ltd, London, UK) along with weight (SECA floor scale, Chasmors Ltd, London, UK) and used to derive BMI (kg/m^2). Grip strength was measured three times for each hand using a Jamar dynamometer; the highest measurement was used for analysis. Customary gait speed in metres per second was calculated using a 3m walk test. Radial and tibial (non-dominant side) peripheral qualitative computed tomography (pQCT) scans (Stratec 2000XL instrument, version 6.00) were performed; the other side was scanned if the non-dominant side had sustained a fracture. Calf muscle area was derived

using default procedures, thresholds, and edge tracking settings to segment muscle from subcutaneous fat. Additional details relating to the pQCT scans have been published previously [231]. At time of assessment of the muscle size, strength, and function measures in this study (2004-2005), 33 (5%) participants were taking bisphosphonates and 113 (18%) were taking medications for the endocrine system. Associations of interest were similar if binary variables for current use of bisphosphonates and medications for the endocrine system were included as additional adjustments as shown in.

5.2.4 **Statistical methods**

Participant characteristics were described using summary statistics. Associations between calf muscle area, grip strength and gait speed in relation to binary outcomes were examined using logistic regression with and without adjustment for age, BMI, social class, smoker status, alcohol consumption, physical activity, dietary calcium intake, hormone replacement therapy use (females only) and time since menopause (females only), use of bisphosphonates and use of medications for the endocrine system. Relationships between predictors and number of falls in the last year (0, 1, >1) were examined using ordinal regression with the same set of adjustments. Sex-stratified analyses were performed; $p<0.05$ was regarded as statistically significant. Analyses were conducted using Stata, release 17.0. The analysis sample comprised 641 participants with data on at least one predictor and at least one outcome; of the 642 participants who attended the 2004-2005 follow-up stage, one participant had missing values for grip strength, gait speed and calf muscle area so they were excluded from the analysis sample.

5.3 **Results**

5.3.1 **Descriptive statistics**

Participant characteristics of the analysis sample are presented in Table 5-1. Mean (SD) age was 69.3 (2.6) years. Calf muscle area, grip strength and gait speed were greater among males than females ($p<0.002$ for all associations). Compared to males, a greater proportion of females had

fallen since age 45 years (61.3% vs 40.2%, p<0.001); fallen in the last year (19.9% vs 14.1%, p=0.053); and had a previous fracture since age 45 years (21.8% vs 18.5%, p=0.302). However, these latter two sex-differences were not statistically significant.

5.3.2 Relationships between muscle size, strength, and function in relation to falls and fractures

Associations between predictors (calf muscle area, grip strength, gait speed) and outcomes (fallen since age 45, fallen in last year, number of falls in last year, fracture since age 45) are presented in Table 5-2. Among females, greater calf muscle area was related to reduced risk of falling in the previous year and fewer falls in the previous year (p<0.05) but only in fully adjusted analysis; higher grip strength was related to lower risk of falls since age 45 in unadjusted analysis only (odds ratio per SD greater grip strength: 0.79 (0.63, 0.99), p=0.045) and lower risk of fracture since age 45 in both unadjusted (0.74 (0.56, 0.97), p=0.030) and fully adjusted analysis (0.74 (0.56, 0.99), p=0.044). No statistically significant associations were observed for gait speed among females, or among males for any of the predictors in relation to any of the outcomes.

Table 5-1: Participant characteristics of the analysis sample [19].

Characteristic	Males (n=322)			Females (n=319)			P-value
	Total N	Mean	SD	Total N	Mean	SD	
Age (years)	322	69.2	2.5	319	69.5	2.6	0.127
Height (cm)	322	173.7	6.7	319	160.5	6.1	<0.001
Weight (kg)	322	82.3	12.4	319	71.7	13.8	<0.001
BMI (kg/m^2)	322	27.3	3.8	319	27.8	4.9	0.106
Dallosso activity score*	322	63.9	14.3	319	61.8	14.3	0.060
Calf muscle area (mm^2)	293	8035	1204	295	6212	981	<0.001
Grip strength (kg)	321	42.2	7.6	318	24.9	5.8	<0.001
Gait speed (m/s)	320	0.92	0.17	317	0.88	0.16	0.001
	Total N	Median	IQR	Total N	Median	IQR	
Dietary calcium (g/day)*	322	1.2	1.0, 1.4	319	1.1	0.9, 1.3	<0.001
Alcohol intake (units/week)	322	7.6	1.5, 16.5	317	1.3	0.0, 4.8	<0.001
	Total N	N	%	Total N	N	%	
Smoker status	322			316			<0.001
Never		121	37.6		200	63.3	
Ex		174	54		99	31.3	

[19] *Ascertained at HCS baseline (1998-2004); all other characteristics were ascertained in 2004-2005

[+] Manual occupations comprise IIIM (Skilled manual), IV (Partly skilled) and V (Unskilled) from the 1990 OPCS Standard Occupational Classification (SOC90) unit group for occupation
p-values for sex-differences in characteristics were calculated using t-tests, Wilcoxon rank-sum tests, or chi-squared tests as appropriate

Current		27	8.4		17	5.4	
Social class (manual)[+]	306	175	57.2	319	182	57.1	0.973
HRT use				319			N/A
Never					185	58	
At least 5 years ago					74	23.2	
Within last 5 years					47	14.7	
Current					13	4.1	
Years since menopause				316			N/A
<10 years					11	3.5	
≥10 and <15 years					49	15.5	
≥15 and <20 years					75	23.7	
≥20 and <25 years					60	19	
≥25 and <30 years					33	10.4	
≥30 years					9	2.8	
Hysterectomy					79	25	
Fallen since age 45 years	321	129	40.2	318	195	61.3	<0.001
Fallen in last year	319	45	14.1	317	63	19.9	0.053
Number of falls in last year	318			317			0.112
0		274	86.2		254	80.1	
1		36	11.3		49	15.5	
2 or more		8	2.5		14	4.4	

Fracture since age 45 years	314	58	18.5	317	69	21.8	0.302

Table 5-2: Odds ratios for outcomes per SD increase in predictors among males and females [20]

Predictor	Outcome	Males				Females			
		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Calf muscle area	Fallen since 45	0.97 (0.77, 1.23)	0.798	1.06 (0.79, 1.44)	0.691	0.93 (0.73, 1.17)	0.534	0.79 (0.58, 1.06)	0.119
	Fallen in last year	1.01 (0.72, 1.42)	0.941	1.13 (0.74, 1.72)	0.586	0.79 (0.59, 1.06)	0.120	0.66 (0.44, 0.97)	0.037
	No. falls in last year	1.04 (0.74, 1.47)	0.823	1.11 (0.72, 1.69)	0.643	0.79 (0.59, 1.06)	0.112	0.64 (0.43, 0.95)	0.025
	Fracture since 45	0.95 (0.70, 1.28)	0.722	0.96 (0.65, 1.42)	0.840	1.03 (0.78, 1.36)	0.838	1.11 (0.78, 1.58)	0.552
Muscle (Grip) strength	Fallen since 45	0.85 (0.68, 1.07)	0.167	0.87 (0.67, 1.12)	0.273	0.79 (0.63, 0.99)	0.045	0.79 (0.61, 1.01)	0.060
	Fallen in last year	0.75 (0.55, 1.03)	0.078	0.76 (0.54, 1.08)	0.129	0.88 (0.67, 1.17)	0.382	0.82 (0.60, 1.11)	0.198
	No. falls in last year	0.77 (0.56, 1.06)	0.105	0.78 (0.55, 1.11)	0.175	0.85 (0.64, 1.13)	0.273	0.77 (0.57, 1.06)	0.109
	Fracture since 45	1.33 (0.98, 1.81)	0.070	1.35 (0.95, 1.92)	0.098	0.74 (0.56, 0.97)	0.030	0.74 (0.55, 0.99)	0.042
Gait speed	Fallen since 45	0.99 (0.79, 1.23)	0.902	1.00 (0.78, 1.28)	0.988	0.85 (0.68, 1.07)	0.173	0.87 (0.67, 1.13)	0.309
	Fallen in last year	0.76 (0.55, 1.05)	0.100	0.83 (0.58, 1.17)	0.287	0.88 (0.67, 1.16)	0.352	0.87 (0.63, 1.19)	0.374
	No. falls in last year	0.77 (0.55, 1.07)	0.124	0.83 (0.58, 1.18)	0.294	0.84 (0.64, 1.12)	0.232	0.84 (0.61, 1.16)	0.289
	Fracture since 45	1.16 (0.87, 1.54)	0.301	1.10 (0.80, 1.52)	0.547	1.06 (0.81, 1.39)	0.688	1.09 (0.80, 1.47)	0.593

[20] OR: Odds ratio; CI: Confidence interval; SD: Standard deviation, Sex-specific z-scores were derived for calf muscle area, grip strength and gait speed to enable the comparison of effect sizes

*Adjusted for age, BMI, social class, smoker status, alcohol consumption, physical activity (ascertained from 1998-2004), dietary calcium intake (ascertained from 1998-2004), hormone replacement therapy use (females only), time since menopause (females only), use of bisphosphonates and use of medications for the endocrine system

Odds ratios for being in a higher category for number of falls in the last year (0, 1 or >1) were estimated using ordinal regression; logistic regression was used for the other outcomes, all participant characteristics were ascertained from 2004-2005 unless stated otherwise

5.4 Discussion

In this study, higher grip strength was related to lower risk of falls and fractures after 45 years and greater muscle size was associated with both reduced risk of falling and fewer falls in the previous year. The association between muscle strength and risk of fractures remained robust after adjustment. Conversely, associations regarding muscle size were only significant in adjusted models. Our findings support previous evidence that muscle strength is a key characteristic in identifying older adults at risk of adverse outcomes including falls and fractures [35]. Our study once again demonstrated sexual dimorphism in relationships observed and in general accord with previous literature, although previous studies have also suggested important relationships between muscle measures and bone outcomes in men [183].

Gait speed was not associated with prevalent falls and fractures in this study. Gait speed has been shown to reflect health and functional status, and to be associated with survival in older adults [272–274]. We previously found no associations of gait speed with measures of bone size, strength and density in the same cohort [9]. Amongst other physical performance tests, gait speed has previously been shown to be weakly associated with risk of hip fractures in participants without walking difficulties [275]. Gait speed is suitable for screening of poor physical performance and is used to identify cases of severe sarcopenia, as defined by the European Working Group on Sarcopenia in older adults (EWSGOP2) [35], but it is possible that it is more adversely affected by gait ability and/or severe weakness that leads to falls and fractures [276]. Two main types of gait speed assessment exist: the short-and long-distance gait test. Some groups favour the use of long distance gait speed for its established relationship to mobility disability and public health relevance [277,278]. Conversely, short gait tests can be used as surrogates for long-distance speed tests for the assessment of functional status in older adults, and are easily implemented into clinical practice [35,279]. Thus, we suggest that gait speed combined with other physical performance measures, such as chair stand test, might perform better as a predictor of falls and fractures when assessing community dwelling older adults [275].

There are several strengths and limitations to this work which was undertaken in a very well characterised cohort that has previously been shown to be representative of the UK population [143]. While the sex differences noted in our study insights into potential differential sex-specific mechanisms, a healthy bias in males, as indicated by the relatively higher mean of grip strength and gait speed, and the use of specific cut-off points to define each sarcopenia components should also be considered as a contributing factor to the absence of associations between sarcopenia and falls and/or fractures in males. However, since the cohort is made up of community dwelling individuals, generalisability of these findings to less healthy or institutionalized groups may be limited. Specifically, we also acknowledge the limitations associated with self-reported outcomes and the need for prospective data.

5.5 **Conclusion**

In conclusion we have observed relationships between muscle mass and strength but not function with falls and fractures in females but not males. Large prospective studies are needed to confirm the above-mentioned relationships, and to further explore the sexual dimorphism observed.

Chapter 6. A study of the impact of the COVID-19 pandemic on diet in older community-dwelling adults in the UK: findings from the Southampton Longitudinal Study of Ageing (SaLSA);

submitting revisions to Frontiers in Nutrition, August 2022.

6.1 Introduction

Adequate nutrition is known to be associated with better musculoskeletal health in later life [280,281]. More specifically, sufficient intake of calcium, protein and other vitamins and minerals have been linked to better bone and muscle health [97]. Several epidemiological studies have explored the association of dietary habits or healthier diets with bone and muscle health, and the association of individual foods and nutrients with fracture, falls and frailty [282–285].

The emergence of the coronavirus disease (COVID-19) declared a pandemic by the World Health Organisation in March 2020, and subsequent restrictive measures introduced in many countries to reduce the transmission of the disease, may have negatively impacted daily routines and lifestyle. This is especially likely among older adults, who are at greatest risk of complications from infection by the COVID-19 virus [286–288]. Potential factors associated with changes in diet quality remain controversial. Since changes in lifestyle related to the pandemic might be expected to have effects on both muscle and bone health, studies of older adults are now required to study these in depth.

We hypothesized that the COVID-19 pandemic may have an impact on lifestyle factors of older adults in the UK. We aimed to report pandemic-related changes in diet and examine correlates of changes in diet quality in a newly established community-dwelling older adult cohort in UK.

6.2 Methods

6.2.1 Southampton Longitudinal Study of Ageing (SaLSA)

In July 2021, we identified all patients who were registered at a large General Practice within Southampton, UK over the age of 75 (osteology reference). Eligibility to participate in the study was decided by their primary care physician. Our sole inclusion criteria were the age of participants (>75 years of age) at the time of recruitment. Our exclusion criteria included patients with safeguarding issues, patients with mental health and capacity issues, patients with dementia or who were unable to provide consent, patients with learning disabilities, patients who were end of life, patients who were permanently bed bound, and patients in residential or nursing homes.

We identified 2523 registered patients over the age of 75 years; of those 2523 patients, 1993 (79%) were deemed eligible to participate in the study by their primary care physician. 1993 patients were invited to participate in the study by postal invitation only. This led to the return of 516 complete questionnaires

6.2.2 Ascertainment of participant characteristics

All participant information was self-reported using postal questionnaires. Sociodemographic factors included: age; sex; ethnicity; educational qualifications achieved; living arrangements; and current marital status. Self-reported height and weight were used to derive BMI (kg/m^2). Information on health behaviours such as smoking, alcohol consumption, and information on malnutrition risk using the DETERMINE tool [289] were also ascertained. Change in the following aspects of lifestyle compared to before the first UK lockdown (23/03/2020) were reported: smoking, alcohol consumption, diet quality (reported as 'healthiness of diet'), amount of food consumed, physical activity, sleep, and social contact. The questions used were taken from the Wellcome COVID questionnaire, which was designed to enable researchers to collect COVID related data using the same validated questions used or adopted by other cohorts (accessed at https://www.bristol.ac.uk/alspac/researchers/wellcome-covid-19/) [290].

Comorbidities were ascertained by asking participants whether they were ever diagnosed by a doctor with any of the following conditions: heart attack or angina; stroke or transient ischaemic attack; hypertension; diabetes; asthma, bronchitis, emphysema, or chronic obstructive pulmonary disease (COPD); depression; osteoporosis; anxiety; memory problems or dementia; Parkinson's disease; osteoarthritis or degenerative joint disease; rheumatoid/inflammatory arthritis; cancer; or high cholesterol. The resulting number of comorbidities reported was used as a marker of morbidity. The Strength, Ambulation, Rising from a chair, Stair climbing and history of Falling (SARC-F) screening tool for sarcopenia [158], and the following Fried frailty questions were also included [4]: 'In the last year, have you lost more than 10 pounds unintentionally?' and 'How often in the last week did the following apply? 'I felt that everything I did was an effort' or 'I could not get going'?'

6.2.3 **Statistical methods**

Summary statistics were used to describe baseline participant characteristics and changes in the following aspects of lifestyle compared to before the first UK lockdown: smoking, alcohol consumption, diet quality, amount of food consumed, physical activity, sleep and social contact. Sex-adjusted ordinal logistic regression was used to examine risk of being in a worse category for change in diet quality (compared to before the first UK lockdown) according to various participant characteristics; sex-interaction effects were not statistically significant. Examples of a worse category for change in diet quality would be 'lower than before' as opposed to 'about the same' or 'about the same' as opposed to 'higher than before'. Participant characteristics considered as exposures included: sociodemographic factors, BMI, current health behaviours, number of comorbidities, SARC-F score, and Fried frailty components (unintentional weight loss and self-reported exhaustion). Cross-tabulations of pandemic-related changes in diet quality and physical activity were examined using chi-squared tests and Fisher's exact tests, as appropriate.

All analyses were conducted using Stata (Stata Corp, College Station, TX, USA), release 17.0; $p<0.05$ was regarded as statistically significant. The analysis sample comprised the 491

participants who had data on self-reported change in diet quality since before the first UK lockdown.

6.3 Results

6.3.1 Descriptive statistics

The participant characteristics of the analysis sample at baseline are presented in Table 6-1. Median (lower quartile, upper quartile) age was 79.8 (77.0, 83.7) years; 482 (99.0%) were of white ethnicity; 420 (87.7%) lived in their own property; and 260 (53.4%) were in a current relationship (married/civil partnership/cohabiting).

Changes in lifestyle compared to before the first UK lockdown are presented in Table 6-2. A greater proportion of participants consumed less alcohol than before (11.6% men, 9.8% women) compared to those that consumed more than before (3.7% men, 3.3% women); over 99% of men and women did not smoke or reported no change in their smoking behaviour. Most participants reported no change in diet quality (88.9% men, 85.7% women) with smaller numbers reporting declines in diet quality (4.9% men, 9.4% women) and increases in diet quality (6.2% men, 4.9% women); a similar pattern was observed for amount of food consumed. Considerably more participants reported declines in physical activity, sleep quality and social contact in comparison to the number who reported increases. For example, 36.0% of men and 42.8% of women reported declines in physical activity whereas only 5.8% of men and 6.4% of women reported increases.

Table 6-1: Baseline participant characteristics.[21]

Participant characteristic	Mean (SD), median (lower quartile, upper quartile) or n (%)	
	Men (n= 225)	Women (n= 266)
Age (years)	79.7 (76.7, 83.3)	80.1 (77.2, 84.4)
Education (University degree / HND / Higher professional qualifications)	55 (24.4%)	41 (15.4%)
Living arrangement		
Own property	191 (87.2%)	229 (88.1%)
Rented accommodation	24 (11.0%)	24 (9.2%)
Residential home	2 (0.9%)	0 (0.0%)
Nursing home	0 (0.0%)	0 (0.0%)
Other	2 (0.9%)	7 (2.7%)
Current marital status		
Single	10 (4.5%)	9 (3.4%)
Married or civil partnership	146 (65.8%)	100 (37.7%)
Divorced or separated	22 (9.9%)	22 (8.3%)
Widowed	35 (15.8%)	129 (48.7%)
Cohabiting	9 (4.1%)	5 (1.9%)
Self-reported height (cm)	174.5 (7.6)	160.6 (6.0)
Self-reported weight (kg)	79.4 (11.5)	68.0 (13.6)
BMI (kg/m^2)	26.0 (3.5)	26.4 (5.2)
Ever smoked regularly	135 (60.5%)	95 (36.0%)
Currently drink alcohol	191 (84.9%)	188 (70.9%)
DETERMINE score	3.0 (1.0, 5.0)	3.0 (1.0, 4.0)
Number of comorbidities$^+$	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)
SARC-F score	0.0 (0.0, 2.0)	2.0 (1.0, 3.0)
Lost more than 10 pounds unintentionally in past year	22 (9.8%)	19 (7.3%)
Self-reported exhaustion in the past week*		
Rarely or none of the time (< 1 day)	116 (52.0%)	115 (44.4%)
Some or a little of the time (1-2 days)	66 (29.6%)	76 (29.3%)
A moderate amount of time (3-4 days)	22 (9.9%)	32 (12.4%)
Most of the time (>4 days)	19 (8.5%)	36 (13.9%)

[21]HND: Higher National Diploma, BMI was calculated from self-reported height and weight
DETERMINE: DETERMINE Your Nutritional Health Checklist, $^+$Number of the following doctor-diagnosed conditions: heart attack or angina; stroke or transient ischaemic attack; hypertension; type 1 or 2 diabetes; asthma, bronchitis, emphysema, or chronic obstructive pulmonary disease (COPD); depression; osteoporosis; anxiety; memory problems or dementia; Parkinson's disease; osteoarthritis or degenerative joint disease; rheumatoid/inflammatory arthritis; cancer; or high cholesterol

Table 6-2:Changes in aspects of lifestyle compared to before the first UK lockdown (23/03/2020).

Participant characteristic	N(%)	
	Men (n=225)	Women (n=266)
Smoking		
More than before	0 (0.0%)	0 (0.0%)
About the same	5 (2.2%)	3 (1.1%)
Less than before	0 (0.0%)	1 (0.4%)
Does not smoke	219 (97.8%)	262 (98.5%)
Alcohol		
More than before	8 (3.7%)	8 (3.3%)
About the same	149 (69.0%)	135 (55.3%)
Less than before	25 (11.6%)	24 (9.8%)
Does not drink alcohol	34 (15.7%)	77 (31.6%)
Diet quality		
Lower than before	11 (4.9%)	25 (9.4%)
About the same	200 (88.9%)	228 (85.7%)
Higher than before	14 (6.2%)	13 (4.9%)
Food consumption		
Less than before	27 (12.1%)	27 (10.2%)
About the same	187 (83.5%)	219 (82.6%)
More than before	10 (4.5%)	19 (7.2%)
Physical activity		
Less than before	81 (36.0%)	113 (42.8%)
About the same	131 (58.2%)	134 (50.8%)
More than before	13 (5.8%)	17 (6.4%)
Sleep		
Worse than before	45 (20.0%)	63 (23.9%)
About the same	174 (77.3%)	193 (73.1%)
Better than before	6 (2.7%)	8 (3.0%)
Social contact		
Less than before	156 (69.3%)	176 (67.2%)
About the same	68 (30.2%)	82 (31.3%)
More than before	1 (0.4%)	4 (1.5%)

6.3.2 Predictors of change in diet quality compared to before the first UK lockdown

Cross-sectional associations between participant characteristics and risk of being in a worse category for change in diet quality (compared to before the first UK lockdown) are presented in Table 6-3. The following participant characteristics were associated with increased risk of being in a worse category for change in diet quality after adjustment for sex: lower educational attainment ($p=0.009$); higher BMI ($p<0.001$); higher nutrition risk score ($p=0.004$); higher SARC-F score ($p=0.013$); and self-reported exhaustion in the previous week on at least three days ($p=0.002$). For example, after adjustment for sex, the odds ratio (95% CI) for being in a worse category for change in diet quality was 1.13 (1.06, 1.19) per unit increase in BMI and 2.76 (1.47, 5.18) for those who reported exhaustion in the previous week on at least three days compared to those who did not.

6.3.3 Association between change in diet quality and change in physical activity

Changes in diet quality and physical activity compared to before the first UK lockdown were correlated among men ($p=0.002$) and women ($p=0.007$). For example, among men who did not report declines in physical activity, only 1.4% reported declines in diet quality, compared to 11.1% among those who did report declines in physical activity; corresponding figures among women were 5.3% and 15.0%, respectively.

Table 6-3:Sex-adjusted odds ratios for being in a worse category for change in diet quality compared to before the first UK lockdown according to participant characteristics.

Participant characteristic	Odds ratio (95% CI) [22]	P-value
Age (years)	0.99 (0.94, 1.05)	0.765
Education (degree/HND/professional qualifications vs lower)	0.40 (0.20, 0.79)	*0.009*
Living arrangement (own property vs not)	1.19 (0.52, 2.71)	0.679
Marital status (married/civil partnership/cohabiting vs not)	0.89 (0.50, 1.56)	0.678
BMI (kg/m^2)	1.13 (1.06, 1.19)	*<0.001*
Ever smoked regularly	0.58 (0.33, 1.03)	0.062
Currently drink alcohol	1.36 (0.71, 2.60)	0.347
DETERMINE score	1.16 (1.05, 1.29)	*0.004*
Number of comorbidities	1.07 (0.91, 1.26)	0.435
SARC-F score	1.19 (1.04, 1.36)	*0.013*
Lost more than 10 pounds unintentionally in past year	1.44 (0.55, 3.76)	0.458
Self-reported exhaustion in past week (≥3 days vs <3 days)	2.76 (1.47, 5.18)	*0.002*

6.4 **Discussion**

This study has described changes in lifestyle factors and examined correlates of change in diet quality compared to before the first UK national lockdown in March 2020. Although self-reported changes in alcohol consumption and smoking were minimal, considerably more participants reported declines in physical activity, sleep quality and social contact in comparison to those who reported increases. Most participants reported no change in diet quality with small proportions reporting declines or increases in diet quality. However, the following were associated with increased risk of being in a worse category for change in diet quality after adjustment for sex: lower educational attainment; higher BMI; higher DETERMINE score; higher SARC-F score; and self-reported exhaustion. This suggests that there is a small subset of older community-dwelling adults whose diet deteriorated over the first year of the COVID-19 pandemic. Worryingly, this included individuals with a higher DETERMINE score, a score used by health professionals to identify older adults at risk of malnutrition and/or higher SARC-F score, where a cut-off of 4 or higher is suggestive of sarcopenia and poor outcomes.

[22] Odds ratios were estimated using sex-adjusted ordinal logistic regression models

Our results are in accord with previous work where in a study of Dutch adults, younger generations were more likely, when compared to older generations, to be influenced by COVID-19 lockdowns and to change their eating behaviours [291]. This observation was also supported by a recent systematic review looking into the impact of the COVID-19 pandemic on diet where 6 out of 10 studies examined observed no significant changes in dietary habits of older adults [292]. However, the included studies were heterogenous in findings, and did not consider correlates of dietary decline or associated health outcomes. For example, in 2 studies, no more than 50% of participants were found not to have altered their dietary habits [293,294].

In other work, older participants tended to be less likely to report changes in food behaviours, overall diet healthfulness, and food security compared to younger participants in the International Food Policy Study conducted across 5 countries [295]. Other researchers have reported that age was negatively associated with healthy dietary change [296,297] and increased intake of junk food [298]. Constant et al. found that individuals aged 40-60 and 60+ years were around 20% less likely to have made a “positive” lifestyle change in eating habits during the lockdown period in France [299]. Similar findings were reported in a recent study by Bevilacqua et al. of participants from two UK cohorts of community-dwelling older adults: during the first months of the pandemic, individuals from the younger cohort (median age 65 years) reported more negative changes to their diets when compared to those from the older cohort (median age 84 years) [300]. In addition, Bevilacqua et al. reported that younger women were more likely to have increased their food intake and reduced the quality of their diet compared to men [300], a tendency that we also notice in our sample population, with more women than men reporting both a decrease in diet quality (9.4% vs. 4.9%) and an increase in food intake (7.2% vs. 4.5%); however, in our study this difference was not statistically significant. Quarantine due to the COVID-19 pandemic had a negative impact on physical and mental health as well as on lifestyle in older adults from five Central American countries; a greater effect was reported on having a balanced diet, frequency of falls, and functional ability amongst others [301]. Luo et al, also report that older individuals were more likely to change dietary habits during the pandemic [302].

Differences in socioeconomic status and food availability, especially during the early phases of the pandemic, may account for some of the differences observed between studies. Energy-dense foods with high sugar and fat may be cheaper and more palatable, with access different in different groups of adults in different countries [303]. Lower educational attainment was associated with an increased risk of being in a worse category for change in diet quality in our cohort. Participants with higher adherence to a Mediterranean diet during the COVID-19 pandemic were more likely to have a higher education level in a study in Spain; education level was related to following a Mediterranean diet while advised to stay at home during early pandemic restrictions [304]. Higher educational level has been commonly associated with higher socioeconomic status which is often related to better diet quality [303]. Finally higher education levels predict an increase in healthier dietary patterns in non-COVID related studies [305].

While dietary change during the pandemic has been studied by other researchers (29,30), far fewer have considered much older adults. The dietary habits of older people living with frailty may have been more strongly affected by social isolation during the COVID-19 pandemic than those who were not frail as reported in one study. In addition, reduced food shopping times during social isolation was significantly higher among frail individuals while frail older adults consumed less high-quality proteins but more protein rich foods and vegetables which might indicate an attempt to improve dietary habits [306]. These observations accord with our work where self-reported exhaustion, one of the elements of the Fried Frailty criteria, was associated with an increased risk of being in a worse category for change in diet quality. Finally, our study complements qualitative work of dietary habits during the pandemic in smaller groups of older adults (32).

This study has some limitations. First, all information was ascertained through self-reported questionnaires. Second, recall bias may have occurred as participants reported changes in lifestyle factors since the UK national lockdown instead of reporting current lifestyle behaviours at two separate time points before and after the lockdown. Third, investigating the impact of having COVID-19 or experiencing COVID-19 related symptoms on changes in lifestyle factors was not

possible as only a very small proportion of participants had a confirmed COVID-19 infection. In our study, 1993 patients were invited to participate in the study by postal invitation which led to the return of 516 complete questionnaires (26% response rate). However, a previous study which tested the feasibility of setting up a UK sarcopenia registry only achieved a 12% response rate when potential participants aged 65 and over were approached via mailshots from local primary care practices [307]. This suggests that our response rate was not unusually low, given that we were contacting participants from the general population. Finally, as in all cohort studies, participants who consented to be included are likely to have been healthier than those who refused. However, as our analyses were internal, substantial bias should only have been introduced if the associations examined differed markedly between those who participated in the study and those who did not; this seems unlikely. To confirm this, we assessed demographic characteristics of our populations against national survey data for England; prevalence of current smoking in our analysis sample (men 3%, women 2%) was slightly lower than reported among participants aged 75 years and older from the nationally representative 2019 Health Survey for England (https://files.digital.nhs.uk/2E/B925DF/HSE19-Adult-health-behaviours-tab.xlsx) (men 6%, women 6%) [308]. However, these are fairly similar, given the variability expected from the reasonably small SaLSA sample and also the Health Survey for England which reported a 3% current smoking prevalence among men aged 75 years and older in 2018. However, mean BMI in our analysis sample (men 26.0, women 26.4) was slightly lower than reported among participants aged 75 years and older from the 2019 Health Survey for England (https://files.digital.nhs.uk/DE/D1D9C5/HSE19-Overweight-obesity-tab.xlsx) (men 27.6, women 27.7), suggesting that our cohort may indeed be slightly healthier than national averages [309].

6.5 Conclusion

Older individuals are a particularly vulnerable population for COVID-19 infection and were commonly advised to shield to reduce exposure to the virus, which may have impacted access to usual food choices. We have found that greater nutritional risk and sarcopenia risk were associated with being in a worse category for change in diet quality, highlighting the need to

consider this when providing support for shopping and nutritional guidance to older adults in any future pandemics.

Chapter 7. Overarching discussion

As part of this thesis, existing data were analysed from the Hertfordshire cohort study to consider relationships between ageing bone and muscle. A close relationship was identified between bone and muscle loss in later life, and we determined that co-existence of sarcopenia and osteoporosis is associated with higher morbidity from falls, fracture, disability, as well as mortality [42,43]. In the first publication (Chapter 3 - 10.1002/jcsm.12870), the relationship between both conditions, and how these relate to frailty are described. Additionally, the prevalence of frailty and pre frailty in the study sample was examined. These associations are ill-understood as they have been previously examined in a few studies [60,188,195–197,310]. Having sarcopenia alone was strongly associated with frailty in the cohort examined, while the association between having osteoporosis alone and frailty was weaker. The likelihood of being frail was substantially higher in the presence of co-existing sarcopenia and osteoporosis.

As the definition of frailty and sarcopenia share similar components, the above-mentioned relationships were anticipated. Hence, the relationship with multimorbidity as another representation of frailty was considered. Having sarcopenia alone and osteoporosis alone were both associated with having 3 or more comorbidities, though this relationship was not stronger with co-existing sarcopenia and osteoporosis. Co-existence of sarcopenia, osteoporosis and frailty was observed in 1% of this population. Two percent of the study sample had sarcopenia and osteoporosis and most participants (73%) had no evidence of sarcopenia, osteoporosis, or frailty. Amongst the participants with frailty, 27.8% were sarcopenic, compared with 8.9% in the pre-frail and 4.0% in the non-frail categories. Frailty was also more common in older participants in this sample.

As the co-existence of sarcopenia and osteoporosis were highly associated with frailty; early identification, intervention and treatment of these conditions could reduce the development of frailty. Furthermore, identifying and treating individuals with pre-frailty and probable sarcopenia, early and in reversible risk-states, may be associated with better healthcare outcomes and lower

risk of developing frailty. Research advances have led to a more accurate assessment of fracture risk and have increased the range of therapeutic options available to prevent fractures. The fracture burden, attributable to osteoporosis alone, is projected to increase; policy-driven development of case finding and treatment of at-risk of osteoporosis population could lower this burden, preventing 6.1 million fractures over the next 22 years while reducing payer and societal costs by $29 and $55 billion, respectively [311]. Conversely, current methods to diagnose sarcopenia are effective only after the onset or progression of the disease (e.g. loss of muscle mass, mobility and disability); current treatment includes nutrition and exercise programmes which might not be adequate in managing more severe cases of sarcopenia [312]. Therefore, determination of factors and predictors of sarcopenia in routine clinical practice is essential, as well as the recognition of individuals at risk of developing sarcopenia and/or osteosarcopenia.

Novel, quicker, and accurate methods of assessing muscle health have value in routine clinical practice. Historically, measurements of muscle quantity have been commonly used in case finding for sarcopenia. However, the reported lack of association between the loss of muscle lean mass and strength with ageing has underscored the need to assess muscle quality, rather than quantity [313]. Muscle density is a proxy measure for muscle quality and is thought to be impacted by an interplay between fat and muscle, an important pathophysiological mechanism in sarcopenia, as discussed in this study (Chapter 1, 1.1.5).

Having examined the relationship of sarcopenia and osteoporosis in the HCS, the determinants of muscle density in this cohort were studied. In the second publication (Chapter 4 – final revisions submitted to the journal Bone), demographic, and anthropometric (female sex, older age, and lower BMI), rather than lifestyle factors, such as physical activity and diet, were associated with lower muscle density as measured by pQCT. Forearm muscle density was associated with previous fractures rather than history of falls. These findings provide further insights into the determinants of future muscle density and the associations of muscle density with clinical outcomes such as falls and fractures in a well characterised community-dwelling cohort of older adults. pQCT-derived muscle density could provide a biomarker to further complement the musculoskeletal

health assessment in older adults and further studies are now warranted. Changes in muscle density over time might precede adverse outcomes such as falls and fractures and may be a long-term predictor of frailty. Therefore, muscle density could be a more clinically meaningful surrogate of functional decline and disability than muscle size or mass, but more in-depth studies in contemporaneous cohorts are needed to support this notion.

Having determined the factors associated with future muscle density and the relationship between muscle density measures and the clinical outcomes of falls and fractures, the same associations of other sarcopenia components, including grip strength, muscle mass and gait speed were explored. As previously described (Chapter 1,Figure 1-1) muscle strength and mass are appropriate tools used to identify individuals at risk of and with sarcopenia. Hence, it is important to understand their associations with adverse outcomes such as falls and fractures.

In the third paper (Chapter 5 – 10.1007/s00223-022-00986-w), higher grip strength was found to be related to lower risk of falls and fractures since the age of 45 years. Greater muscle size was also associated with both reduced risk of falling and fewer falls in the previous year. These findings support previous evidence that muscle strength is a key characteristic in detecting older adults at risk of adverse outcomes including falls and fractures [35]. Muscle strength, especially handgrip strength, has been proven to be a valid and clinically practicable test for screening early onset sarcopenia [11]; it has been associated with the strength of other muscles making grip strength a possible singular indicator of overall strength [314] and it is thought to be a better indicator of overall strength if used in conjunction with a measure of lower limb strength [315,316]. Even though grip strength is not directly required for the performance of functional activities such as walking, it has been proven a criterion able to distinguish older adults on the basis of their mobility and functionality [317–319].

Sexual dimorphism is present in the observed relationships and in accord with previous literature, although previous studies have suggested important relationships between muscle measures and bone outcomes particularly in males [183] in contrary to the findings of this study showing such an association in females. Sexual dimorphism in the development of the skeleton and in the

incidence of skeletal diseases is well described in the literature [320]. The risk of falling and fracture has been previously described to be higher in females [185,321–326]; the reasons for the differences are multiple and include the actions of sex steroids, genetics, and immunity [327,328]. Sex differences in the prevalence of sarcopenia are also reported and might therefore affect the risk of falls and subsequent fractures [329]. Epidemiological data for discordance in sarcopenia prevalence between older males and females have been conflicting [329,330]. Therefore, sex differences should be considered when studying outcomes in older adults [35,269,324] .

Gait speed was not associated with falls and fractures in the examined cohort. In the same cohort, gait speed was found previously not to be associated with bone measurements, such as bone size, strength, and density[9]. Gait speed has been previously reported to be associated with muscle strength and incident fractures, change over time in older adults, reflect health and functional status, and be associated with survival in older adults [272–274,331–334]. It is also a suitable metric for screening poor physical performance and is used to identify cases of severe sarcopenia [35]. However, it can be affected by factors other than sarcopenia, such as gait ability and severe weakness that leads to falls and fractures [276]. Therefore, gait speed combined with other physical performance measures, such as chair stand tests, might perform better as a predictor of falls and fractures when assessing community dwelling older adults [275,335,336].

Further longitudinal large studies are needed, to better understand the life course influences on muscle and bone health. Given the burden of musculoskeletal disease in late adulthood, research in this age-group group is crucial. Although the rationale for such studies is clear, the feasibility of establishing a cohort of septa and octogenarians during a global pandemic is untested.

To take this work further, the inception of a new cohort of community-dwelling older adults is described in Chapter 2, section 2.2. SaLSA was established during the COVID19 pandemic when many older adults' lifestyle was significantly impacted. The coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organisation in March 2020. To date, the rapid spread of this virus has brought to more than 360 million of infections and caused the death of well over 5 million

people globally (https://covid19.who.int/table, World Health Organisation, accessed 27 Jan 2022). In the early stages of the pandemic, several countries introduced a number of measures and restrictions aimed at reducing human-to-human transmission of the disease; these included social distancing, staying at home requirement, and prohibiting gatherings. Older adults were deemed particularly vulnerable to the COVID-19 virus, with increased risk of disease severity, morbidity, and mortality. The United Kingdom entered its first national lockdown in March 2020. While the social distancing and self-isolation strategies proved successful in reducing numbers of new infections, hospitalisations, and deaths, they may have had a negative impact on lifestyle factors such as physical activity and diet. This was explored in HCS and Health and Employment After Fifty Study (HEAF) study; a younger cohort of participants with a mean age of 65 years. Changes in alcohol intake and eating habits, with negative changes taking place more frequently in the younger cohort and among women, were recorded during the 1st wave of the pandemic. Physical activity levels decreased for high proportions of respondents in both cohorts while age and sex were suggested to determine the impact of the lockdown on lifestyle factors [300].

The SaLSA data were analysed considering the findings from the HCS and HEAF that eating habits, diet, and other lifecourse factors such as physical activity, alcohol intake and smoking decreased during the pandemic. Pandemic related changes in diet were reported and their correlation to changes in diet quality were examined. Lower educational attainment, higher BMI, higher nutrition risk score determined by the DETERMINE score, higher SARC-F score, and self-reported exhaustion in the previous week on at least three days were associated with increased risk of being in a worse category for change in diet quality. This showed that there is a small subset of older community-dwelling adults whose diet deteriorated over the first year of the COVID-19 pandemic; those individuals were identified as an at-risk population for malnutrition and frailty.

It is now apparent that older individuals are particularly vulnerable to lifestyle changes. Understanding lifestyle factors that may lead to accelerated musculoskeletal ageing is important as it allows us to consider the possible preventative strategies we may adopt in the future. Using SaLSA, I aim to establish relationships between muscle and bone micro-architecture in more detail

and to consider further the impact of the COVID19 pandemic on other lifestyle factors relevant for musculoskeletal health; future plans for this cohort are described below, and in the next section (7.2-Future work). The clinical outcomes of particular interest are fractures and frailty. Fractures are important as they are associated with a huge personal and public health burden, as described in Chapter 1. Individuals with both sarcopenia and osteoporosis are described as being at increased risk of developing frailty as described in Chapter 3. Frailty is of great importance as it impacts ability to self-care and live independently.

Prospective data collection in SaLSA, the detailed phenotypic characterisation of participants including physiological measurements over time, and the follow up for incident clinical events and mortality is paramount to ageing research.

7.1 Limitations and challenges

7.1.1 Hertfordshire cohort study

7.1.1.1 Study cohort

The HCS cohort participants are a unique group of individuals. All participants were born in Hertfordshire and have either remained there throughout their life or left and returned to live there again in older age. This might suggest that might be different to people that migrate to different geographic locations during their lifetime. Hertfordshire has a markedly higher proportion of residents with higher qualifications and higher level of earnings than nationally [337].

It is well recognised that recruiting participants from ethnic minority communities can be difficult and challenging [338]. Despite efforts to increase diversity in research, racial/ethnic groups remain underrepresented [339]. All participants were Caucasian in the HCS cohort [340]. Participants in the HCS cohort study are all community living, and therefore might be expected to show a healthy cohort bias, limiting our ability to discern some relationships.

In a sub study of HCS, the Hertfordshire Ageing Study, between the first (1994-1995) and second follow up study (2003-2005), mortality in the intervening period was associated with poorer cognition, poorer grip strength, greater likelihood of having no teeth, and a higher prevalence of smoking, memory problems, fracture since the age of 50 years and slow walking speed at the first follow-up in men [341]. Among women, mortality was associated with somewhat poorer cognition, a higher hearing threshold, and a poorer assessment of how the woman felt for her age at the first follow-up [341]. It is therefore clear that the representativeness of the participants in HCS cohort might be questioned, and survival-related selection bias might be present. However, when comparing the ageing characteristics of the HCS ageing study participants with those in the nationally representative Health Survey for England were comparable despite small reported differences in grip strength and chair stand rises [341].

Unsurprisingly, some cohort member differences have been reported in demographic and anthropometric parameters, when compared to national figures, but these were small [144]. Lower rates of smoking and alcohol intake, high dietary calcium intakes, and better self-related general health were reported in the HCS, providing some evidence of a healthy participant effect [144]. This is reflected by the relatively low number of sarcopenic and frail individuals, and by the fact that participants for whom data were available at follow up and developed frailty, were overall healthier (Chapter 3). They were younger, heavier, taller, stronger, faster walkers and had better physical activity compared to those for whom data were not available on incidence frailty. We suspect that the lack of association of calf muscle density in our cohort with prior fracture reflects a health survivor bias making calf muscle density less reflective of functional limitations, whereas forearm muscle density may be more reflective of site-specific loading on the radius as described in Chapter 4.

Additionally, we found evidence of sex differences in our cohort (Chapter 4). While the sex differences noted in our study insights into potential differential sex-specific mechanisms, a healthy bias in males, as indicated by the relatively higher mean of grip strength and gait speed, and the use of specific cut-off points to define each sarcopenia components should also be

considered as a contributing factor to the absence of associations between sarcopenia and falls and/or fractures in males.

However, HCS participants have been compared with those in the nationally representative Health Survey for England and have been found to be broadly comparable in terms of their health and lifestyle [144]. We have also demonstrated that the Hertfordshire population studied have similar bone density relative to national figures [144]. We therefore suggest that the results from the current studies could be reasonably generalised to the wider population of Caucasian older males and females. However, it must be taken under consideration when interpreting the results that since the cohort is made up of community dwelling individuals from a specific geographic region, generalisability of these findings to less healthy, institutionalized groups or from other geographical regions and of different ethnic origins may be limited.

7.1.1.2 Data from questionnaires

Data collected in the HCS tend to be self-reported rather than objectively measured. However, questionnaires were administered according to strict protocols by highly-trained fieldworkers [143]. Non vertebral fracture status was ascertained at each phase of follow up and as with the fall's history, demographic and lifestyle factors, it was self-reported. Data were not available to distinguish between high and low trauma, upper or lower limb fractures so the number of fractures were used for analysis; this may constitute another limitation, as low trauma fractures are the recognised clinical outcomes of osteoporosis [342]. It seems likely that a high proportion of fractures were upper limb distal forearm fractures, as the majority occurred in women in midlife [326]. However, individuals with osteoporosis compared to healthy individuals, suffer fractures from high-energy trauma at a greater frequency [343].

7.1.1.3 Definitions

7.1.1.3.1 Multimorbidity

Multimorbidity is recognised to be the co-existence of multiple health conditions ($\geq$ 2 long term conditions) in an individual [344,345]. Multimorbidity is a growing public health challenge as it has

been associated with poorer outcomes and increase of health care and social care systems with associated costs [346]. There is no international consensus in regards to the best way to define and measure multimorbidity; its prevalence varies across population examined and differences in the operational definition of multimorbidity [344,347].

We have used the number of self-reported comorbidities to assess for multimorbidity which is believed to be an acceptable way in predicting outcomes [348]; we defined multimorbidity the presence of 3 or more comorbidities. Simple counts of diseases or medications perform almost as effectively as complex measures in predicting most outcomes [347]; the most common cut-off being two or more [347]. It has been suggested that an attempt to define multimorbidity using a cut off of 3 or more co-existent diseases would permit an accurate estimation of the prevalence of multimorbidity, and likely its association with adverse clinical outcomes [345]. The prevalence of multimorbidity is certainly affected by the cut-off selected and it is expected that a higher cut-off would select individuals with a higher burden of multimorbidity; this limitation should be considered in our study and could affect its generalisability.

7.1.1.3.2 Sarcopenia

As previously described in Chapter 1 (1.2), several scientific groups have developed operational definitions and diagnostic criteria for sarcopenia from 2010 to date [35,40,41,349,350]. The prevalence of sarcopenia based on different definitions can vary significantly and the agreement between definitions is reported to be very low. Few studies have examined the association between different definitions of sarcopenia and clinically relevant outcomes such as falls and fractures [210,274,351–354], identifying further discrepancy and variation, making the choice of sarcopenia definition to be an important part of a study methodology. We defined sarcopenia for this thesis according to EWSGOP 2019 criteria [11]. This might have contributed to the low numbers of sarcopenic individuals we report in our studies. In a recent systematic review, the prevalence of sarcopenia in older adults decreased by ~ 7% when diagnosed according to EWGSOP 2019 compared to EWGSOP1 2010 criteria, suggesting that EWSGOP2 2019 criteria might be a worse predictor of unfavourable clinical outcomes [355]. Similar reports exist when

assessing the prevalence of severe sarcopenia, highlighting the variety in reporting sarcopenia prevalence [356]. Other studies have suggested that the prevalence was more dependent on cut-offs than on operational definition, and that differences between EWSGOP1 and EWSGOP2 criteria were small [357,358].

Some of these conclusions are based on limited evidence and more studies are needed evaluating which sarcopenia consensus better predicts adverse health outcomes and mortality in older adults The use of different diagnostic criteria may lead to different conclusions and may have different implications for treatment, so reaching a concordant diagnostic criterion will enable the translation of research findings into clinical practice.

7.1.1.3.3 Gait speed

Two main types of gait speed assessment exist: the short-and long-distance gait test. In a systematic review, was reported that the overall median absolute gait speed results were faster for longer (6 to10 meters) than for shorter distances (2.4-5 meters) [359], while a statistically significant, but clinically irrelevant, difference of 0.01 m/sec between gait speed measured over 2.4 m and 6.1 m distances also reported [360]. Some groups favour the use of long distance gait speed for its established relationship to mobility disability and public health relevance [277,278]. Conversely, short gait tests can be used as surrogates for long-distance speed tests for the assessment of functional status in older adults [361,362], and are easily implemented into clinical practice [11,279]. For the above-mentioned reasons, we used the short distance gait tests.

7.1.2 Southampton Longitudinal Study of Ageing

7.1.2.1 Study cohort

SaLSA is unique as it will allow the assessment of the feasibility and practicality of recruiting older adults from the community who are likely research naïve. It will establish a platform for future observational and interventional studies to identify at risk groups or normal ageing participants. The cohort data will enable the development and evaluation of interventions targeted at

improving health care outcomes for older adults. Specifically, data will be used to identify at-risk groups such as osteoporosis, sarcopenia, osteosarcopenia and/or frailty.

A particular challenge of this work has been its initiation while the pandemic is continuing. Recruitment of participants to non-COVID related studies has been negatively impacted worldwide [363,364]. Hospital attendance at scheduled appointments have dropped significantly[365,366]. The rollout of vaccinations have undoubtedly altered the trajectory of the pandemic and might have an effect on reducing anxiety of participants attending clinics [367].

However, recruitment of community participants for clinical research studies has been and continues to be challenging in context of primary care workload, staff availability and time constraints [368,369]. However, through SaLSA, I have shown that recruiting participants from general practice is feasible.

There are of course limitations to our SaLSA including the low number of non-Caucasian participants currently recruited, and our decision to exclude residential and nursing home residents, which might affect the implementation of our results to this group of older adults. Recruiting participants other than Caucasian is proven even more challenging due to lack to time and access to these groups. We are currently working with the LWP PPG group in understanding and finding ways of recruiting participants from other ethnic groups in SaLSA; it is proposed that access to faith groups in the community might enable to promote our research in these groups. Flexibility, and respecting of cultural and religious sensitivities were previously highlighted as key factors to promote participation in research [370]. Growing internet use among racial and ethnic groups represents an opportunity to invite, design and even deliver intervention via the internet [368]. We will consider the characteristics of our study population against national census data at the conclusion of phase 1 of this study.

7.2 Future work

There are a number of plans for future work arising from this thesis. There is an aspiration to perform detailed muscle and bone phenotyping in SaLSA as described in Chapter 2, section 2.2.2. This will allow us to investigate further the muscle-bone crosslink. In future work in SaLSA another exciting area of sub-study is in-depth muscle and bone phenotyping. Muscle–bone interrelationships was previously explored in the HCS [9,162], but SaLSA provides an opportunity to perform detailed investigation of bone trabecular and cortical microarchitecture using HRpQCT [163–167], muscle ultrasound [54], and muscle biopsy—a technique which we have previously shown to be acceptable to older adults [161].

I have already described in Chapter 1 that both genetic and environmental factors are important for sustaining musculoskeletal health [371] (Figure 7-1). Current challenges with regard to the genetics of osteosarcopenia include lack of GWAS focused on the aged population and of a functional annotation for a majority of identified variants and loci. Focus on the population at risk of osteosarcopenia is required in parallel with applying sophisticated phenotyping and SaLSA could provide this opportunity. An example was made from the collaboration of the Hertfordshire Sarcopenia Study (HSS) with Multi-ethnic MOLecular determinants of human SArcopenia (MEMOSA) study where cutting edge scientific techniques, such as deep sequencing of RNA as well as high coverage methylation arrays, were examined [143]. Our vision is to create a biobank from muscle cells obtained from biopsies of older males and females' participants in SaLSA, that will have been cultured in vitro, and together with RNA and methylation data, will permit the investigation of genetic and epigenetic pathways in musculoskeletal ageing. Telomere attrition and epigenetic alterations could also be associated with age related conditions and SaLSA could provide an opportunity to study these associations further. Research involving human participants, are valuable to address questions pertaining to skeletal muscle biology and regeneration.

Studies such as SaLSA are critical, as muscle–bone crosstalk is an important and an emerging area of research. Pathophysiological findings are common to both sarcopenia and osteoporosis, thus suggesting that the two are closely linked (Figure 7-1) [170]. Given the interrelation between bone and muscle, future studies, such as SaLSA, might allow us to develop comprehensive methods in order to identify new factors that contribute to this dynamic muscle-bone crosstalk and gain a better insight into biomarkers with potential diagnostic and therapeutic value as well as epidemiological studies to understand the lifecourse influences leading to osteosarcopenia [372].

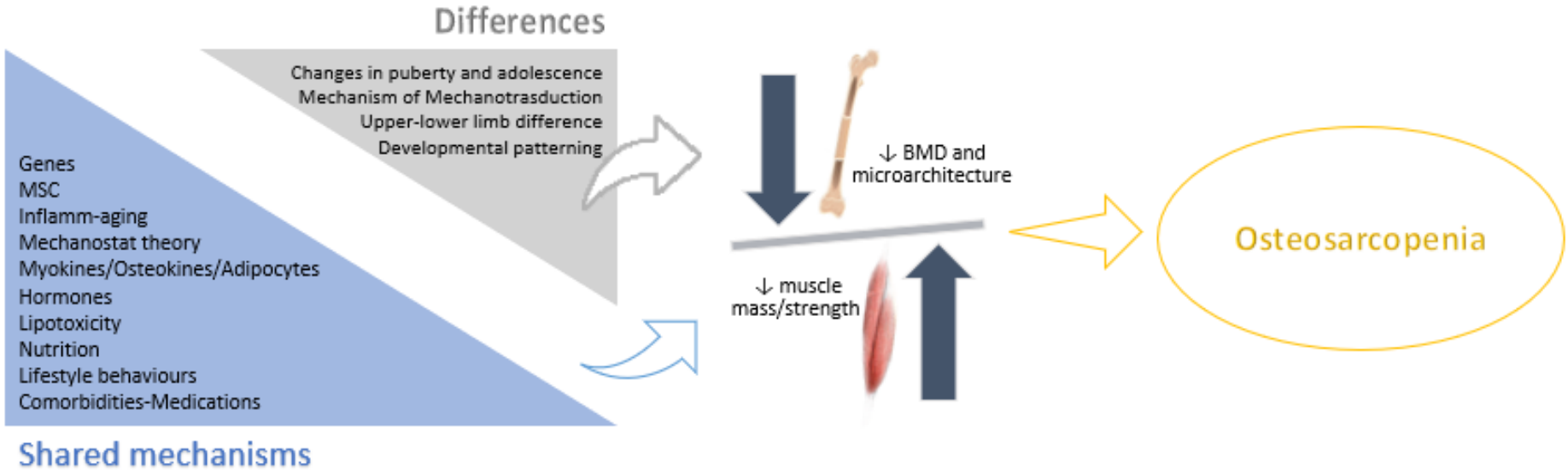


Figure 7-1: Shared mechanisms and differences in 'muscle-bone unit' progressing to osteosarcopenia

Imaging modalities have been developed in recent years for the more accurate identification of those individuals with sarcopenia. The implementation of ultrasonographic assessment of muscle in the study of sarcopenia is relatively new; ultrasound is a reliable and valid imaging tool for the assessment of skeletal muscle mass; muscle thickness is the most common parameter used in the assessment of sarcopenia [373–376]. Cross sectional area, fascicle length, pennation angle, strain ratio, shear modulus, elastic modulus, shear wave velocity and microvascular blood measurements (volume, velocity, and flow) are the sonographic parameters assessed in previous studies [374]. The identification of the best anatomical site of assessment is of paramount importance and conflicting evidence exists in this matter, which requires further justification and research [373,377,378]. The applications of this technique seem promising and particularly in situations where dual-energy X-ray absorptiometry (DXA) or other imaging modality is not feasible for the assessment of sarcopenia. We are aiming to investigate the use of ultrasound for the assessment of sarcopenia in SaLSA and compare its use to HRpQCT and DXA scan.

Other future sub studies could also explore determinants related to healthy ageing including relevant psychosocial factors such as isolation, attitudes to ageing, social networks, satisfaction with life and many more. The impact of musculoskeletal diseases and frailty on the ability to self-care has been previously explored in HCS, indicating that musculoskeletal diseases are associated with informal receipt of care, and the presence of two or more of these diseases convey similar informal care requirements to those living with frailty [379]. Additionally, sleep quality is a fundamental aspect of optimal health and function [380], showing to decrease with age [381]. Association with sleep duration to osteoporosis has been previously made. Perceived sleep quality is shown to be associated with altered bone density and microarchitecture in older adults in HCS, and these differences varied according to biological sex and site [382]; these association can be further explored in SaLSA.

7.3 **Concluding comments**

The occurrence of musculoskeletal health disorders is expected to increase in proportion with the ageing population. Ageing is closely associated with loss of bone and muscle, two interdependent

organs. In this study, the presented evidence suggests that the combination of sarcopenia and osteoporosis increase the risk of frailty, contributing to poorer health outcomes in older individuals. Further insights into the determinants of muscle density, a surrogate of muscle quality, and the association of muscle density to falls and fractures were provided, suggesting that pQCT-derived muscle density could become a meaningful clinical biomarker for predicting sarcopenia. Muscle mass and strength were, on the other hand, associated with falls and fractures in females only, demonstrating sexual dimorphism, and supporting evidence that muscle strength, measured by handheld dynamometers, is a valuable mean in identifying older adults at risk of adverse clinical outcomes.

Lifestyle factors are believed to play a central role on muscle and bone loss and are associated with better musculoskeletal health in later life. Changes of these lifestyle factors were examined in this study using the SaLSA cohort. Respondents that reported deterioration in diet quality during the pandemic were found to be at higher risk of malnutrition and sarcopenia. Further investigating the factors leading to these changes, understanding of whether they are reversible, and recognising the consequences to the musculoskeletal health is required.

By establishing an interdisciplinary team of investigators, SaLSA will lead to novel research projects, facilitate the introduction of novel, in-depth bone and muscle assessments, and highlight their importance in day-to-day clinical practice. SaLSA will also promote training opportunities for early career researchers conducting both quantitative and qualitative studies. Adopting a community-based recruitment strategy will allow for an efficient coordination of activities between researchers in university, secondary care establishments and the community. SaLSA has set an example and will allow the establishment of a unique community dwelling cohort which in time will provide clinicians, researchers, and policymakers with insights in improving health care of the community dwelling older people.

Appendices

Appendix A HRA and Health and Care Research Wales (HCRW) Approval Letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS Health Research Authority

Dr Harnish/ HP Patel
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17 March 2021

Dear Dr Patel

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**LIFESTYLE, MUSCULOSKELETAL HEALTH AND WELLBEING IN OLDER ADULTS DURING COVID-19 PANDEMIC**
IRAS project ID:	**288051**
Protocol number:	**RHM MED1757**
REC reference:	**21/SC/0036**
Sponsor	**University hospital Southampton**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **288051**. Please quote this on all correspondence.

Yours sincerely,
Gemma Warren

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Mrs Sharon Davies-Dear*

Appendix B MSK Southampton invitation letter

Letter of invitation

LIFESTYLE, MUSCULOSKELETAL HEALTH AND WELLBEING IN OLDER ADULTS DURING COVID19 PANDEMIC

Dear[insert salutation and name],

We are writing to invite you to participate in an important research study called "Lifestyle, musculoskeletal health and wellbeing in older adults during COVID19 pandemic". This study is part of a research project that is funded by the National Institute for Health Research (NIHR) in Southampton.

Good bone and muscle health are crucial for independence in daily living. We know that nutrition and exercise affect bone and muscle health. Many people's lifestyles have changed a lot since the start of the pandemic, and the purpose of this study is to understand what impact changes in lifestyle may have had on muscle and bone health. We also hope to study the impact of COVID19 infection on muscle and bone health in those people who suspect, or know, that they were infected by COVID19.

We hope to obtain information by asking you to complete a questionnaire and this may help inform the development of future beneficial interventions to improve musculoskeletal health.

Your participation in this study is completely voluntary. There are no known risks to participation and your responses will remain confidential.

In the future, we hope to invite people to attend a research clinic where we would assess physical performance, such as your muscle strength and how fast you can walk as well as bone and muscle quantity through simple tests such as bone density scans and blood tests. For this reason, we will also ask you if you would consider receiving information in due course about attending this research clinic.

This study may be beneficial to you by having your muscle and bone health assessed by specialists in musculoskeletal health who can advise you, where appropriate, on ways to improve your muscle and bone health. Relevant information that may be generated by this study will be shared with your GP for future care. This unique population-based study of older men and women is the first of its kind in Southampton and you will be part of pioneering this as well as future studies.

Attached with this letter are the following: a patient information sheet; two consent forms (one copy is returned and one copy is retained by yourself); the questionnaire we ask you to complete, a contact detail form if you would like to hear more about future studies and a prepaid envelope. Expressing an interest now does to commit you to anything in the future.

If you have any questions about this study, please feel free to contact the research team at any time by email (faidra.laskou@soton.ac.uk) and/or by phone (**07883421614**).

Thank you very much for taking the time to read the provided documents and for considering taking part in this study.

Yours sincerely,

Dr Faidra Laskou, Senior Research fellow and Specialist Trainee in Rheumatology

Dr Harnish Patel, Consultant Physician in Geriatric Medicine, Southampton General hospital

Appendix C MSK Southampton study - Participant information sheet

Participant ID:

LIFESTYLE, MUSCULOSKELETAL HEALTH AND WELLBEING IN OLDER ADULTS DURING COVID19 PANDEMIC

Participant Information Sheet

We would like to invite you to participate in an important research study which is part of a postgraduate research project [Doctor of Medicine (DM)] that is funded by the National Institute for Health Research (NIHR) in Southampton. Before you decide, it is important for you to understand why the research is being done and what it will involve. This form gives detailed information about the research study and is yours to keep. Please take time to read the following information carefully and discuss it with others like members of your family, if you wish, before you decide to take part. Please ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

The loss of bone and muscle with age are called osteoporosis and sarcopenia, respectively. These conditions can have a significant effect on an individual's health and wellbeing, and may be interconnected, leading to frailty, risk of falls and fractures. We know that many factors affect bone and muscle function in later life, including illnesses, physical activity levels and dietary factors. In the current COVID19 pandemic we anticipate that these relationships may have been affected and, in this study, we hope to understand how restrictions on lifestyle, and possible COVID19 infection, may have affected muscle and bone function.

We aim to gather information, on lifestyle, diet and physical activity factors which affect muscle and bone health with the use of a questionnaire. We also hope to determine your interest in taking part, in a face to face research clinic in Southampton General hospital at a later stage, where we would test physical performance, bone and muscle health through simple non-invasive tests in order to better measure muscle and bone health in more detail. During the current lockdown restrictions we do not think is appropriate to conduct face to face visits, so at this stage we simply ask you to complete the questionnaires attached and to let us know if you want to continue participating in the study in due course; if continuing in the study is something you would rather not do, please let us know. We would be very grateful if you would still consider completing the questionnaires. We quite understand that people's

circumstances change, and an expression of interest now does not commit you to anything at any time and you are welcome to withdraw at any time as it will not affect the care you get from your doctor in any way.

Why have I been chosen?

We are asking you to consider participating in this study because you are an adult over the age of 75 years registered with the Living Well Partnership (LWP). You have been identified by your GP surgery as someone who would be eligible to be approached and they have forwarded our letter and information pack for this reason.

Do I have to take part?

No, this is entirely up to you. If you would like to take part, you will be asked to sign a consent form. Even after you have signed this consent form and agreed to join the study, you are free to withdraw from the study at any time. If you decide not to take part, or withdraw from the study, it will not affect any future interactions that you may have with your GP surgery. **Please inform any member of the research team if you no longer wish to participate in the study.**

What will happen to me if I take part?

You have been sent 6 documents:

1. A cover letter,
2. Participant Information Sheet
3. The consent forms
4. The questionnaire
5. A pre-paid envelope ,and
6. A contact details form .

- If you decide to take part in this study, we will ask you to sign the consent forms provided, keep one copy for your records and complete the questionnaire. We estimate that It will take you 30min to an hour to answer all question and would advise you take all the necessary time you need to complete the questionnaire as accurately as possible. You can take breaks if you need to rather than complete it in one go.

- We then ask you to post your completed questionnaire and a copy of the consent form back to the research team at the MRC Lifecourse Epidemiology unit Southampton using the pre-paid envelope provided.
- We also ask if you would be happy to be contacted by the research team for any future research on this subject by providing your consent (Item 8 on consent form) and completing your contact details using the contact details form. By providing your contact details you are under no obligation to participate in any future studies, but it allows us to send further information regarding possible further research that might involve attendance at a research clinic at a later date. We are not committing to such research at this time as we feel it is inappropriate in the current COVID19 pandemic

What are the risks in taking part?

There are no potential risks taking part in the study. You can, though, contact a member of the research team to discuss any concerns or questions that may arise after you read this leaflet. Contact details are given at the end of this information sheet.

What are the possible benefits of taking part?

You may benefit, by taking part, from having your muscle and bone health assessed by specialists in Musculoskeletal health and advise you, where appropriate, on ways to improve your muscle and bone health.

Also, the information we get from this research will enable us to better understand the relationship between bone and muscle health and the impact of COVID19 pandemic and infection on this relationship. This will inform us on how we can develop future beneficial interventions to preserve musculoskeletal health in the population. This unique population-based study of older men and women is the first of its kind in Southampton and you will be part of pioneering this as well as future studies.

Will my taking part in this study be kept confidential?

Yes. All of the information about participation and the data collected will be kept confidential.

University Hospital Southampton NHS Foundation Trust is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller in conjunction with LWP for this study. This means that we are responsible for looking after your information and using it properly. University Hospital Southampton will keep information about you for 10 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will ask you if we can keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible. You can find out more about how we use your information at https://www.hra.nhs.uk/information-about-patients/.

The MRC Lifecourse Epidemiology Unit based at Southampton General Hospital will use this information to explore how factors affect bone and muscle health, will contact you about future research studies, and make sure that relevant information generated from the study is shared with your GP and oversee the quality of the study. Certain individuals from University Hospital Southampton and regulatory organisations may look at your medical and research records to check the accuracy of the research study. University Hospital Southampton will only receive information without any identifying information. Your data will be anonymised and the statistician who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

The MRC Lifecourse Epidemiology Unit Southampton will keep identifiable information about you, including your consent for 10 years after the study has finished.

If you would like to contact the hospital Data Protection Officer with any questions or concerns regarding how we store or use your data, please contact the data protection office via dataprotection@uhs.nhs.uk or telephone 023 8120 4743.

What will happen to the results of the research study?

The results of the study will be analysed by the research team and presented at medical conferences and published in scientific journals. You will not be identified in any report or presentation arising from the research. Any relevant results generated from the study that is relevant to your future health may be shared with your GP; You can also request a summary report of our findings at the end of the study. Please indicate on the consent form (item 7) if you would like to receive a summary report at the end of the study.

What happens if I withdraw?

You can leave the study at any time without giving any reason. To withdraw from the project, please inform the investigators using the email or phone number provided at the end of this

sheet . The data collected during the consent period will be stored and no further data from you will be recorded in the case you decide to withdraw from the study. Should you ask to withdraw and delete your data from the project, the research team will destroy identifiable data relating to you and keep a record of this action.

Will I be paid for taking part in the study?

I'm afraid that we're unable to pay you for your participation in this study. A pre-paid envelope is provided to send your questionnaire and consent form back to the research team at no cost to you.

What will happen to my data?

We will use the data collected to study and understand how the COVID19 pandemic has affected muscle and bone health. After the study's completion your data will be stored in anonymised format for 10 years, accordance with data protection procedures before being destroyed. During this time, data will be password-protected and encrypted. Any paper files will be kept in a locked cabinet accessible only to the investigators of this study.

Who has reviewed the study?

This study has been reviewed by the NHS Research Ethics Committee (REC).

Who is organising and funding the research study?

The project is part of an DM (Doctor of Medicine) research project that is funded by the National Institute for Health Research through the NIHR Southampton Biomedical Research Centre.

Insurance statement

University hospital Southampton holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that University hospital Southampton NHS Foundation Trust (UHS) is at fault. This does not affect your legal rights to seek compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during this study then you should immediately inform the Investigators. The normal National Health Service complaints mechanisms are also available to you.

Appendix C

Contact detail for further information:

This information sheet is yours to keep as is a copy of the consent form.. Please take your time to consider participating in this study. When you have decided please return the consent form, questionnaire and contact details form to us using the prepaid envelope. To request further information please contact Dr Faidra Laskou, who may be reached by telephone at **07883 421614** or via email at faidra.laskou@soton.ac.uk who will be happy to answer any questions.

Address:

MRC Lifecourse Epidemiology unit

University of Southampton,

Southampton General hospital,

Tremona Road, Southampton, SO16 6YD Email: mrcleu@mrc.soton.ac.uk

Co-investigators

Dr Faidra Laskou, Specialist Trainee in Rheumatology

Dr Harnish Patel, Consultant Geriatrician,

Mr Leo Westbury, Senior Statistician,

Prof. Elaine Dennison, Professor of Rheumatology,

Prof Cyrus Cooper, Professor of Rheumatology

We would like to thank you for reading the Participant Information Sheet and to consider taking part in this study

Appendix D MSK Southampton study – Consent from

Participant ID:

CONSENT FORM

LIFESTYLE, MUSCULOSKELETAL HEALTH AND WELLBEING IN OLDER ADULTS DURING COVID19 PANDEMIC

Investigators:

Dr Faidra Laskou, Dr Harnish Patel, Mr Leo Westbury, Prof. Elaine Dennison, Prof Cyrus Cooper

	Please Initial the boxes
1. I confirm that I have read and understand the participant information sheet dated 25/02/2021, Version 2 for the above study and have had the opportunity to ask questions.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, and without my medical care, education or legal rights being affected. I understand that in the case I withdraw from the study, the data collected with consent would be retained and used in the study, but no further data would be collected after my withdrawal.	☐
3. I agree to my anonymised data being stored on password protected computer systems at MRC Lifecourse Epidemiology Unit Southampton.	☐
4. I understand that the information collected about me will be anonymised and used to support other research in the future and may be shared with other researchers.	☐
5. I understand that relevant sections of my data collected during the study may be looked at by the investigators or by individuals from regulatory authorities, from MRC Lifecourse Epidemiology unit Southampton or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
6. I agree to take part in the above study.	☐
7. I understand that I may request a summary report of findings at the end of the study. (This is optional.).	Yes ☐
	No ☐
8. I agree to provide my contact details so that the study team can contact me about future studies that would involve coming to a research clinic. I understand that providing these details now in no way commit me to participation in any future study. A separate contact details form is provided. (This is optional)	Yes ☐
	No ☐

Appendix E MSK Southampton study questionnaire

Participant ID:

QUESTIONNAIRE

Lifestyle, musculoskeletal health, and wellbeing in older adults during COVID-19 pandemic

Dear Participant,

Thank you for taking the time to complete this questionnaire.

Please complete it as thoroughly and as accurately as you can, to help us with our research. All your answers will be treated as strictly confidential and will only be seen by the research team.

If you require this questionnaire in large print, in an electronic form or have any difficulties with the questions, please contact the research team by email or phone:

Email: faidra.laskou@soton.ac.uk

Telephone: +44 (0) 788 342 1614

Date of questionnaire completion (Day/Month/Year): ☐☐/☐☐/☐☐

Participant ID:

A. Demographics

1. Name:

2. Date of birth (Day/Month/Year): ☐☐/☐☐/☐☐

3. Male ☐ Female ☐

4. Ethnic group:

White	☐	Black-Caribbean	☐	Black-African	☐
Black-other	☐	Indian	☐	Pakistani	☐
Bangladeshi	☐	Chinese	☐	Other	☐

5. Weight: ☐☐st ☐☐lbs *or* ☐☐☐*Kg*

6. Height: ☐☐ft ☐☐in *or* ☐☐☐cm

B. Household/Education/Lifestyle

1. Do you live in:

Your own property	☐	Rented accommodation	☐	Residential home	☐
Nursing home	☐	Other (please specify below):			☐

2. What is your current marital status? (Tick one box)

Single	☐	Married or civil partnership	☐	Divorced or separated	☐
Widowed	☐	Cohabiting	☐		

Participant ID:

3. At what age did you leave school? ☐☐

4. Did you do any further education or training after school? (Tick all boxes that apply)

a. Apprenticeship ☐
b. Full time college or university course ☐
c. Part time college or university course (including day release or night classes): ☐
d. Other (please specify below) ☐

_____

5. Do you have any of the following qualifications? (Tick all boxes that apply)

e. O levels/GCSEs (or equivalent) ☐
f. A levels (or equivalent) ☐
g. Vocational training certificate (s) (e.g. City and Guilds, National Vocational Qualification) ☐
h. University degree(s) or Higher National Diploma: ☐
i. Higher professional qualifications (e.g. in accountancy, law etc.) ☐

6. Have you ever smoked regularly (at least once a day for a year or more)?

Yes **(see below, question a)** ☐ No **(Go to question 7)** ☐

a. Do you still smoke regularly?

Yes **(see below, question b)** ☐ No **(Go to question c)** ☐

b. How much do you smoke now?

Cigarettes per day: _____

Cigars per week _____

Roll-up tobacco per day (g): _____

Pipe tobacco per week (g): _____

c. How old were you when you last smoked regularly? ☐☐

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Participant ID:

7. Do you ever drink alcohol?

Yes (**see below, question a**) ☐ No (**Go to the next section C**) ☐

a. How often do you currently drink shandy/low alcohol beer/lager/cider? (don't include alcohol-free drinks)

0.	Never	☐	4.	1-2 times per week	☐
1.	Once every 2-3 months	☐	5.	3-6 times per week	☐
2.	Once a month	☐	6.	Once a day	☐
3.	Once a fortnight	☐	7.	More than once a day	☐

When you drink these, how many <u>pints</u> would you normally have on average?

_____

b. How often do you currently drink beer/stout/lager/cider? (don't include alcohol-free drinks)

0.	Never	☐	4.	1-2 times per week	☐
1.	Once every 2-3 months	☐	5.	3-6 times per week	☐
2.	Once a month	☐	6.	Once a day	☐
3.	Once a fortnight	☐	7.	More than once a day	☐

When you drink these, how many <u>pints</u> would you normally have on average?

_____

c. How often do you currently drink low alcohol wine?

0.	Never	☐	4.	1-2 times per week	☐
1.	Once every 2-3 months	☐	5.	3-6 times per week	☐
2.	Once a month	☐	6.	Once a day	☐
3.	Once a fortnight	☐	7.	More than once a day	☐

When you drink these, how many <u>glasses</u> would you normally have on average?

_____

Participant ID:

e. How often do you currently drink wine/sherry/port /Martini/Cinzano?

0.	Never	☐	4.	1-2 times per week	☐
1.	Once every 2-3 months	☐	5.	3-6 times per week	☐
2.	Once a month	☐	6.	Once a day	☐
3.	Once a fortnight	☐	7.	More than once a day	☐

When you drink these, how many glasses would you normally have on average?

_____

f. How often do you currently drink spirits/liqueurs?

0.	Never	☐	4.	1-2 times per week	☐
1.	Once every 2-3 months	☐	5.	3-6 times per week	☐
2.	Once a month	☐	6.	Once a day	☐
3.	Once a fortnight	☐	7.	More than once a day	☐

When you drink these, how many measures would you normally have on average?

_____

C. Medical conditions

1. Please list your current regular medications

a.	b.
c.	d.
e.	f.
g.	h.
i.	j.
k.	l.
m.	n.

Participant ID:

2. Has a doctor ever told you that you have got any of the following conditions? (Tick if yes)

Heart attack or angina	☐
Stroke or mini stroke/ transient ischaemic attack (TIA)	☐
High blood pressure/hypertension	☐
Type 1 or 2 Diabetes	☐
Asthma, bronchitis, emphysema, or chronic obstructive pulmonary disease (COPD)	☐
Depression	☐
Osteoporosis	☐
Anxiety	☐
Memory problems or dementia	☐
Parkinson's disease	☐
Osteoarthritis or degenerative joint disease	☐
Rheumatoid arthritis or inflammatory arthritis	☐
Cancer (If yes, where?)	☐
High cholesterol	☐
Other conditions (Please indicate here):	☐

Participant ID:

D. COVID-19 Questionnaire

1. Have you had COVID-19 (coronavirus)?

a. Yes, COVID-19 (coronavirus) was confirmed on testing **(see below, question 2)** ☐

b. Not formally diagnosed but suspected **(Go to question 3)** ☐

c. Not that I know of **(Go to question 3)** ☐

2. If COVID-19 (coronavirus) was confirmed on testing:

a. Did you have any symptoms?

Yes **(see below and then go to question b)** ☐ No **(Go to question 3)** ☐

On what date did your symptoms start? (Day/Month/Year): ☐☐/☐☐/☐☐

b. Were you admitted to hospital?

Yes **(see below, question c)** ☐ No **(Go to question d)** ☐

c. If you were admitted to hospital:

I. On what date were you admitted to hospital (Day/Month/Year)?

☐☐/☐☐/☐☐

II. On what day were you discharged from the hospital (Day/Month/Year)?

☐☐/☐☐/☐☐

III. You fully recovered from it ☐

IV. You have not fully recovered from it ☐

(**Please select below the symptoms you still have**):

Breathlessness	☐	Loss of taste	☐	Palpitations	☐
Muscle pains	☐	Weakness	☐	Exhaustion	☐
Fever	☐	Other (please state):			☐

_____

7

Participant ID:

d. If you were not admitted to hospital, please select which applies:

I. You fully recovered from it ☐

II. You have not fully recovered from it ☐

(Please select the symptoms you still have):

Breathlessness	☐	Loss of taste	☐	Palpitations	☐
Muscle pains	☐	Weakness	☐	Exhaustion	☐
Fever	☐	Other (please state):			☐

3. Please indicate how much the following aspects of your lifestyle have changed compared to before the first lockdown began on 23rd March 2020:

SLEEP	Much worse than before	☐	Worse than before	☐	About the same	☐	Better than before	☐	Much better than before	☐
DIET	Less healthy than before	☐			About the same healthiness as before	☐			More healthy than before	☐
SMOKING	More than before	☐			About the same	☐	Less than before	☐	I don't smoke	☐
ALCOHOL	More than before	☐	Less than before	☐	About the same	☐			I don't drink	☐
FOOD	Less than before	☐			About the same	☐			More than before	☐
SOCIAL CONTACT	Less than before	☐			About the same	☐			More than before	☐
PHYSICAL ACTIVITY	Less than before	☐			About the same	☐			More than before	☐

Participant ID:

E. Physical activity: PASE (Physical activity scale for the elderly)

Leisure time activity

1. Over the past 7 days, how often have you participated in sitting activities such as reading, watching TV, or doing handcrafts?

Never ☐ Seldom (1-2 days ☐ Sometimes (3-4 days) ☐ Often (5-7 days) ☐

a. What were these activities?

b. On average, how many hours did you spend doing these sitting activities?

Less than 1 hour ☐ 1- 2 hours ☐ 2-4 hours ☐ More than 4 hours ☐

2. Over the past 7 days, how often have you taken a walk outside your home for any reason? For example, for fun or exercise, walking to work, walking the dog, etc

Never ☐ Seldom (1-2 days ☐ Sometimes (3-4 days) ☐ Often (5-7 days) ☐

a. On average, how many hours per day did you spend walking?

Less than 1 hour ☐ 1- 2 hours ☐ 2-4 hours ☐ More than 4 hours ☐

3. Over the past 7 days, how often have you engaged in light sport or recreational activities? For example, bowling, golf with a cart shuffleboard, fishing from a boat or a pier.

Never ☐ Seldom (1-2 days ☐ Sometimes (3-4 days) ☐ Often (5-7 days) ☐

a. What were these activities?

b. On average, how many hours did you spend doing these recreational activities?

Less than 1 hour ☐ 1- 2 hours ☐ 2-4 hours ☐ More than 4 hours ☐

4. Over the past 7 days, how often have you engaged in moderate sport and recreational activities? For example, doubles tennis, ballroom dancing, hunting, golf without a cart.

Never ☐ Seldom (1-2 days ☐ Sometimes (3-4 days) ☐ Often (5-7 days) ☐

Participant ID:

a. What were these activities?

b. On average, how many hours did you spend doing these moderate sport or recreational activities?

Less than 1 hour ☐ 1- 2 hours ☐ 2-4 hours ☐ More than 4 hours ☐

5. Over the past 7 days, how often have you engaged in strenuous sport and recreational activities such as jogging, swimming, aerobic dance?

Never ☐ Seldom (1-2 days ☐ Sometimes (3-4 days) ☐ Often (5-7 days) ☐

a. What were these activities?

b. On average, how many hours did you spend doing these strenuous sport or recreational activities?

Less than 1 hour ☐ 1- 2 hours ☐ 2-4 hours ☐ More than 4 hours ☐

6. Over the past 7 days, how often did you do any exercises specifically to increase muscle strength and endurance, such as lifting weights or push-ups, etc.?

Never ☐ Seldom (1-2 days ☐ Sometimes (3-4 days) ☐ Often (5-7 days) ☐

a. What were these activities?

b. On average, how many hours did you spend doing these exercises?

Less than 1 hour ☐ 1- 2 hours ☐ 2-4 hours ☐ More than 4 hours ☐

<u>Household activity</u>

7. During the past 7 days, have you done any light housework, such as dusting or washing dishes?

Yes ☐ No ☐

Participant ID:

8. During the past 7 days, have you done any heavy housework or chores, such as vacuuming, scrubbing floors, washing windows, or carrying wood?

Yes ☐ No ☐

9. During the past 7 days, have you done any of the following?

a. Home repairs like painting, wallpapering, electrical work etc.

Yes ☐ No ☐

b. Heavy gardening, including snow or leaf removal, wood chopping, etc

Yes ☐ No ☐

c. Other outdoor gardening

Yes ☐ No ☐

d. Caring for another person, such as children, dependent spouse, or another adult

Yes ☐ No ☐

Work related activity

10. During the past 7 days, did you work for pay or as a volunteer?

Yes (**see question a**) ☐ No (**Go to the next section F**) ☐

a. How many hours per week did you work for pay and/or as a volunteer?

_____

b. Which of the following categories best describes the amount of physical activity required for your job and/or volunteer work?

I. Mainly sitting with some slight arm movement (Examples: office worker, watchmaker, seated assembly line worker, bus driver, etc.) ☐

II. Mainly sitting with some slight arm movement (Examples: office worker, watchmaker, seated assembly line worker, bus driver, etc.) ☐

III. Sitting or standing with some walking (Examples: cashier, general office worker, light tool, and machinery worker) ☐

IV. Walking with some handling of materials generally weighing less than 50 pounds (Examples: mailman, waiter/waitress, construction worker, heavy tool, and machinery worker) ☐

V. Walking and heavy manual work often requiring handling of materials weighing over 50 pounds (Examples: lumberjack, stone mason, farm, or general labourer) ☐

11

Participant ID:

F. Self-reported walking speed

1. Which of the following best describes your walking speed?

Fast	☐	Fairly brisk	☐
Normal speed	☐	Stroll at an easy pace	☐
Very slow	☐	Unable to walk	☐

G. Physical capability

FRIED

1. In the last year, have you lost more than 10 pounds unintentionally (not due to diet or exercise)?

Yes	☐	No	☐

2. How often in the last week did the following apply?
   "I felt that everything I did was an effort" or "I could not get going"

Rarely or none of the time (< 1 day)	☐	Some or a little of the time (1-2 days)	☐
A moderate amount of time (3-4 times)	☐	Most of the time (>4 days)	☐

Participant ID:

H. Bone health

1. Have you had any falls since the age of 45?

Yes (**see below, question a**) ☐ No (**Go to question 2**) ☐

a. At what age did you first fall (since the age of 45)? ☐☐

b. Did any of these falls result in injury?

Yes ☐ No ☐

2. Have you had any falls in the past year?

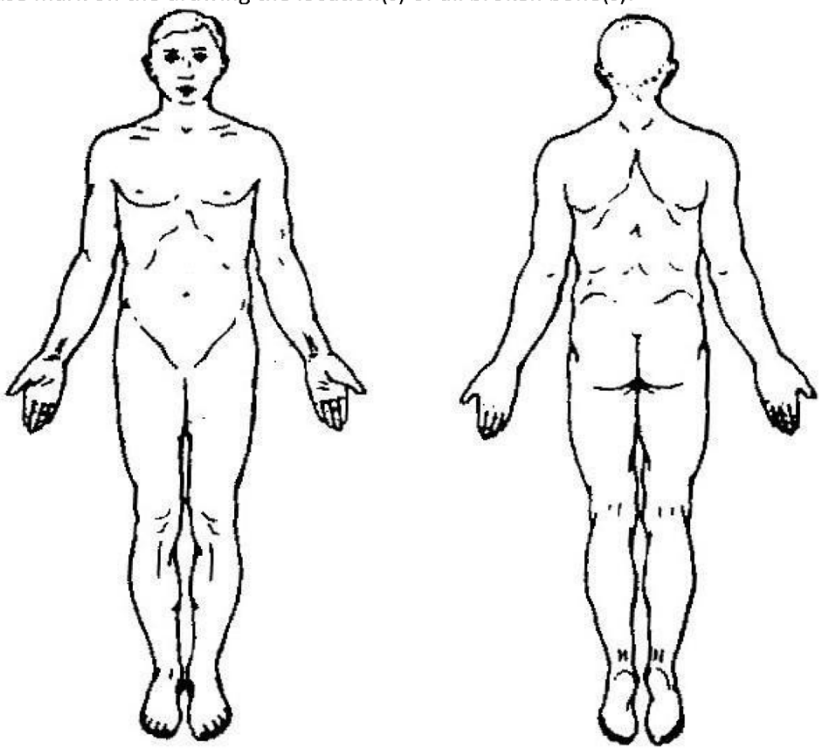
Yes (**see below, question a**) ☐ No (**Go to question 3**) ☐

a. If yes: How many? ☐☐

3. Have you broken/fractured/chipped any bones since the age of 45?

Yes (**see below, question a and b**) ☐ No (**Go to section I**) ☐

a. Please mark on the drawing the location(s) of all broken bone(s):



Participant ID:

b. Please provide details of the broken bone(s) below:

Name of bone	Age when fracture occurred	Low- or high-level trauma (if applicable) (see Explanation a below)
		High trauma ☐ Low trauma ☐ N/A☐
		High trauma ☐ Low trauma ☐ N/A☐
		High trauma ☐ Low trauma ☐ N/A☐
		High trauma ☐ Low trauma ☐ N/A☐
		High trauma ☐ Low trauma ☐ N/A☐
		High trauma ☐ Low trauma ☐ N/A☐
		High trauma ☐ Low trauma ☐ N/A☐

Explanation a: If you sustained a fracture following a fall only, please indicate if it was high- or low-level trauma. A high trauma fracture is from a fall from greater than standing height and a low trauma fracture is from a fall from standing height or low-level trauma.

4. Have you broken/fractured/chipped any bones since the first lockdown started (23rd March 2020)?

Yes ☐ No ☐

a. If yes: How many? ☐☐

Participant ID:

I. Muscle health (SARC-F)

1. How much difficulty do you have in lifting and carrying 10 pounds/4.5 kg/ 0.7 stone?

   None ☐ Some ☐ A lot of trouble or unable ☐

2. How much difficulty do you have walking across a room?

   None ☐ Some ☐ A lot of trouble or unable ☐

3. How much difficulty do you have transferring from chair to bed?

   None ☐ Some ☐ A lot of trouble or unable ☐

4. How much difficulty do you have climbing a flight of stairs?

   None ☐ Some ☐ A lot of trouble or unable ☐

5. How many times have you fallen in the past year?

   None ☐ Some ☐ A lot ☐

<u>If you have had COVID19, have any of the above worsened?</u>

Yes ☐ No ☐ Not applicable as I've not had confirmed COVID-19 ☐

a. If yes, which one (select all that apply from 1-5 as above):

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Participant ID:

J. SF-36

General health

1. In general, would you say your health is:

Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor ☐

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	☐	Somewhat better than one year ago	☐
About the same	☐	Somewhat worse than one year ago	☐
Much worse than one year ago	☐		☐

Limitations of activities

3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports

Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf

Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

5. Lifting or carrying groceries

Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

6. Climbing several flights of stairs

Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

7. Climbing one flight of stairs

Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

8. Bending, kneeling, or stooping

Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

9. Walking more than a mile

Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

Participant ID:

10. Walking several blocks

Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

11. Walking one block

Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

12. Bathing or dressing yourself

Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

Physical health problems

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities because of your physical health?

13. Cut down the amount of time you spent on work or other activities

Yes ☐ No ☐

14. Accomplished less than you would like

Yes ☐ No ☐

15. Were limited in the kind of work or other activities

Yes ☐ No ☐

16. Had difficulty performing the work or other activities (for example it took extra effort)

Yes ☐ No ☐

Emotional health problems

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your emotional health?

17. Cut down the amount of time you spent on work or other activities:

Yes ☐ No ☐

18. Accomplished less than you would like:

Yes ☐ No ☐

19. Didn't do work or other activities as carefully as usual:

Yes ☐ No ☐

Participant ID:

Social activities

20. Has emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all ☐ Slightly ☐ Moderately ☐ Severely ☐ Very severely ☐

Pain

21. How much bodily pain have you had during the past 4 weeks?

None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe ☐

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely ☐

Energy and Emotions

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

23. Did you feel full of pep?

All of the time ☐ Most of the time ☐ A good bit of the time ☐

Some of the time ☐ A little bit of the time ☐ None of the time ☐

24. Have you been a very nervous person?

All of the time ☐ Most of the time ☐ A good bit of the time ☐

Some of the time ☐ A little bit of the time ☐ None of the time ☐

25. Have you felt so down in the dumps that nothing could cheer you up?

All of the time ☐ Most of the time ☐ A good bit of the time ☐

Some of the time ☐ A little bit of the time ☐ None of the time ☐

Participant ID:

26. Have you felt calm and peaceful?

All of the time	☐	Most of the time	☐	A good bit of the time	☐
Some of the time	☐	A little bit of the time	☐	None of the time	☐

27. Did you have a lot of energy?

All of the time	☐	Most of the time	☐	A good bit of the time	☐
Some of the time	☐	A little bit of the time	☐	None of the time	☐

28. Have you felt downhearted and blue?

All of the time	☐	Most of the time	☐	A good bit of the time	☐
Some of the time	☐	A little bit of the time	☐	None of the time	☐

29. Did you feel worn out?

All of the time	☐	Most of the time	☐	A good bit of the time	☐
Some of the time	☐	A little bit of the time	☐	None of the time	☐

30. Have you been a happy person?

All of the time	☐	Most of the time	☐	A good bit of the time	☐
Some of the time	☐	A little bit of the time	☐	None of the time	☐

31. Did you feel tired?

All of the time	☐	Most of the time	☐	A good bit of the time	☐
Some of the time	☐	A little bit of the time	☐	None of the time	☐

Social activities

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives)?

All of the time	☐	Most of the time	☐	A good bit of the time	☐
Some of the time	☐	A little bit of the time	☐	None of the time	☐

Appendix E

Participant ID:

General health

How true of false is each of the following statements for you?

33.I seem to get sick a little easier than other people

Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false ☐

34.I am as healthy as anybody I know

Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false ☐

35.I expect my health to get worse

Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false ☐

36.My health is excellent

Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false ☐

Participant ID:

K. Nutrition

Please tick yes or no to the questions below:

I have an illness or condition that made me change the kind and amount of food I eat	Yes ☐	No ☐
I eat fewer than 2 meals per day	Yes ☐	No ☐
I eat few fruits, vegetables, or milk products:	Yes ☐	No ☐
I have 3 or more drinks of beer, liquor, or wine almost every day:	Yes ☐	No ☐
I have tooth or mouth problems that make it hard for me to eat:	Yes ☐	No ☐
I cannot always afford to buy the food I need:	Yes ☐	No ☐
I eat alone most of the time:	Yes ☐	No ☐
I take 3 or more different prescribed or over the counter drugs a day:	Yes ☐	No ☐
Without wanting to, I have lost or gained 10 pounds in the last 6 months	Yes ☐	No ☐
I am not always physically able to shop, cook and/or feed myself:	Yes ☐	No ☐

FOOD FREQUENCY QUESTIONNAIRE (FFQ)

1. Now we would like to ask you how often over the past 3 months you have eaten particular foods.

FOOD	Never	<1 per month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day
White bread (1 slice)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Brown and wholemeal bread (1 slice)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Biscuits e.g. digestive (one)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Apples (1 fruit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bananas (1 fruit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Melon, pineapple, kiwi, and other tropical fruits (medium serving)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Appendix E

Participant ID:

FOOD	Never	<1 per month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day
Green salad e.g. lettuce, cucumber, celery	☐	☐	☐	☐	☐	☐	☐	☐	☐
Garlic – raw and cooked dishes	☐	☐	☐	☐	☐	☐	☐	☐	☐
Marrow and courgettes	☐	☐	☐	☐	☐	☐	☐	☐	☐
Peppers: cooked & fresh	☐	☐	☐	☐	☐	☐	☐	☐	☐
Yogurt (125g pot)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Eggs as boiled, fried, scrambled etc. (1 egg)	☐	☐	☐	☐	☐	☐	☐	☐	☐
White fish e.g. cod, haddock, plaice, sole (not in batter/crumbs)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Oily fish, e.g. mackerel, tuna, salmon	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bacon and gammon	☐	☐	☐	☐	☐	☐	☐	☐	☐
Meat pies, e.g. pork pie, pasties, steak & kidney, sausage rolls	☐	☐	☐	☐	☐	☐	☐	☐	☐
Boiled, mashed and jacket potatoes (1 egg size potato)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Chips	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pasta e.g. spaghetti, macaroni	☐	☐	☐	☐	☐	☐	☐	☐	☐
Which is the main spreading fat you have used for example on bread or vegetables and how often do you use it?									
Name of spreading fat (teaspoon) _____	☐	☐	☐	☐	☐	☐	☐	☐	☐

Participant ID:

2. Please select which types of milk you have used regularly in drinks and added to breakfast cereals over the past three months. How much of each milk have you consumed per day in pints?

Whole pasteurised	☐	Pints/day:	_____
Semi-skimmed pasteurised (include 1% milk)	☐	Pints/day:	_____
Skimmed pasteurised	☐	Pints/day:	_____
Whole UHT (Long life)	☐	Pints/day:	_____
Semi-skimmed UHT (Long life)	☐	Pints/day:	_____
Skimmed UHT (Long life)	☐	Pints/day:	_____
Other	☐	Pints/day:	_____
None	☐		

3. Have you added sugar to tea, coffee, or breakfast cereals in the past 3 months?

Yes ☐ No ☐

a. If yes: How many teaspoons of sugars each day? ☐☐

L. Future studies

Please indicate below if you are happy to be contacted again about future studies on musculoskeletal health from our Unit. Your participation will remain completely voluntary and you can opt out at any time in the future. Please remember to send back to the research team the contact details form, if applicable.

Yes ☐ **No** ☐ **Not sure** ☐

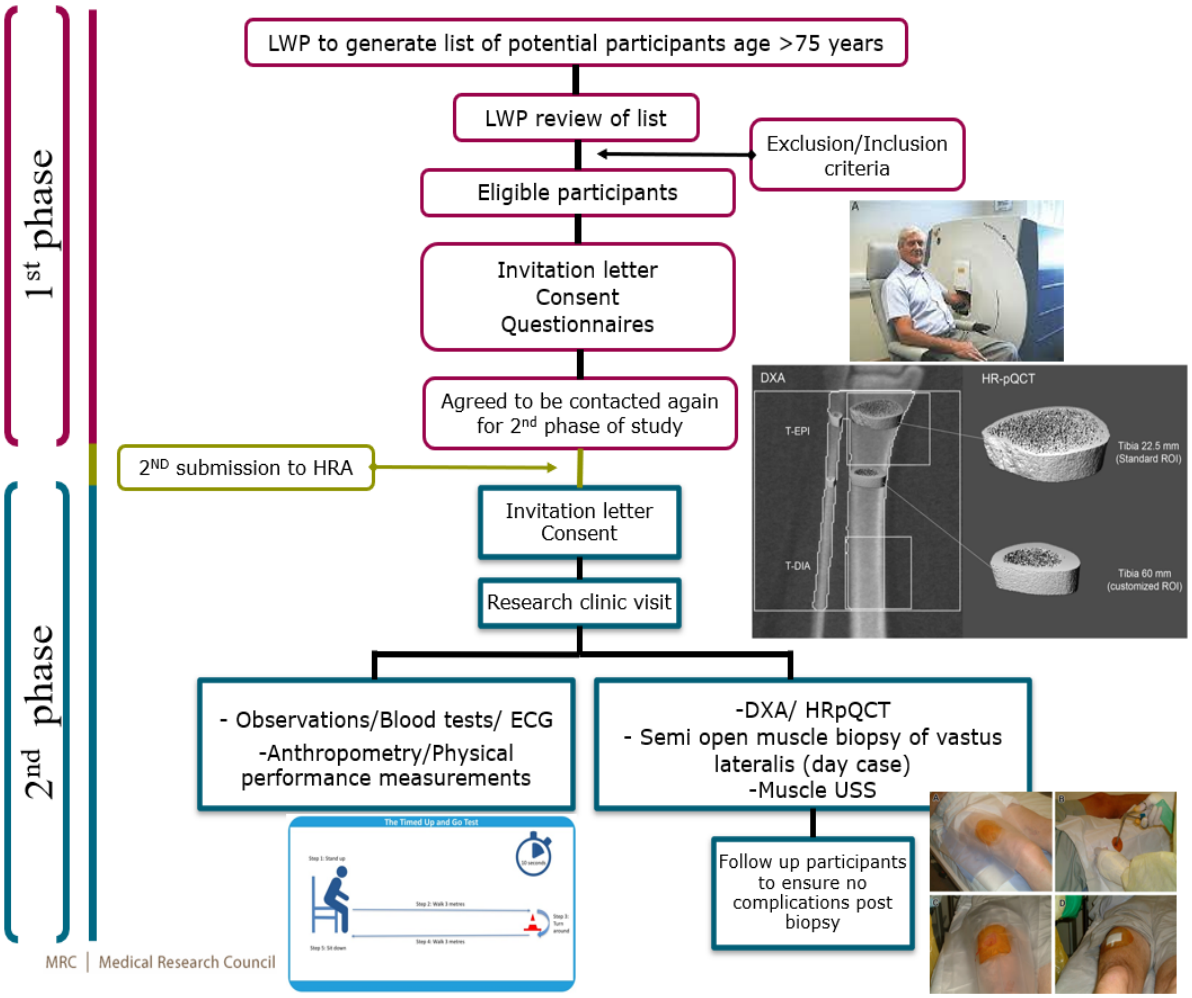
Please contact the research team for any questions/queries:

Email: faidra.laskou@soton.ac.uk

Telephone: +44 (0) 788 342 1614

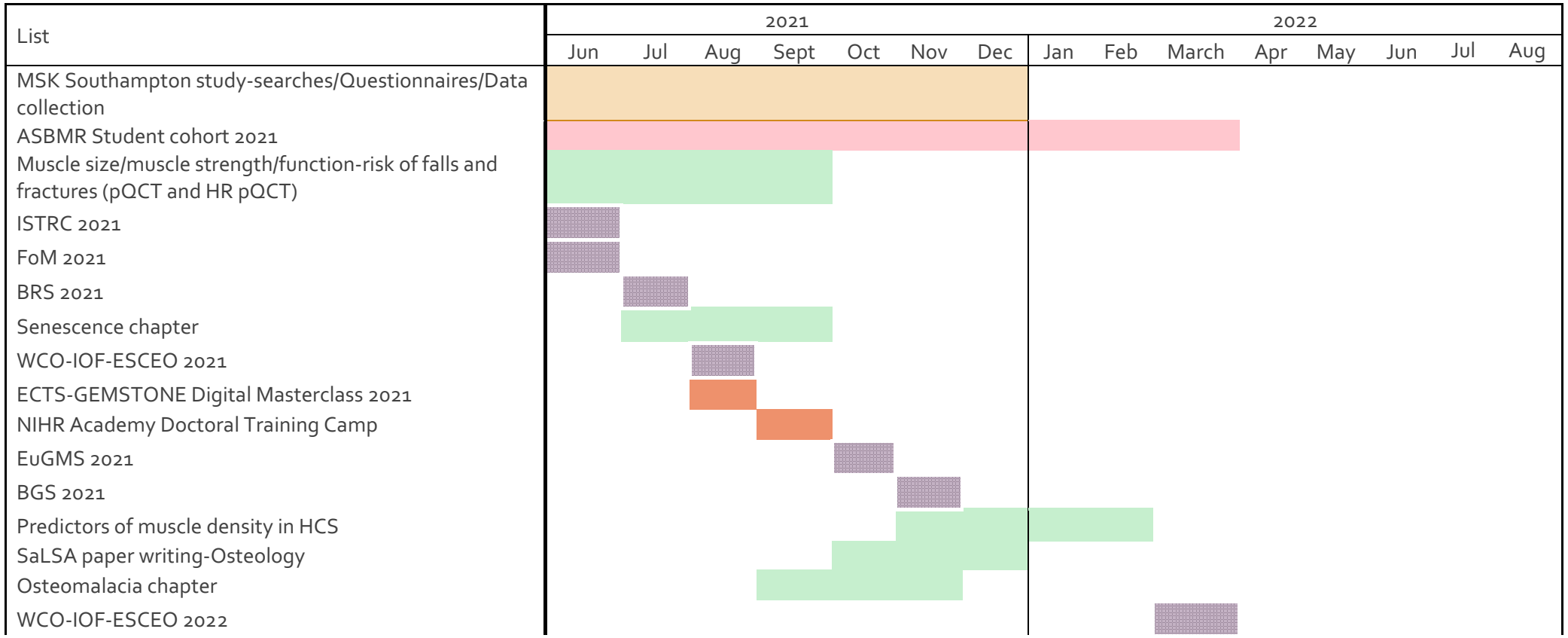
THANK YOU VERY MUCH FOR TAKING PART IN OUR STUDY AND COMPLETING THE QUESTIONNAIRE

Appendix F Southampton Longitudinal Study of Ageing (SaLSA)



Appendix G Southampton Longitudinal Study of Ageing Logo

Appendix H Gantt Chart[23]



[23] ASBMR: American Society for Bone and Mineral Research, ISTRC: International Sarcopenia Translation Research Conference, FoM: Faculty of medicine conference, BRS: Bone research society, WCO-IOF-ESCEO: World congress on osteoporosis, osteoarthritis, and musculoskeletal diseases, ECTS: European Calcified Tissue Society, EuGMS: European Geriatric Medicine Society, BGS: British Geriatrics Society, BSR: British Society of Rheumatology.

Appendix H


The interrelationship between sarcopenia and bone health, sarcopenia relation to functional capacity and ageing
ASBMR Student cohort 2022
BSR 2022
FoM 2022
Muscle ultrasound training
Lab experience in Immunohistochemistry - muscle biopsy tissue
MSK Southampton study- Data cleaning and analysis
SaLSA major amendments- ethics approval
Thesis
MSK Southampton study/SaLSA related activity
Participation in student cohorts-education
Literature review/Paper and chapter writing/presenting findings
Presentation in conferences
Participation in masterclass - writing/submitting application for funding/ transferable skills
Lab/technical skills training
Thesis writing and production

Appendix I A pas de deux of osteoporosis and sarcopenia: Osteosarcopenia

Climacteric

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A pas de deux of osteoporosis and sarcopenia: osteosarcopenia

F. Laskou, H. P. Patel, C. Cooper & E. Dennison

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REVIEW

A pas de deux of osteoporosis and sarcopenia: osteosarcopenia

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ABSTRACT

The musculoskeletal conditions osteoporosis and sarcopenia are highly prevalent in older adults. Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone, whereas sarcopenia is identified by the loss of muscle strength, function and mass. Osteoporosis represents a major health problem contributing to millions of fractures worldwide on an annual basis, whereas sarcopenia is associated with a range of adverse physical and metabolic outcomes. They both affect physical and social function, confidence and quality of life as well as contributing to high health-care costs worldwide. Osteosarcopenia is the term given when both conditions occur concomitantly and it has been suggested that interactions between these two conditions may accelerate individual disease progression as co-existence of osteoporosis and sarcopenia is associated with higher morbidity from falls, fracture, disability as well as mortality. In this review, we will outline the epidemiology, pathogenesis and clinical consequences of osteosarcopenia and discuss available management strategies.

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Osteoporosis; sarcopenia; osteosarcopenia; postmenopausal women; epidemiology; management

Introduction

Musculoskeletal health disorders including osteoporosis and sarcopenia are highly prevalent in older adults. Osteoporosis, a disease characterized by low bone mass and structural deterioration of bone tissue, is the most common chronic metabolic bone disease and represents a major global health problem, contributing to 8.9 million fractures worldwide on an annual basis [1]. Osteoporosis incurred an estimated £1.8 billion in UK health costs in 2000; this is predicted to increase to £2.2 billion by 2025 [2]. Sarcopenia is characterized by progressive and generalized decline in muscle strength, function and muscle mass with increasing age or secondary to disease [3]. It is associated with a range of adverse physical and metabolic outcomes in terms of disability, morbidity, impaired quality of life and mortality [4], and has also been identified as a predictor of fracture risk [5]. In terms of cost, sarcopenia incurred an estimated $18.5 billion in health-care costs to the USA in 2000. In the UK, the annual excess cost associated with muscle weakness was estimated to be £2.5 billion [6,7]. Several varying definitions of sarcopenia have contributed to differences in prevalence estimates worldwide, ranging from 3 to 30% [4,8–10]. Currently, a global consensus definition for sarcopenia does not exist but there are well-constructed diagnostic algorithms that provide a mechanism for clinical case finding [4].

Growing interest has emerged in the coexistence of osteoporosis and sarcopenia in some individuals, which is often termed osteosarcopenia, and is associated with higher morbidity from falls, fracture, disability as well as mortality [11,12]. Knowledge of the overlap in the pathophysiology of osteoporosis and sarcopenia can inform the development of potential treatments for osteosarcopenia [13]. Given the urgent need to educate clinicians and researchers on the importance of identifying osteosarcopenia early, this article aims to review and appraise relevant and available literature on osteosarcopenia, providing an update on the epidemiology (prevalence, risk factors and diagnosis) and management for osteosarcopenia.

Coexistence of poor bone and muscle measurements

The concept that individuals with low bone mass might also have low muscle mass has been investigated previously in several studies. For example, in 1998, a study assessed the relationship between whole-body bone mineral content and lean mass in males and females between 2 and 87 years of age, indicating that bone mass is closely and linearly associated with muscle mass throughout life [14]. In other studies, lean mass was a better predictor of whole-body bone mineral density (BMD) than fat mass as well as incident fractures [15–17]. In the Hertfordshire Cohort Study, muscle size and muscle strength were positively associated with bone size and strength [18]. Greater loss of bone mass was noted in

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osteosarcopenic patients compared to osteoporotic patients in a study conducted in Ecuador dominated by female participants [19]. A positive relationship between muscle and bone mass decline over a year was recognized in older individuals in the SarcoPhAge study [20], whereas an increase in the risk of fracture and a decline in muscle strength were associated with a decrease in spine and hip BMD [20]. In the Copenhagen Sarcopenia Study, BMD was lower among individuals with sarcopenia [21] and a large study of women in Japan showed that the relative skeletal muscle index was positively correlated with BMD of the lumbar spine and total hip [22]. Finally, in a cross-sectional study of premenopausal, perimenopausal and postmenopausal women, a linear decline in both muscle mass and bone density was noted, showing significant changes in postmenopausal compared to premenopausal women [23].

Approaches to defining osteosarcopenia

Awareness of complex muscle and bone interrelationships will inform construction of diagnostic pathways for osteosarcopenia and allows the construction of a pathway to identify coexistence of osteoporosis and sarcopenia (Figure 1).

In clinical practice, falls, fractures, slower gait speed, difficulty rising from a chair, weight loss, low body mass index or muscle wasting should all highlight the need for further diagnostic evaluation for osteoporosis and sarcopenia. There are available tools at the clinician's disposal to aid the identification of both sarcopenia and osteoporosis separately. SARC-F, a 5-point sarcopenia self-questionnaire, has high specificity but low sensitivity, making it the most accurate in detecting those with sarcopenia [24] (Table 1). The most widely used definition for sarcopenia has been proposed by the European Working Group on Sarcopenia in Older People (EWGSOP2) [4]. The EWGSOP2 diagnostic algorithm uses normative grip strength reference values for young healthy adults where possible, with cut-off points usually set at −2 or −2.5 standard deviations compared to mean reference values [4]. In recent years, there has been much more emphasis on muscle strength as the primary parameter characterizing sarcopenia, as opposed to muscle mass [4,8]. Sarcopenia is probable when low muscle strength is present; this is assessed by grip strength (measured with the use of a hand-held dynamometer) or time taken to complete five chair rises (Table 2). A diagnosis of sarcopenia is confirmed by the presence of low muscle quantity measured, for example, by dual-energy X-ray absorptiometry. A diagnosis of severe sarcopenia is made when low muscle strength is accompanied by low muscle quantity and decline in physical performance (i.e. slower gait speed) (Table 2). Other modalities of imaging previously used to measure muscle mass include bioelectrical impedance analysis, but equations used to derive lean mass values are population and device specific, and lack standardization [25]; the same difficulties apply to ultrasound scanning use but interest in its application is growing, especially in view of the ready access to equipment [26,27]. Computed tomography and magnetic resonance imaging are mostly used in research settings or when other diseases or conditions are suspected [25].

The FRAX score is now widely used as a validated tool for risk stratification for osteoporosis, so decisions can be facilitated in the need for treatment in all postmenopausal women and men aged 50 years or over who have risk factors for fracture [28,29]. The diagnosis of osteopenia and of osteoporosis is made using dual-energy X-ray absorptiometry scanning. According to World Health Organization (WHO) criteria, *T*-scores of BMD below −1 and −2.5 standard deviations categorize the patient as osteopenic and osteoporotic, respectively [30].

As already discussed, the presence of sarcopenia associated with low BMD (osteopenia or osteoporosis) with or without clinical fracture has been defined as osteosarcopenia by some researchers (Figure 1).

Prevalence of osteosarcopenia

The prevalence of osteosarcopenia among community-dwelling populations increases with age and is greater in women than in men [31,32]. Estimates vary considerably, between 5 and 37% depending on the population and definition of sarcopenia used. The highest rates were observed in those with fractures [21,31]. In a study of 316 community-dwelling Chinese adults aged 65 years and over, 10.4% of men and 15.1% of women were found to be osteosarcopenic [33]. The prevalence of osteosarcopenia was found to be 37% in 680 community-dwelling older individuals in Australia with a history of falls [11]. The prevalence of sarcopenia was found to be 58% among 313 older women following hip fractures in an Italian study [34]. BMD values were significantly lower in sarcopenic older women, and sarcopenic adults had a fourfold higher risk of having co-existing osteoporosis compared with non-sarcopenic adults in a Belgian study [35]. Lastly, studies have shown that being diagnosed with sarcopenia was associated with a high risk of having osteoporosis and vice versa [20–22,36–38].

Risk factors and pathophysiology

Many factors have been implicated in the pathology of osteosarcopenia. Data from the UK Biobank show that muscle strength is partially genetically regulated and genetic factors are important in the achievement of peak bone mass [39,40]. No single gene or single nucleotide polymorphisms have been associated with the loss of bone mass, muscle strength or mass in conjunction, but genome-wide association studies have identified several genes that are associated with bone and muscle wasting, with *GDF8* the most well characterized [41]. Genetic background might also determine responsivity of the muscle–bone unit to mechanical stimuli; several quantitative trait loci have been associated with the specific response to mechanical stimulation [42].

The mechanostat hypothesis first described by Frost suggests that increasing loads imposed by larger muscle forces on bone in childhood and adolescence lead to higher bone strength in midlife [43,44]. Conversely, a decline in muscle

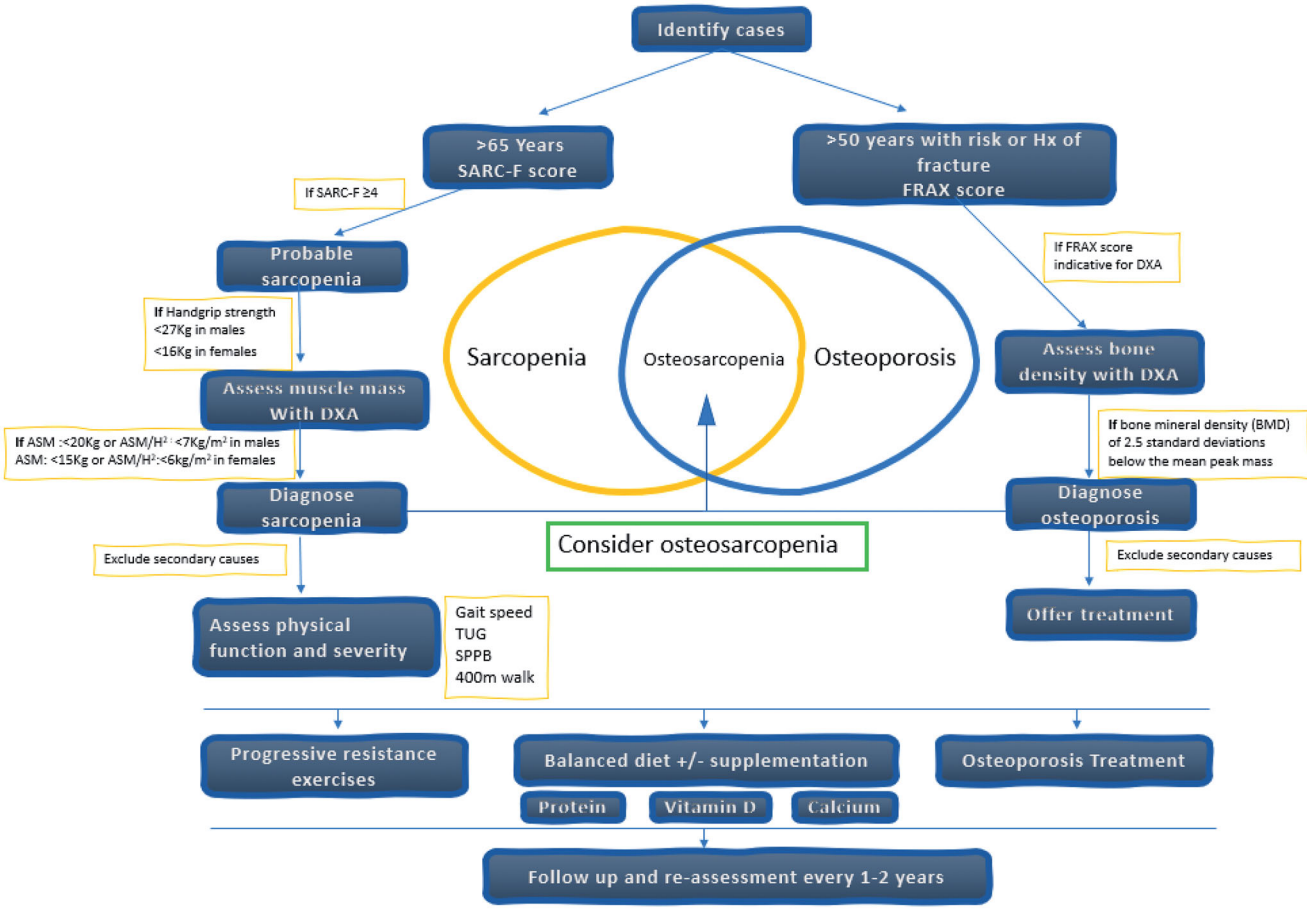

Figure 1. Risk stratification strategy for osteosarcopenia. ASM, appendicular skeletal muscle mass; DXA, dual-energy X-ray absorptiometry; H, height; Hx, history; SPPB, Short Physical Performance Battery; TUG, timed up and go.

Table 1. SARC-F questionnaire: 5-point sarcopenia self-questionnaire for detecting those with sarcopenia.

Component	*Question*	*Scoring*
Strength	Difficulty in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Walking	Difficulty walking across a room?	None = 0 Some = 1 A lot or unable = 2
Chair rise	Difficulty transferring from a chair or bed?	None = 0 Some = 1 A lot or unable = 2
Stairs	Difficulty climbing a flight of 10 stairs?	None= 0 Some= 1 A lot or unable = 2
Falls	Times have you fallen in the past year?	None = 0 Some = 1 A lot or unable = 2

SARC-F score ≥4 best predicts the need for further, more comprehensive evaluation to confirm evidence of sarcopenia.

strength with age put bones into partial disuse and remodeling [44]. This highlights the importance of mechanical loading in the maintenance of the muscle–bone unit as loss of both bone and muscle mass are intrinsically linked to the reduction in physical performance observed with aging [45].

Aging is a significant risk factor for both osteoporosis and sarcopenia [46]. However, the molecular mechanisms linking bone to muscle function as we age are not very well defined. Factors known as myokines (released from muscle, such as myostatin or irisin) and osteokines (released from bone, such as osteocalcin) are thought to be the mechanism of communication between the two tissues. Myostatin and the Wnt–β-catenin signaling pathway have been extensively studied in mediating muscle–bone crosstalk by controlling both osteoblastic activity and muscle regeneration [47,48].

Inflamm-aging, the chronic low-level and long-term physiological stimulation of the immune system, occurs as a consequence of lifelong exposure to antigenic stimuli interacting with complex genetic, environmental and age-related mechanisms, including mitochondrial dysfunction [49,50]. These changes can affect muscle proteolysis and lead to a reduction in bone mineralization [51], while it has been suggested that low-grade and chronic inflammation can shift mesenchymal stem cell lineage toward adipogenesis instead of myogenesis and osteoblast genesis, resulting in decreased muscle and bone quality [52]. Finally, fat infiltration is one of the hallmarks of sarcopenia and osteoporosis, as high levels of marrow adipose tissue are associated with bone loss and osteoporosis, and myosteatosis is associated with a decrease in myocyte dysfunction and impaired muscle quality [52].

Sex hormones have several effects on muscle and bone. Notably, with aging, their concentration and activity on tissues alter. Menopause, which is characterized by a sharp decline in circulating prostaglandin estradiol in women, is an important influence on the further decline in muscle and bone; the same abrupt decline does not apply to men. Early menopause without treatment is a strong risk factor for

Table 2. Clinical tools and cut-offs for measurement of muscle strength, lean mass and physical performance in sarcopenia according to the EWGSOP2 criteria and pathway.

Criterion		*Tool*	*Cut-offs for women*	*Cut-offs for men*
Identify cases		SARC-F	≥ 4	
Assess sarcopenia	Muscle strength	Grip strength or	<16 kg	<27 kg
		chair stand test	>15 s for 5 rises	
Confirm sarcopenia	Muscle quantity or quality	ASM by DXA or	<15 kg	<20 kg
		ASM/height^2	<5.5 kg/m^2	<7 kg/m^2
Assess severity	Physical performance	Gait speed or	≤0.8 m/s	
		SPPB or	≤8-point score	
		TUG or	≥20 s	
		400-m walk	≥6 min for completion or non-completion	

ASM, appendicular skeletal muscle mass; DXA, dual-energy X-ray absorptiometry; EWGSOP2, European Working Group on sarcopenia in Older People; SPPB, Short Physical Performance Battery; TUG, timed up and go.

future fragility fracture [53] and hormone replacement therapy in postmenopausal women is able to both preserve bone and muscle mass [54]. Growth hormone (GH) and insulin growth factor-1 both exert a positive influence on osteoblasts in addition to their anabolic actions on muscle [55].

Lifestyle factors such as nutrition, alcohol and smoking have been shown to have effects on bone and muscle. Active smoking is associated with worse bone health in female smokers [56] and has been linked to the development of sarcopenia [57,58]. While moderate alcohol intake is not thought to be associated with low muscle mass, heavy alcohol consumption is likely to lead to low muscle mass secondary to poor nutrition, lower physical activity and hormonal abnormalities [59].

Specific nutrients affect both bone and muscle. Low levels of vitamin D are commonly found in osteosarcopenic patients [11]. In a study conducted in Korea, vitamin D deficiency was associated with low BMD and was more pronounced in those with sarcopenia [60], while low Appendicular Lean Mass (ALM) was associated with low vitamin D in the Minocycline to Improve Neurologic Outcome in Stroke (MINOS) study [57]. Low vitamin D levels are likely to contribute to muscle weakness and increased risk of falls in addition to increased bone fragility [61,62]. Finally, vitamin K is essential for the effective function of proteins including those involved for bone remodeling and it has been shown that *in vitro* vitamin K improves the proliferation and migration of primary bovine skeletal satellite cells, with potential in maintaining normal muscle function, as well as facilitating several pathways in muscle–bone crosstalk [63,64].

Management of osteosarcopenia

Non-pharmacological management – lifestyle and nutritional modifications

Both sarcopenia and osteoporosis are amenable to preventative and therapeutic interventions in the form of exercise and nutritional support, the multicomponent nature of which remains the core of osteosarcopenia management.

Physical exercise has been shown to have a positive impact on muscle mass and function, with greater benefits on physical performance in adults over the age of 60 years [65]. Furthermore, a meta-analysis of 14 prospective studies has shown a significant inverse relationship between increasing level of physical activity and risk of hip fracture in older women [66]. Randomized controlled trials have demonstrated the efficacy of progressive resistance exercise to stimulate osteoblastogenesis and muscle protein synthesis [67,68]. Low-repetition, light-load power training also showed improved pelvis BMD and knee extensor strength over the course of 6 weeks in a small study of postmenopausal women with sarcopenia [69]. Emphasis on resistance training for individuals with osteoporosis is also given [70]. A recent systematic review showed that chronic resistance training is safe and effective in improving characteristics of osteosarcopenia such as lumbar spine BMD, muscle mass, strength and quality, but not physical performance [71]. Multimodal programs that incorporate traditional and high-velocity progressive resistance training, weight-bearing exercises and balance/mobility activities might be the best approach for osteosarcopenia [72].

A nutritional approach focuses on vitamin D, calcium and protein intake. Despite the lack of information regarding the intake of high-quality protein in older individuals, it has been suggested that adequate intake should be ensured. The recommended dietary allowance for protein of 0.8 g protein/kg/day might be inadequate for older people to meet their metabolic and physiological needs and should be increased to 1.5 g protein/kg/day [73]. Higher protein intake was protective against physical function decline in older individuals, including those with a previously sufficient protein intake, independent of physical activity [74]. Protein supplementation above the recommended daily amount in combination with resistance exercise or endurance type exercises is advised [75]. This combination has demonstrated an increase in muscle and bone mass, muscle strength, balance and functional capacity [68,76]. A recent systematic review suggested that protein supplementation and muscle strengthening exercise were associated with gain in lean muscle mass in people at risk of sarcopenia [77]. Enhanced protein intake has benefited patients with osteosarcopenia [78]. Dairy food provides nutrients such as calcium, phosphate and protein that are important in the maintenance of bone health [79], but there have been mixed reports regarding their benefit [76,80,81].

An adequate vitamin D status is associated with better BMD, muscle mass and function [82,83] and reduced number of falls in postmenopausal women [84]. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends a vitamin D intake of 800 IU/daily to maintain

25(OH)D levels >50 nmol/l in postmenopausal women [85]. Conversely, an annual oral administration of high-dose cholecalciferol was associated with an increased risk of falls and fractures [86]. However, to date no interventional and randomized controlled studies have been performed to assess its effect on osteosarcopenic patients [87]. Finally creatine has also been reported to increase muscle mass and strength as well as bone density, but studies are required to show benefit in osteosarcopenic patients [75].

Pharmacologic treatments

Commonalities in pathophysiology could lead to the identification of potential pharmacological targets for treatment of osteosarcopenia [88,89]. Currently, however, there are no randomized controlled trials of drug treatments for osteosarcopenia.

Interventions with drugs that have anti-inflammatory properties including non-steroidal anti-inflammatory drugs (NSAIDs) have been examined in sarcopenia [90]. Their exact mechanism of action is still not clearly described, but some studies have shown that cyclooxygenase-inhibiting NSAIDs might be effective in improving muscle protein metabolism [91], and participants in a cross-sectional study taking long-term NSAIDs had a lower risk of sarcopenia compared to non-NSAID users [92]. On the contrary, a negative effect of skeletal muscle regeneration has also been reported [93]. Due to conflicting results from studies and the potential side effects associated with NSAIDs, long-term use is not recommended, especially in older adults.

Testosterone replacement in men has demonstrated positive effects in muscle strength, gait and volumetric BMD [94,95]. Hormone replacement therapy in women at the onset of menopause has been shown to preserve muscle strength [96] and prolonged use is associated with high muscle mass [97]. Hormone replacement therapy use also reduces fractures, although the unfavorable risk/benefit balance in older postmenopausal women limits its use to younger postmenopausal women who are at high risk of fracture and also have menopausal symptoms [28]. Side effects and variable anabolic actions seen in studies of selective androgen receptor modulators, classes of androgen receptor ligands that display tissue selective anabolic and androgenic activity, have precluded their widespread use. For example, though andarine and ostarine use were associated with an increase lean mass and physical function in older males and postmenopausal females [98,99], no clear advantage was shown for bone health.

GH supplementation has shown no clear benefit in muscle mass, function or strength, despite initial reports that low GH levels contribute to a decrease lean mass and increase in adipose tissue [89]. GH replacement has been shown to be possibly beneficial in the management of postmenopausal women with osteoporosis; a recent meta-analysis indicated a role in fracture prevention although not an increase in BMD [100].

In conclusion, there are currently no approved pharmacological agents for osteosarcopenia, although treatments for osteoporosis have been explored to understand whether their actions outwit their effects on bone. For example, denosumab has shown beneficial effects on falls risk [101], has been associated with increased handgrip strength and lean body mass [102], and has been associated with reduced fear of falling, better balance and physical action [103] when compared to intravenous zoledronic acid.

Considering novel therapies, lower levels of myostatin, a negative regulator of muscle development and growth [104], have been found in animal and human studies of increased musculature and strength [105–107]. Myostatin inhibitors have been suggested as a possible treatment for osteosarcopenia. However, in a phase II trial in older adults with a history of falls, myostatin inhibition was associated with an increase in lean body mass and improved functional measures but no benefit in bone health [108]. Initial reports of bimagrumab, a human monoclonal antibody that binds to type II activin receptors and prevents the binding of myostatin and activin A, has demonstrated significant increases in lean body mass and strength in older adults [109], but those results were not sustained [110]. Irisin, another myokine, has also been suggested as a target to treat osteosarcopenic subjects as it retrieves disuse-induced bone loss and muscle atrophy in mice [111] and is proposed as a biomarker for sarcopenia in postmenopausal women [112]. Finally, prevention of fat infiltration [113] and use of melatonin [114], adiponectin [115] and exosomes [116] have been proposed as potential therapeutic targets, but further research and studies are needed.

Conclusion

Osteoporosis and sarcopenia are age-related conditions and are associated with significant morbidity and mortality. Their prevalence is expected to increase over the years with important consequences for individuals and health-care systems. These two conditions share common pathophysiological mechanisms, resulting in an interest in and attempts to treat and manage these pathologies simultaneously. Early recognition and intervention of both conditions is important to decrease morbidity and mortality and preserve independence of older individuals. Combined resistance and balance exercises with nutritional supplementation and treatment of osteoporosis are the current strategies to manage osteosarcopenia. Further basic science research to gain a better insight into biomarkers with potential diagnostic and therapeutic value as well as epidemiological studies to understand the life course influences leading to osteosarcopenia are needed.

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Appendix J Establishing a Resource to Assess Musculoskeletal Health in Older Adults: The Southampton Longitudinal Study of Ageing (SaLSA)

osteology

MDPI

Brief Report

Establishing a Resource to Assess Musculoskeletal Health in Older Adults in the Post-COVID-19 Era: Time to SaLSA?

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Abstract: Sarcopenia and osteoporosis are associated with morbidity and mortality. The development and progression of these two interrelated conditions are related to genetic and lifestyle factors, including nutrition and physical activity. Restrictions placed on individuals due to the COVID-19 pandemic and infection have led to widespread lifestyle modifications, with data suggesting a negative impact on physical activity levels. There is an urgent need to understand the effect of the pandemic on musculoskeletal health in older adults, at a time when COVID-19 infection and restrictions remain a barrier to research studies. We tested the feasibility of recruiting local community-dwelling older people to establish a new cohort investigating musculoskeletal health—the Southampton Longitudinal Study of Ageing (SaLSA). We invited 1993 community-dwelling older adults registered at the Living Well GP partnership in Southampton, UK, to participate in a study. Questionnaires were completed by participants on health, lifestyle, medication use, comorbidities, physical activity, nutrition, sarcopenia, osteoporosis, and quality of life. Permission was sought for future contact. Descriptive statistics were used on the initial pilot of 175 returned questionnaire data. The median age of participants was 80.4 years in both sexes, 81.3 years (77.9–84) in females, and 81.1 years in males (77.3–83.6). The majority (N = 168/171, 98%) of participants were of white Caucasian background; 36/53 (68%) female participants and 38/119 (32%) male participants lived alone. Over 80% (295/353) consented to be contacted for future studies. Recruitment of participants from a primary care practice into a research study was feasible. The next steps are to perform detailed musculoskeletal phenotyping through physical performance measures, grip strength dynamometry, DXA scanning, high-resolution peripheral quantitative computed tomography (HRpQCT), thigh ultrasound, and muscle biopsy, in a subset of participants. Our vision for SaLSA is to build a platform for discovery science and mechanistic studies, with the goal of improving the health care of older people.

Keywords: older adults; musculoskeletal health; sarcopenia; osteoporosis; ageing; COVID-19; longitudinal cohort study

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1. Introduction

Musculoskeletal health disorders, including osteoporosis and sarcopenia, are highly prevalent in older adults, and are associated with a very significant public health burden. Osteoporosis, a disease characterised by low bone mass and structural deterioration of bone tissue, is the most common chronic metabolic bone disease, and contributes to 8.9 million fractures worldwide on an annual basis [1]. Osteoporosis incurred an estimated GBP

1.8 billion in UK health costs in 2000; this is predicted to increase to GBP 2.2 billion by 2025 [2]. Sarcopenia is characterised by progressive and generalised decline in muscle strength, function, and mass with age, or secondary to disease [3]; it is associated with a range of adverse physical and metabolic outcomes in terms of disability, morbidity, impaired quality of life, and mortality [4], and has also been identified as a predictor of fracture risk [5]. In terms of cost, sarcopenia incurred an estimated USD 18.5 billion in health care costs to the USA in 2000. In the UK, the annual excess cost associated with muscle weakness was estimated to be GBP 2.5 billion [6,7]. Several varying definitions of sarcopenia have contributed to differences in prevalence estimates worldwide, ranging from 3 to 30% [4,8–10]. Currently, a global consensus on the definition of sarcopenia does not exist, but there are well-constructed diagnostic algorithms that provide a mechanism for clinical case identification [4].

Lifestyle factors such as levels of physical activity, nutrition, alcohol, and smoking have been shown to have effects on both bone and muscle. Physical activity is a very important contributor to bone and muscle health in later life [11]. Along with advancing age, physical inactivity is a major risk factor for both osteoporosis and sarcopenia. Furthermore, specific nutrients affect both bone and muscle—including vitamin D, calcium, vitamin K, and protein—and are critical to musculoskeletal health in later life [12–14].

The COVID-19 pandemic has led to widespread changes in lifestyle globally, as "stay at home" guidance was widely invoked. Older adults—the group most vulnerable to severe disease—were commonly asked to shield, or voluntarily severely restricted their activities. In a recent work, we evaluated how the first wave of the pandemic affected older adults in a pilot study (Nutrition and Physical Activity Study (NAPA)) conducted in the Hertfordshire Cohort Study (HCS) [15]. In total, 71 eligible Caucasian, community-dwelling participants—39 male and 32 female, with a mean age (SD) of 83.6 (2.5) years—were surveyed. In this modest sample, more than half (52%) of respondents reported being less physically active than before the pandemic. A number of variants of the SARS-CoV-2 virus have been identified, with rolling restrictions remaining in many countries. Widespread vaccination has provided reassurance to many older adults, but many are still fearful of engaging in activities that they previously would have enjoyed [16]. Changes in lifestyle might be expected to have effects on both muscle and bone health, with studies of older adults now required to study these in depth. Given the burden of musculoskeletal disease in late adulthood, research in this group is crucial. Although the rationale for studying this age group is hence clear, the feasibility of establishing a cohort of octogenarians living in their own homes in a global pandemic is untested. We have provided our own experience of recruitment in order to (a) highlight the need to consider these issues in older adults, and (b) advertise the study to invite collaboration early in the study process. Specifically, this study represents a research partnership across the primary–secondary care interface that is unusual in the UK, and might be replicated elsewhere. Here, we report our experience of this, before describing the methodology of the study that is planned.

2. Materials and Methods

Study Design

In July 2021 we identified all patients over the age of 75 who were registered at a large GP partnership in Southampton, UK (Living Well Partnership (LWP), https://livingwellpartnership.nhs.uk). Eligibility to participate in the study was decided by their primary care physician. Our sole inclusion criterion was the age of participants (>75 years of age) at the time of recruitment, as we aim to consider musculoskeletal health in this specific age group. Our exclusion criteria included the following:

- Patients with safeguarding issues;
- Patients with mental health and capacity issues;
- Patients with dementia or who were unable to provide consent;
- Patients with learning disabilities;
- Patients in end-of-life care;

- Patients with learning disabilities;
- Patients in end-of-life care;
- Patients who are permanently bedbound;
- Patients in residential or nursing homes.

All eligible participants were sent a study pack from LWP, consisting of a participant information sheet (PIS), two copies of a consent form, a questionnaire, and the contact details form.

Initial searches of the Egton Medical Information Systems (EMIS) database identified 2523 registered patients over the age of 75 years from any sex and ethnic group. Of those 2523 patients, 1993 (78%) were deemed eligible to participate in the study by their primary care physician (Figure 1).

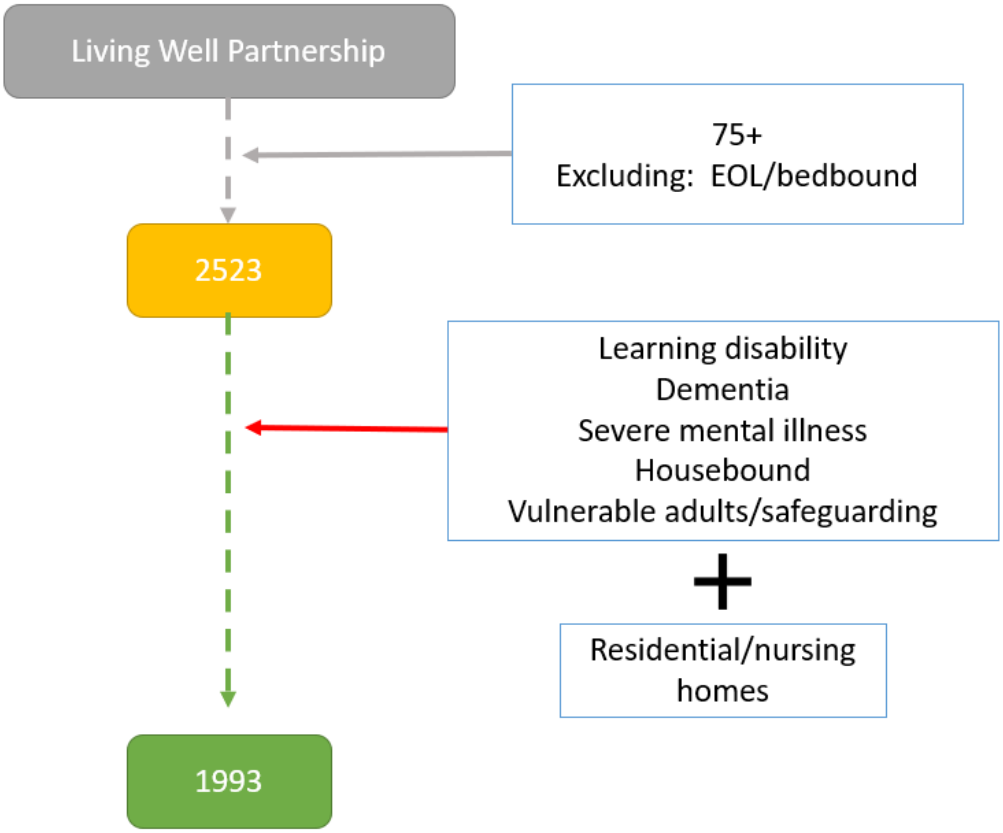

Figure 1. Flowchart of selection of eligible participants (EOL: end of life).

In total, 1993 participants were invited to participate in the study via postal invitation only. Participants indicated their willingness to be involved in the study and returned the copy of the signed consent form, along with the completed questionnaire and the contact details form to the research team at the MRC Lifecourse Epidemiology Centre (MRC LEC) Southampton, using a prepaid envelope. Participants had the opportunity to contact the research team using a dedicated research mobile phone and/or email that was provided for further queries. The returned documents were reviewed by a research team member in order to ensure the validity of those documents, and to identify any missing information. An anonymised ID number was allocated to each participant after ensuring that consent was obtained. A research team member contacted those participants who did not fully complete the consent or contact details forms via email, phone, or in writing.

Invitations were sent out in batches to manage workflow, as researchers were still largely working from home. Phase 1 led to the return of 175 complete questionnaires (Table 1). The questionnaire participants completed, included information on household, lifestyle factors, comorbidities, medical history, physical activity and capability, level of frailty, nutrition, self-reported walking speed, quality of life, and wellbeing. Where available, questions were sourced from validated questionnaires [17–22] (Table 2). Self-

reported walking speed has been shown to be a good marker of measured walking speed, and has previously been validated in the Hertfordshire Cohort Study [21]. The remaining questionnaires used in the study have previously been used in the HCS, which was also conducted by the MRC LEC Southampton [23].

Table 1. Preliminary baseline characteristics of participants in SaLSA (Southampton Longitudinal Study of Ageing).

Characteristic	Female				Male			
	N	**Median**	**IQR**	**%**	**N**	**Median**	**IQR**	**%**
Age	53	80.53	77–84		119	80.4	77–83	
Number of medications	53	5	3–7.75		117	4	3–7	
Polypharmacy (>=5)	33			62.2	22			18.8
Number of comorbidities	53	3	2–4		119	3	1–3	
Multimorbidity (>=2)	22			82	86			71
	N	N		%	N	N		%
Ethnic group	53				118			
White		50		94		118		100
Indian		2		4		0		0
Black Caribbean		1		2		0		0
Marital status	53				119			
Alone		36		68		38		32
Not alone (lives with friend/partner/family)		17		32		81		68
Age leaving school	52				119			
<=14		2		4		17		14
>14		50		96		102		86
Education after school	52				119			
None		24		46.1		33		27.7
Apprenticeship		7		13.4		47		39.4
Part-time college		8		15.3		45		37.8
Full-time college		8		15.3		15		12.6
Other		9		17.3		12		10
Higher qualifications								
None		22		40		41		34
O levels		23		42		48		40
A levels		10		18		20		17
Vocational training certificate		12		22		42		35
University degree		1		2		20		17
Higher professional qualifications		7		13		13		11
Smoking status	53				118			
Ex-smoker		20		71.6		78		66
Current smoker		0		0		5		3.38
Alcohol	54				121			
More than recommended units/week (14)		1		1.85		25		20.6
COVID-19 infection	50				117			
Yes		0		0		4		3.41
No		48		96		111		95
Suspected but not confirmed		2		4		2		1.7
Self-reported walking speed	54				121			
Fast		2		4		1		1
Fairly brisk		8		15		22		18
Normal speed		13		24		40		33
Stroll at an easy pace		15		28		34		28
Very slow		15		28		23		19
Unable to walk		1		2		1		1
	N	N		%	N	N		%
Falls past year	52				114			
>=1 fall	17			32.6	28			24.5

Table 1. *Cont.*

Characteristic	Female				Male			
	N	Median	IQR	%	N	Median	IQR	%
Fracture since age 45	52				112			
Yes		19		36.5		15		31.25
No		33		67		97		87
Self-rated health (SF-36)	53				120			
Excellent		3		5.66		4		3.33
Very good		13		24.5		27		22.5
Good		19		35.8		51		42.5
Fair		17		32		32		26.6
Poor		1		1.88		6		5

Table 2. List of subsections of questionnaires and data collected.

Questionnaires
Living circumstances and lifestyle factors
COVID-19 questionnaire
Medical conditions and medication history
Physical activity scale for the elderly (PASE)
Self-reported walking speed
Bone health questionnaire
Fried frailty questionnaire
Sarcopenia questionnaire (SARC-F)
Quality of life questionnaire (SF-36)
DETERMINE checklist
Food frequency questionnaire (FFQ)

In the planned next phases of the study, participants will be invited to attend a face-to-face clinic visit, where anthropometry, grip strength, gait speed, appendicular lean mass, and bone mineral density will be measured. Ultrasound scans, as a new screening method to diagnose sarcopenia, will also be performed [24]. Standardised effect sizes for objectively measured physical activity in relation to grip strength, walking speed, and appendicular mass index were estimated as 0.11, 0.26, and 0.15, respectively, in a cohort of a similar age [25]. The sample sizes required to detect these effect sizes with 80% power and a 5% significance level are 651 for grip strength, 119 for walking speed, and 351 for appendicular lean mass index; Statistics Kingdom was used for these calculations [26]. A subset of patients who are willing and have given consent will also undergo a high-resolution pQCT scan, before undergoing a percutaneous muscle biopsy of the vastus lateralis [27]. Outcome measures for SaLSA are summarised in Table 3.

Table 3. Overview of the measures to be collected during the 1st and 2nd phases of the study.

Variables	Instrument/Scale	Type of Assessment	1st Phase	2nd Phase
Age	Calculated based on the date of birth given	Questionnaire	√	
Sex	Female or male stated	Questionnaire	√	
Ethnicity	As self-reported	Questionnaire	√	
Marital status	Self-reported marital status	Questionnaire	√	
Education	Age of leaving school	Questionnaire	√	
	Self-reported education after school and/or higher qualifications	Questionnaire		
Living arrangements	Self-reported: own property/rented accommodation/residential home/nursing home/other	Questionnaire	√	

Table 3. *Cont.*

Variables	Instrument/Scale	Type of Assessment	1st Phase	2nd Phase
Smoking history	Self-reported as current or ex-smoker/packs/year	Questionnaire	√	
Alcohol consumption	Self-reported as drinking or not alcohol and units/week	Questionnaire	√	
Social status	Maastricht Social Participation Profile (MSSP), Hospital Anxiety and Depression Scale (HADS)	Questionnaire		√
Social isolation/loneliness	Six-item Lubben Social Network Scale (LSNS-6), De Jong Gierveld Short Loneliness Scale	Questionnaire		√
Occupation history	Self-reported current or previous employments	Questionnaire		√
Medical history/comorbidities	Self-recorded list of current regular medications including anti-osteoporosis medications	Questionnaire	√	
Number of medications	List of medical conditions provided used previously in HCS study	Questionnaire	√	
COVID-19 status	COVID-19 questionnaire developed during the pandemic and used previously in the HCS study. Assess COVID-19 infection status and symptomatology/long-term consequences; COVID-19 vaccination status	Questionnaire	√	
Physical activity	Physical Activity Scale for the Elderly (PASE)	Questionnaire	√	
Physical capability	Self-reported walking speed	Questionnaire	√	
Frailty	Fried frailty criteria	Questionnaire and research visit	√	√
	Clinical frailty scale	Research visit		√
	Frailty index (eFI)	Research visit		√
Fractures/falls	Self-reported number of fractures since the age of 45 and in the past year	Questionnaire	√	
	X-rays and vertebral fracture assessment			
	Self-reported number of falls since the age of 45 and in the past year	Questionnaire	√	
Muscle health	Strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F)	Questionnaire	√	
	Sarcopenia status (EWGSOP2)			
Bone, muscle, fat: density/microarchitecture/morphology	DXA scan of lumbar spine and femoral neck	Research visit		√
	High-resolution peripheral quantitative computed tomography (HRpQCT)	Research visit		√
	Percutaneous muscle biopsy of vastus lateralis	Research visit		√
	Muscle ultrasound	Research visit		√
Perceived health state	SF-36	Questionnaire	√	
	SarQoL (sarcopenia and quality of life)			
Nutrition	DETERMINE checklist—identifying malnutrition	Questionnaire	√	
	Food frequency questionnaire—assessing habitual diet	Questionnaire	√	
Anthropometric measurements	Weight, height, BMI, waist, hip, mid–upper arm, and thigh circumferences	Research visit		√
	Triceps, biceps, subscapular, and supra-iliac skinfold thicknesses	Research visit		√
Cardiovascular assessment	Blood pressure, pulse rate	Research visit		√
	Standard 12-lead electrocardiograph	Research visit		√
Blood profile	Fasting blood samples to be taken from the anterior cubital fossa for subsequent glucose, insulin, HbA1c, bone profile, albumin, lipid profile, vitamin D, vitamin C, hormonal, inflammatory, and DNA analyses, for posterity and further assays;	Research visit		√
Physical performance	Grip strength (Jamar hand-grip dynamometer)	Research visit		√
	Quadriceps strength			
	Timed 6 m up-and-go test and 3 m walk			
	Chair rises			
	Timed one-legged stand			
Cognitive function	AMTS [1]/MoCA [2]	Research visit		√

[1] Abbreviated mental test score; [2] Montreal Cognitive Assessment.

3. Patient and Public Involvement (PPI)

Key to the success of SaLSA will be PPI. A research team member attended a virtual patient and public coffee morning meeting organised by the Patient and Public Group (PPG) of LWP. PPG representatives highlighted the importance of making sure that we ask the potential participants about their willingness to attend a future clinic, and advised that patients need to be seen in a "COVID-19-safe environment". We are continuing our engagement with the PPG group during the next phases of the study, in order to understand what COVID-19 mitigations would be required for participants to feel safe.

4. Data Access

A steering committee will be established to review all data access requests in due course. It will not be possible for participants to be identified from any of the statistical analysis outputs/results.

5. Results

Preliminary Sample

In total, 1993 participants were invited to participate, by post only; 450 (22.5%) participants returned a questionnaire; 353 (79%) questionnaires were complete; 295 participants (84%) said they were happy to be contacted again to participate in future studies, while 35 (10%) were not sure.

The summarised demographics of participants who returned the first 175 questionnaires are presented in Table 1. The median age of participants was 80.4 (77–83) years in both sexes (80.5 years (77.9–84) in females and 80.4 years in males (77.3–83.6)). The majority (N = 168/171, 98%) of participants were of white ethnic background. Two (2) females of Indian origin and one (1) female of Black Caribbean origin were included. In total, 36/53 (68%) female participants and 38/119 (32%) male participants live alone; 152/171 participants left school over the age of 14 (50/52 females and 102/119 males). Over half of female participants (28/52 (53%)), and 86/119 (72%) male participants continued with education after school; 29/54 female and 78/121 male participants obtained a higher qualification degree; 58% (98/171) of participants are ex-smokers, and only 5/171 still smoke, all of whom are males (3%). Only 1/54 of females and 25/121 of male participants who drink alcohol consume more than the recommended units/week (14 UI/week). Only 2/50 (4%) females suspect that they have had COVID-19, and 4/117 (2%) male participants had confirmed COVID-19 infection.

Over 70% of female and male participants (n = 149/175) reported having >=2 comorbidities, and so would fulfil the definition of multimorbidity. Over 60% of female participants (33/53) reported polypharmacy, defined as >=5 regular medications, compared to 18% (22/117) of male participants. Walking speed was self-reported by all participants. Around one-third of participants self-reported walking at a normal speed (13/54 (24%) females and 40/121 (33%) males) and strolling at an easy pace (15/54 (28%) females and 34/121 (28%)) in both sexes.

One-third of female participants (17/52) and one-quarter of male participants (28/114) reported at least one fall in the past year. One-third of all participants (19/52 and 15/112 female and male participants, respectively) reported a fracture since the age of 45.

Most participants rated their health to be "good" (70/175 (40%)). Their health was rated as "fair" in 28% (49/175) and "very good" in 23% of participants in both sexes (40/175). Only 4% self-rated their health as "excellent" (7/175) or "poor" (7/175) in this cohort.

We have previously studied the impact of the COVID-19 pandemic on participants in the HCS. We were therefore interested to understand how comparable the two cohorts were. Participants recruited in the SaLSA and NAPA studies were septuagenarians and octogenarians (Median age (IQR) in females: 80.5 (77–84)) and 83.8 (81.5–85.9) years, respectively; and in males: 80.4 (77–83) and 83.1 (81.5–85.5) years, respectively). Polypharmacy was common in both cohorts (the median number of medications used was 5 in females in both the NAPA and SaLSA studies, and in males in the NAPA study). Most female participants

in SaLSA live alone (68%), whereas in NAPA less than half of female participants reported living alone (45.1%).

6. Discussion

Musculoskeletal conditions such as osteoporosis and sarcopenia are a public health burden, and treatment strategies, including the development of novel therapeutic targets, are urgently required. This manuscript reports the first stages in establishing a new resource for the study of musculoskeletal health, which began at the time of a global pandemic, when many older adults experienced significant disruptions to their lifestyles as a result of public health messages designed to protect them from the risk of COVID-19 infection. The work is indicated now as there is an even greater need to consider musculoskeletal health in this group. Currently, it is uncertain whether these lifestyle changes will be reversible, in the context of widespread vaccination. Previous research in the HCS and elsewhere has shown that lifestyle risk factors cluster together to impact on physical function in later life, and contribute to the progression of sarcopenia, osteoporosis, and/or osteoarthritis, so information on this topic is urgently required [23].

A particular challenge of this work has been its initiation while the pandemic is ongoing. Recruitment of community participants for clinical research studies is often a challenging task. SaLSA is unique, as it will enable the assessment of the feasibility and practicality of recruiting older adults from the community who are likely research-naïve; it will establish a platform for future observational and interventional studies to identify at-risk groups or normal ageing participants. The cohort data will enable the development and evaluation of interventions targeted at improving health care outcomes for older adults. Specifically, data will be used to identify at-risk groups such as those suffering from osteoporosis, sarcopenia, osteosarcopenia, and/or frailty.

There has recently been growing interest in the coexistence of osteoporosis and sarcopenia in some individuals, often termed osteosarcopenia. There appears to be higher morbidity from falls, fractures, disability, and mortality in individuals diagnosed with osteosarcopenia [12,28]. However, there are limited epidemiological data on the subject, and more work is needed in order to understand the interrelationships between the two conditions. Specifically, knowledge of the overlap in the pathophysiology of osteoporosis and sarcopenia might inform the development of potential treatments for osteosarcopenia [29]. A variety of physical assessments is at the clinician's disposal when assessing for osteosarcopenia, and will be assessed in this study. The choice of physical assessment(s) is largely dependent on the clinician's preferred definition of sarcopenia. The two most useful physical assessments are the measurement of hand grip strength (kg) using a handheld dynamometer, and calculation of walking speed (m/s) over 4 m, as per the European Working Group on Sarcopenia in Older Adults (EWSGOP2) [4].

An exciting area of sub-study is in-depth muscle and bone phenotyping. We have previously studied muscle–bone interrelationships in the HCS [30,31], but SaLSA provides an opportunity to perform detailed investigation of bone trabecular and cortical microarchitecture using HRpQCT [32–36], muscle ultrasound [24], and muscle biopsy—a technique which we have previously shown to be acceptable to older adults [27]. These studies are critical, as muscle–bone crosstalk is an important and emerging area of research. Genetic, mechanical, and endocrine factors may explain the age-related association between muscle and bone loss [37]. There is accumulating evidence that other localized and systemic factors are involved, including mesenchymal stem cells residing in connective tissue (muscle, bone, and fat), myokines and osteokines (molecules released from muscle and bone cells, respectively), inflamm-ageing, and fat infiltration [38]. These pathophysiological findings are common to both sarcopenia and osteoporosis, thus suggesting that the two are closely linked [39].

There are, of course, limitations to our study, including the low number of non-Caucasian participants currently recruited, and our decision to exclude residential and nursing home residents, which might affect the implementation of our results to this group

of older adults. We will consider the characteristics of our study population against national census data at the conclusion of phase 1 of this study. However, the strengths of the study include a strong collaboration with LWP and their PPG group, supported by an experienced team of multidisciplinary team of researchers from the MRC LEC.

7. Conclusions

We have demonstrated that the recruitment of participants from primary care is feasible, with high levels of consent to contact for future study to establish a longitudinal study of ageing. Through SaLSA, we aim to study bone–muscle interrelationships in depth, and to provide an opportunity to collaborate with other researchers working in similar cohorts globally. Other future sub-studies could also explore determinants related to healthy ageing, including relevant psychosocial factors such as isolation, attitudes to ageing, social networks, satisfaction with life. and many more. In addition, having an interdisciplinary team of investigators encourages collaboration, and enables the introduction of in-depth and novel health assessments contributing to generating novel ideas for future research, allowing comparison with other cohorts such as the HCS. SaLSA will also promote training opportunities for both quantitative and qualitative early-career researchers. Adopting a community-based recruitment strategy will enable efficient coordination of activities between researchers in universities, secondary care establishments, and the community. SaLSA will set an example, enabling the establishment of a unique community-dwelling cohort, and in time we hope it will provide clinicians, researchers, and policymakers with a rich resource for further collaborative study, with the ultimate aim of improving health care for our local community-dwelling older people.

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Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Research Ethics Committee (REC) Health Regulator Authority (HRA) (REC reference 21/SC/0036, 17 March 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions (REC reference 21/SC/0036, 17 March 2021). Data are collected and retained in accordance with the Data Protection Act 1998 (GDPR from May 2018). All study data are anonymised from the initial data collection stage. Study data are stored on a password-protected computer held at the MRC LEU which is operated by a designated data protection officer.

Conflicts of Interest: F.L., A.L. and P.A. have nothing to declare. H.P.P. has received lecture fees from Abbott, Pfizer, and HC-UK conferences outside of the submitted work. E.D. declares consultancy and speaker fees from Pfizer, UCB, and Lilly.

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Appendix K Associations of sarcopenia and osteoporosis with frailty and multimorbidity

ORIGINAL ARTICLE

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Associations of osteoporosis and sarcopenia with frailty and multimorbidity among participants of the Hertfordshire Cohort Study

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Abstract

Background Ageing is commonly associated with sarcopenia (SP) and osteoporosis (OP), both of which are associated with disability, impaired quality of life, and mortality. The aims of this study were to explore the relationships between SP, OP, frailty, and multimorbidity in community-dwelling older adults participating in the Hertfordshire Cohort Study (HCS) and to determine whether coexistence of OP and SP was associated with a significantly heavier health burden.

Methods At baseline, 405 participants self-reported their comorbidities. Cut-offs for low grip strength and appendicular lean mass index were used according to the EWSGOP2 criteria to define SP. OP was diagnosed when *T*-scores of < -2.5 were present at the femoral neck or the participant reported use of the anti-OP medications including hormone replacement therapy (HRT), raloxifene, or bisphosphonates. Frailty was defined using the standard Fried definition.

Results One hundred ninety-nine men and 206 women were included in the study. Baseline median (interquartile range) age of participants was 75.5 (73.4–77.9) years. Twenty-six (8%) and 66 (21.4%) of the participants had SP and OP, respectively. Eighty-three (20.5%) reported three or more comorbidities. The prevalence of pre-frailty and frailty in the study sample was 57.5% and 8.1%, respectively. Having SP only was strongly associated with frailty [odds ratio (OR) 8.28, 95% confidence interval (CI) 1.27, 54.03; $P = 0.027$] while the association between having OP alone and frailty was weaker (OR 2.57, 95% CI 0.61, 10.78; $P = 0.196$). The likelihood of being frail was substantially higher in the presence of coexisting SP and OP (OR 26.15, 95% CI 3.13, 218.76; $P = 0.003$). SP alone and OP alone were both associated with having three or more comorbidities (OR 4.71, 95% CI 1.50, 14.76; $P = 0.008$ and OR 2.86, 95% CI 1.32, 6.22; $P = 0.008$, respectively) although the coexistence of SP and OP was not significantly associated with multimorbidity (OR 3.45, 95% CI 0.59, 20.26; $P = 0.171$).

Conclusions Individuals living with frailty were often osteosarcopenic. Multimorbidity was common in individuals with either SP or OP. Early identification of SP and OP not only allows implementation of treatment strategies but also presents an opportunity to mitigate frailty risk.

Keywords Sarcopenia; Osteoporosis; Osteosarcopenia; Frailty; Multimorbidity; Prevalence

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Introduction

Sarcopenia (SP), osteoporosis (OP), and frailty are highly prevalent in older adults but are frequently under-recognized. They have all been shown to have an adverse impact on quality of life and are associated with disability and mortality.[1] United Nations estimations showed that in 2010 there were 524 million people in the world aged 65 years old and over, with projections indicating that this number will increase to 1.5 billion by 2050 (a three-fold increase).[2] Hence, identification of individuals who might be particularly vulnerable to the adverse outcomes of musculoskeletal ageing is of clinical and public health concern.

Sarcopenia is characterized by progressive and generalized decline in muscle strength, function, and muscle mass with increasing age or secondary to a disease process. SP increases the likelihood of falls and adversely impacts on functional independence and quality of life.[3,4] OP, the commonest metabolic bone disease in older people, is characterized by both low bone mass and microarchitectural deterioration that predisposes to low-energy transfer fragility fractures. These are associated with chronic pain, impaired physical function, loss of independence, and a higher risk of short-term and longer-term institutionalization.[5] Consequently, both these conditions confer a high health burden for the individual as well as health care systems. 'Osteosarcopenia' is the term given when OP and SP occur in consort and recent intense focus has been on their combined effects on current and future health.

The syndrome of frailty is associated with, but not an inevitable consequence of ageing and is characterized by a vulnerability to stressor events that can be both internal and external.[6] Both frailty and pre-frailty, the prodromal state before the onset of clinically identifiable frailty, are associated with adverse outcomes.[7] The most widely used definitions of physical frailty are the phenotype model described by Fried, where frailty is identified by the presence of at least three out of five physical characteristics: weight loss, exhaustion, low energy expenditure, slow walking speed, and low handgrip strength.[8] The cumulative deficit model of frailty described by Rockwood *et al*. also predicts adverse health outcomes and comprises age-associated accumulation of deficits that range from symptoms, sensory deficits, clinical signs, diseases, disabilities, and abnormal laboratory test results.[9]

Few other studies have considered interrelationships between SP, OP, and frailty. For example, participants with SP were reported to have a high incidence of OP, a higher incidence of falls and fractures,[10–19] but in these analyses frailty was not considered the outcome. For instance, patients with SP had 12.9 times higher odds of having OP and 2.7 times higher odds of having fractures than the non-sarcopenic ones in a population-based Finnish study,[20] and similarly, bone mineral density (BMD) was found to be lower in sarcopenic individuals in the Copenhagen Sarcopenia study, increasing the risk of having OP.[21] Older males with a diagnosis of probable and definite SP were eight times more likely to have a diagnosis of osteopenia or OP,[22] where in postmenopausal Brazilian women, SP and severe SP was shown to impose a higher risk for OP adding to the growing evidence that SP and OP frequently co-occur.[23]

However, studies that have considered frailty as an outcome suggest that the risks of serious morbidity are notably higher when OP and SP coexist.[24–26] Individuals with osteosarcopenia have also increasingly higher risk of mortality compared with those with SP or OP alone.[27]

Given that ageing is commonly associated with SP and OP, the aims of this study were (1) to explore associations between SP and OP, individually or in combination, with frailty in community-dwelling older adults participating in the Hertfordshire Cohort Study (HCS), and (2) to determine if coexistence of both SP and OP (osteosarcopenia) carries a higher likelihood of being frail. Given the importance of multimorbidity on health outcomes,[28] and the association that previously has been described between osteosarcopenia and chronic diseases,[29] we also considered (3) whether the coexistence of SP and OP was associated with a significantly heavier health burden, as assessed by the number of concurrent long-term conditions. The wealth of phenotypic information collected in the HCS, a cohort study of community-dwelling older adults, has allowed us to describe the prevalence and pre-frailty in this group and to consider whether the coexistence of SP and OP in individuals interacted to amplitude risk of frailty. This is of high clinical relevance as the identification of coexistent SP and OP coexistence not only allows early treatment and management strategies but might also offer an opportunity to mitigate frailty risk.[5,6]

Methods

Study participants

The HCS was designed to examine the relationship between growth in infancy and the subsequent risk of common adult diseases, including OP and SP, and has been described in detail elsewhere.[30] Participants have been followed up at a number of time points since its inception. The present study was performed using baseline data collected in 2011. All study participants provided written informed consent, and ethical approval was obtained from the Hertfordshire Research Ethics Committee. All participants gave written informed consent.

Data collection

Questionnaire and anthropometry

Participants completed questionnaires that comprised questions related to lifestyle including smoking habits, alcohol consumption, physical activity (LASA Physical Activity Questionnaire—LAPAQ), and nutrition (Short Food Frequency Questionnaire—FFQ). Anthropometric measurements including height and weight were measured to calculate body mass index (BMI).

Physical performance and muscle mass

Grip strength was measured three times in each hand using a Jamar hand-held isokinetic dynamometer using a standardized protocol.[31] The maximum value was used in analyses. Gait speed (metres per second) determined after timed 8 foot walk test. The use of assistive devices was permitted, if required. For chair rises (also used to assess for physical function), the time taken for participants to stand up and sit down again (with their arms crossed across their chest) a total of five times was recorded.

Skeletal muscle mass was measured with a body composition dual-energy X-ray absorptiometry (DXA) scan (Lunar Prodigy Advanced) to quantify regional as well as total lean mass, fat mass, and bone mineral content. Proximal femur BMD values were determined using standard DXA.

Definitions of sarcopenia, osteoporosis, frailty, and comorbidity

Sarcopenia

Sarcopenia was defined using the revised EWSGOP2 criteria for low muscle strength measured by hand grip strength ($<$27 kg in men and $<$16 kg in women) or slow chair rise time ($>$15 s for five rises) and low muscle quantity [appendicular skeletal mass (ASM) index (ASM/height^2) $<$ 7.0 kg/m^2 in men and $<$5.5 kg/m^2 in women].[32]

Osteoporosis

Osteoporosis was defined according to the World Health Organization criteria and diagnosed when BMD *T*-scores were lower than the peak bone mass by 2.5 SD at the femoral neck or the use of osteoporotic treatment including hormone replacement therapy (HRT), bisphosphonates, or raloxifene was reported.

Frailty

Frailty was defined using the standard Fried definition using similar cut-offs for muscle strength that were used to define SP (grip strength $<$27 kg in men and $<$16 kg in women) in addition to the presence of unintentional weight loss, self-reported exhaustion, and lowest sex-specific fifth of activity time: 0 out of 5 domains = non-frail, 1 or 2 domains = pre-frail, and $\geq$3 domains = frail. The presence of unintentional weight loss was defined as a positive answer to the question: 'In the last year, have you lost more than 10 pounds (4.5 kg) unintentionally (i.e. not due to dieting or exercise)?'. The presence of self-reported exhaustion was defined as an answer of a moderate amount of time or most of the time (i.e. $\geq$3 days) to the question: How often in the last week did you feel 'everything I did was an effort' or 'I could not get going'.

Comorbidity

Participants were asked to self-report their comorbidities with the use of a questionnaire. We then categorized the number as none, one, two, and three or more. Multimorbidity was defined when participants self-reported three or more comorbidities.

Statistical analysis

Descriptive statistics for continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables were expressed as frequency (*N*) and percentage (%). Differences between groups (such as frailty status) were assessed using analysis of variance (ANOVA), Kruskal–Wallis tests, Pearson's χ^2 tests, or Fisher's exact tests as appropriate. Logistic regressions were performed to analyse associations of OP at femoral neck, SP, and coexistence of OP and SP as explanatory variables for frailty adjusting for sex only initially, then further adjusting for age, BMI, current smoker, and alcohol consumption.

Results

Complete baseline data were available for 405 participants (199 men and 206 women). The median (SD) age of participants at baseline was 75.5 (73.4–77.92) years. The characteristics of this population are shown in *Table* 1; 4.5% of men and 2.9% of women were current smokers with no sex difference (P = 0.391). There was a significant difference between women and men at baseline in the median (IQR) alcohol consumption [men: 6.2 (1.0–12.3) units per week; women: 0.3 (0.0–3.1) units per week; $P < 0.001$]. Over half of participants reported to have low walking speed ($\leq$0.8 m/s) (55.2%, 217/393) and one-fifth of them had low physical activity (80/394). One-fifth of participants had evidence of OP and 8% had evidence of SP; 20.5% (83/405) self-reported three or more comorbidities.

There were significant differences between non-frail, pre-frail, and frail participants with respect to age (P = 0.002), height (P = 0.035), BMI (kg/m^2) ($P < 0.001$), alcohol consumption (P = 0.027), physical activity in the last 2 weeks ($P < 0.001$), walking speed ($P < 0.001$), and grip strength

Table 1 Baseline characteristics of all participants

	All participants		
	N	Median	IQR
Age (years)	405	75.5	73.4–77.9
Weight (kg)	405	76.0	68.2–85.8
BMI (kg/m^2)	402	27.4	25.1–30.9
Alcohol consumption (units per week)	405	2.0	0.1–8.3
Activity time in the last 2 weeks (min/day)	394	190	124–283
	N	Mean	SD
Height (cm)	402	165.7	9.3
Maximum grip (kg)	405	28.7	10
Gait speed (m/s)	393	0.75	0.18
ALM index (kg/m^2)[a]	295	7.27	1.08
Femoral neck BMD (g/cm^2)[b]	306	0.889	0.139
	Total *N*	*N*	%
Female sex	405	206	50.9
Unintentional weight loss	404	16	4.0
Self-reported exhaustion	405	48	11.9
Low grip strength (<27 kg men; <16 kg women)	405	47	11.6
Low walking speed (≤0.8 m/s)	393	217	55.2
Low physical activity[c]	394	80	20.3
Emaciated (BMI < 18.5 kg/m^2)	402	2	0.5
Current smoker	405	15	3.7
Osteoporosis[d]	308	66	21.4
Sarcopenia	323	26	8.0
Having 3 or more comorbidities	405	83	20.5

BMI, body mass index; IQR, interquartile range; SD, standard deviation.
[a]ALM = appendicular lean mass.
[b]Minimum of left and right femoral neck bone mineral density.
[c]Low physical activity = lowest 20% of activity time.
[d]Osteoporosis = femoral neck *t*-score < −2.5 or taking hormone replacement therapy, bisphosphonates, or raloxifene.

($P < 0.001$) as shown in *Table* 2. Of the five Fried frailty components, low walking speed and low physical activity followed by self-reported exhaustion were the most prevalent (96.6%, 87.5%, and 75.8%, respectively) among frail participants.

In our sample, the prevalence of frailty and pre-frailty at baseline was 8.1% (men 7.0%, women 9.2%) and 57.5% (men 54.3%, women 60.7%), respectively. *Figure* 1 illustrates the prevalence of frailty in the 70–74, 75–79, and ≥80 year age groups. These were 5.8%, 9.8%, and 14.3%, respectively, and that of pre-frailty was 55.3%, 59.3%, and 61.9%, respectively. *Figure* 1B and 1C also shows the age-stratified and gender-stratified prevalence of frailty and pre-frailty. There were no significant differences in frailty status between men and women nor between the age groups in both sexes.

We next considered interrelationships between SP, OP, or both with frailty. Coexistence of SP, OP, and frailty was observed in 1% of this population. Two per cent of the study sample had SP and OP. Seventy-three per cent had no evidence of SP, OP, or frailty (*Figure* 2). Among the participants with frailty, 27.8% had a concomitant diagnosis of SP, compared with 8.9% in the pre-frail and 4.0% in the non-frail categories ($P = 0.005$). In a model of SP/OP status, having SP only was strongly associated with frailty [odds ratio (OR) 8.28, 95% confidence interval (CI) 1.27, 54.03; $P = 0.027$] while the association between having OP alone and frailty was weaker (OR 2.57, 95% CI 0.61, 10.78; $P = 0.196$). The likelihood of being frail was substantially higher in the presence of coexisting SP and OP (OR 26.15, 95% CI 3.13, 218.76; $P = 0.003$) (*Table* 3). Having SP alone and OP alone were both associated with having three or more comorbidities (OR 4.71, 95% CI 1.50, 14.76; $P = 0.008$ and OR 2.86, 95% CI 1.32, 6.22; $P = 0.008$, respectively) although this relationship was not stronger with coexisting SP and OP (OR 3.45, 95% CI 0.59, 20.26; $P = 0.171$) (*Table* 4).

Discussion

In this study, we examined the association between SP, OP, or coexistence of SP and OP, with frailty and multimorbidity in 405 community-dwelling older men and women. We also report prevalence and incidence of frailty in the same group of community-dwelling older adults. As might be anticipated, SP was associated with frailty, but the association of OP with frailty was weaker. However, we also reported that the likelihood of being frail was markedly higher in the presence of coexisting SP and OP than with SP alone. We had anticipated relationships between SP and frailty because of

Table 2 Characteristics of individuals by frailty category; frailty components and association with sarcopenia and osteoporosis categories

	Non-frail			Pre-frail			Frail			
	N	Median	IQR	*N*	Median	IQR	*N*	Median	IQR	*P*-value[a]
Age (years)	139	74.7	73.1–76.8	233	75.7	73.7–78.5	33	77.0	74.7–78.9	0.002*
Weight (kg)	139	74.3	68.2–81.9	233	76.6	68.2–88.0	33	78.5	70.6–88.7	0.143
BMI (kg/m^2)	139	26.5	24.4–29.2	230	28.4	25.6–31.2	33	29.4	25.4–32.8	<0.001*
Alcohol consumption (units per week)	139	3.3	0.3–10.0	233	2.0	0.1–7.5	33	0.5	0.0–5.0	0.027*
Activity time in the last 2 weeks (min/day)	139	231	178–327	223	176	107–240	32	63	42–91	<0.001*
	N	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*P*-value[a]
Height (cm)	139	167.3	9.1	230	165.0	9.3	33	163.9	9.9	0.035*
Maximum grip (kg)	139	32.4	9.3	233	27.7	9.5	33	20.6	10.1	<0.001*
Gait speed (m/s)	139	0.90	0.1	225	0.69	0.15	29	0.53	0.14	<0.001*
ALM index (kg/m^2)[b]	110	7.28	1.08	168	7.28	1.08	17	7.08	1.10	0.745
Femoral neck BMD (g/cm^2)[c]	115	0.892	0.127	172	0.892	0.148	19	0.853	0.134	0.500
	Total *N*	*N*	%	Total *N*	*N*	%	Total *N*	*N*	%	*P*-value[a]
Female sex	139	62	44.6	233	125	53.6	33	19	57.6	0.174
Unintentional weight loss	139	0	0	232	8	3.4	33	8	24.2	<0.001*
Self-reported exhaustion	139	0	0	233	23	9.9	33	25	75.8	<0.001*
Low grip strength (<27 kg men; <16 kg women)	139	0	0	233	27	11.6	33	20	60.6	<0.001*
Low walking speed (≤0.8 m/s)	139	0	0	225	189	84.0	29	28	96.6	<0.001*
Low physical activity[d]	139	0	0	223	52	23.3	32	28	87.5	<0.001*
Emaciated (BMI < 18.5 kg/m^2)	139	2	1.4	230	0	0	33	0	0	0.277
Current smoker	139	2	1.4	233	12	5.2	33	1	3.0	0.169
Osteoporosis[e]	118	24	20.3	173	36	20.8	17	6	35.3	0.375
Sarcopenia	126	5	4.0	179	16	8.9	18	5	27.8	0.005*
Having 3 or more comorbidities	139	19	13.7	233	48	20.6	33	16	48.5	<0.001*

BMI, body mass index; IQR, interquartile range; *N*, number of participants; SD, standard deviation.
[a]*P*-value for the difference between the frailty categories.
[b]ALM = appendicular lean mass.
[c]Minimum of left and right femoral neck bone mineral density.
[d]Low physical activity = lowest 20% of activity time as measured by LAPAQ.
[e]Osteoporosis = femoral neck *t*-score < −2.5 or taking hormone replacement therapy, bisphosphonates, or raloxifene.
*P-value < 0.05.

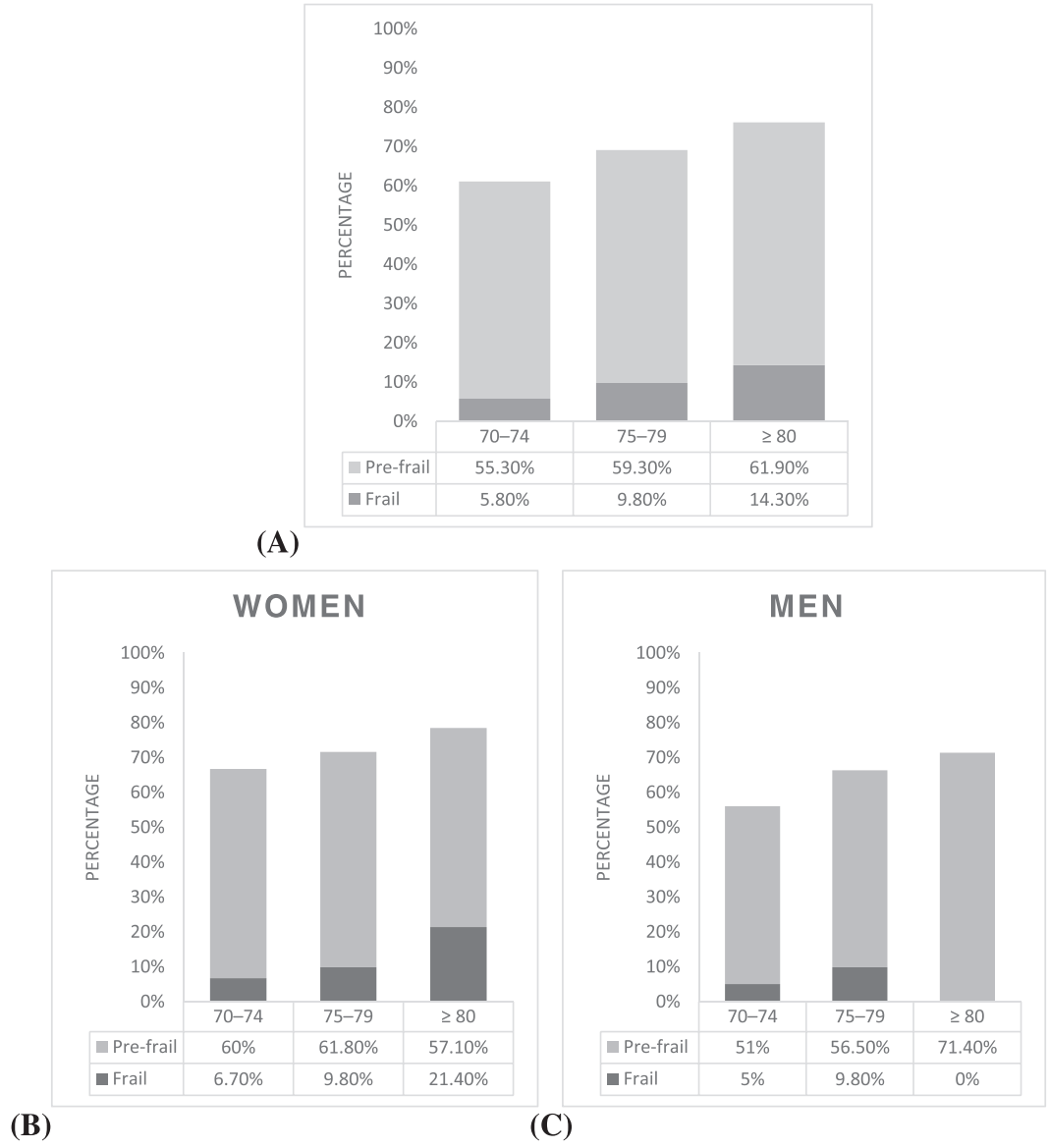

Figure 1 Pooled prevalence of frailty and pre-frailty at baseline (*A*) and age-stratified and gender-stratified prevalence of frailty and pre-frailty at baseline (*B* and *C*).

the diagnostic criteria for the two conditions.[33] For this reason, we also considered relationship with multimorbidity as a proxy marker for frailty. Both SP and OP were associated with multimorbidity, but in this case there did not appear to be an interaction between the two conditions.

The concept of osteosarcopenia is relatively new, but in previous work coexistence of SP and OP has been associated cross-sectionally with depression, malnutrition, peptic ulcer disease, inflammatory arthritis, and reduced mobility.[34] Studies from Australia and China have demonstrated that individuals with both OP and SP are at higher risk of falls and fractures than those with OP or SP alone.[24,34] Only a few studies have examined the association between both OP and SP with frailty in community-dwelling older adults. In the Women's Health and Aging Studies II, the likelihood of being frail was higher in the presence of these two conditions, but the association was not statistically significant. The criteria used in this study to assess SP was appendicular lean mass by height^2 without taking into account muscle strength, possibly leading to an under-recognition of sarcopenic participants.[35] In the SARCOS study, low lean mass together with OP showed an association with frailty; cut-offs for lean mass were based on FNIH criteria, and the authors aimed to characterize the phenotype of sarcopenic older adults only based on lean mass.[36] In a study of octogenarians in China, women were more likely to have osteosarcopenia compared with men; SP and OP alone or in combination were associated with frailty.[24] OP, risk of falls, and SP were

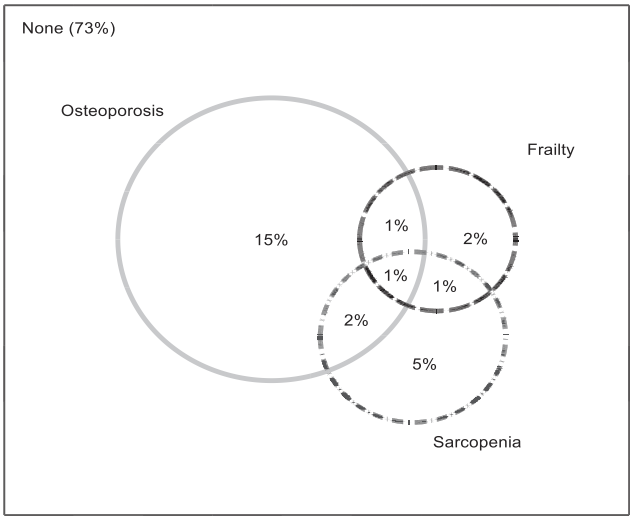

Figure 2 Venn diagram illustrating the relationships of osteoporosis, sarcopenia, and frailty at baseline.

Table 3 Relationship of sarcopenia, osteoporosis, and frailty at baseline

	Adjusted for sex only				Fully adjusted			
	N	OR	95% CI	*P*-value	*N*	OR	95% CI	*P*-value
OP and SP status	293				284			
Neither OP nor SP (reference)								
OP only		2.24	0.53, 9.56	0.274		2.57	0.61, 10.78	0.196
SP only		3.77	0.68, 20.90	0.129		8.28	1.27, 54.03	0.027*
Both OP and SP		9.98	1.60, 62.22	0.014*		26.15	3.13, 218.76	0.003*

CI, confidence interval; *N*, number of participants; OP, osteoporosis; OR, odds ratio; SP, sarcopenia.
Values in the fully adjusted categories are adjusted for sex, age, body mass index, current smoking history, and alcohol consumption. OP values refer to a femoral neck *T*-score of < -2.5 or taking hormone replacement therapy, bisphosphonates, or raloxifene. SP was defined using the EWSGOP2 criteria.
*P-value < 0.05.

Table 4 Relationship of sarcopenia, osteoporosis, and multimorbidity (≥3 comorbidities) at baseline

	Adjusted for sex only				Fully adjusted			
	N	OR	95% CI	*P*-value	*N*	OR	95% CI	*P*-value
OP and SP status	288				286			
Neither OP nor SP (reference)								
OP only		2.76	1.35, 5.67	0.006*		2.86	1.32, 6.22	0.008*
SP only		2.98	1.02, 8.74	0.047*		4.71	1.50, 14.76	0.008*
Both OP and SP		2.12	0.39, 11.64	0.385		3.45	0.59, 20.26	0.171

CI, confidence interval; *N*, number of participants; OP, osteoporosis; OR, odds ratio; SP, sarcopenia.
Values in the fully adjusted categories are adjusted for sex, age, body mass index, current smoking history, and alcohol consumption. OP values refer to a femoral neck *T*-score of < -2.5 or taking hormone replacement therapy, bisphosphonates, or raloxifene. Comorbidities self-reported by participants. SP was defined using the EWSGOP2 criteria.
*P-value < 0.05.

reported in the I-Lan Longitudinal Aging Study to be associated with frailty independently.[37] In a hospital-based study, SP was strongly associated with frailty ($P < 0.001$) while relationships with OP were weaker ($P = 0.055$).[38] Finally, in a retrospective study among postmenopausal patients with known OP attending a hospital bone clinic, those with a diagnosis of osteosarcopenia were more likely to be frail than those with OP alone.[25]

As expected, frailty and pre-frailty were more prevalent in individuals over the age of 80 in both sexes. Both the prevalence of frailty and pre-frailty were increased with age in women, but only pre-frailty was increased with age in men;

however, the number of men aged over 80 in our study was low. Previous UK-based studies report similar prevalence of frailty to our study, but sex differences were noted.[39] Weighted prevalence in the English Longitudinal Study of Ageing (ELSA) study was 14% among participants age 60–90 years[40]; prevalence did increase with age, was more common in women, and was associated with a burden in regard to mobility, and everyday activities.

Other groups studying an older population have found the prevalence of frailty and pre-frailty to be similar to our study,[37,41–43] although different population sampling and definitional approaches may lead to differences in findings. For example, in a community-dwelling cohort of men and women in Japan with mean age of 70.3 (SD 11.0) years, the prevalence of frailty was estimated to be 5.6% in both sexes (in the same cohort, frailty was more common in the presence of both SP and OP).[44] In a recent systematic review and meta-analysis, the pooled prevalence of frailty for community dwellers aged ≥50 years, using full and recognized modifications of Fried's criteria, was 12% across 62 counties worldwide compared with 24% when other measures of frailty were used, highlighting that instrument selection influences prevalence proportions. In Europe specifically, the prevalence of frailty was 8%, a percentage close to our calculated prevalence, when using physical frailty measures and that of pre-frailty was 42%.[45] Far fewer data are available regarding the prevalence of pre-frailty in community-dwelling populations. The Survey of Health, Aging and Retirement in Europe (SHARE) was one of the few studies assessing pre-frailty and found that the prevalence of pre-frailty in individuals over the age of 50 in 10 European countries ranged between 34.6% and 50.9%.[46] In our study, the prevalence of pre-frailty was higher, ranging from 55.3% to 61.9%. Approximately 43.4 and 150.6 per 1000 person-years was the estimated incidence of frailty and pre-frailty, respectively, in a recent systematic review and meta-analysis,[47] a higher incidence compared with our study although there is likely to be substantial geographic variation when measuring incidence.[48]

Our study has some limitations. Participants in the HCS cohort study are all community living and therefore might be expected to show a healthy cohort bias, limiting our ability to discern some relationships. This is reflected by the relatively low number of sarcopenic and frail individuals and by the fact that participants for whom data were available at follow-up and developed frailty were overall healthier. They were younger, heavier, taller, stronger, and faster walkers and had better physical activity compared with those for whom data were not available on incidence frailty. However, this study has been able to draw on the detailed phenotypic information available in the HCS to report the epidemiology of coexisting OP and SP, and its association with multimorbidity and frailty. Furthermore, HCS participants have been compared with those in the nationally representative Health Survey for England and have been found to be broadly comparable in terms of their health and lifestyle. We therefore suggest that the results from the current study could be reasonably generalized to the wider population of older men and women.

Our study suggests that the likelihood of being frail was markedly higher when SP and OP were coexistent. However, the relationship may be bidirectional given the risk factors and pathophysiological pathways that drive individual conditions. Future longitudinal cohort studies of older people who are diverse in both ethnicity and socio-economic status may provide a more comprehensive understanding to the relationship between osteosarcopenia and frailty.

Conclusions

We have shown an overall prevalence of frailty in community-dwelling older UK adults of 8.1% with the risk increasing with age. Corresponding figures for pre-frailty were 57.5% with the risk increasing with age only in females. We found that the presence of baseline SP and OP together are associated with a much higher risk of frailty cross-sectionally than either condition alone and that SP and OP are both closely linked with multimorbidity. As the presence of coexisting SP and OP were highly associated with frailty, appropriate treatment and early intervention of these conditions can have a clinical benefit to reduce the progression to frailty. Furthermore, identifying and treating individuals with pre-frailty and probable SP as early and reversible risk states may be associated with better health care outcomes and lower risk of developing frailty. Muscle and bone interrelationships need to be further studied in large prospective longitudinal cohorts as better understanding of the epidemiology of osteosarcopenia is extremely relevant to inform the development of future interventions and therapeutics to maintain older people's independence.

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The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[49]

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Conflict of interest

E.D. declares consultancy and speaker fees from Pfizer, UCB, and Lilly. C.C. has received lecture fees and honoraria from Amgen, Danone, Eli Lilly, GSK, Kyowa Kirin, Medtronic, Merck, Nestlé, Novartis, Pfizer, Roche, Servier, Shire, Takeda, and UCB outside of the submitted work. N.F. declares travel bursaries from Pfizer and Eli Lilly. H.P.P. has received lecture fees from Abbott, Pfizer, and HC-UK conferences outside of the submitted work. K.J. has nothing to declare.

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Appendix L Determinants of muscle density and clinical outcomes: findings from the Hertfordshire Cohort Study

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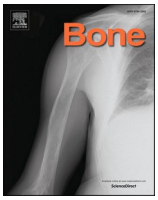

Full Length Article

Determinants of muscle density and clinical outcomes: Findings from the Hertfordshire Cohort Study

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ABSTRACT

Purpose: The age-related loss of skeletal muscle mass and strength is associated with adverse health outcomes. However, to date, peripheral quantitative computed tomography (pQCT)-derived muscle density has been little studied. We used a well characterised cohort of older adults to identify lifestyle and anthropometric determinants of pQCT-derived muscle density measured 11 years later, and to report relationships between pQCT-derived muscle density with history of falls and prevalent fractures.

Methods: A lifestyle questionnaire was administered to 197 men and 178 women, aged 59–70 at baseline. After a median of 11.5 (IQR 10.9, 12.3) years, pQCT (Stratec XCT2000) of the radius and tibia was performed to measure forearm muscle density (FMD) and calf muscle density (CMD). Presence of falls and fractures since the age of 45 were determined through participant recall; vertebral fractures were also ascertained through vertebral fracture assessment using iDXA. Total hip BMD (TH aBMD) was assessed using DXA. Baseline characteristics in relation to muscle density at follow-up were examined using linear regression; associations between muscle density and prior falls and fractures were investigated using logistic regression. All analyses were adjusted for sex and age.

Results: Mean (SD) age at muscle density measurement was 76.3 (2.6) years. Mean (SD) FMD was 79.9 (3.1) and 77.2 (3.2) among males and females, respectively; CMD was 80.7 (2.6) and 78.5 (2.6) among males and females, respectively. Significant sex-differences in muscle density were observed at each site ($p < 0.001$). Female sex, lower weight, and lower body mass index were associated ($p < 0.05$) with both lower FMD and CMD. Additional correlates of lower CMD included older age and shorter stature. Lifestyle measures were not associated with muscle density in this cohort. Lower FMD was related to increased risk of previous fracture (odds ratio (95 % CI) per SD lower FMD: 1.42 (1.07, 1.89), $p = 0.015$) but not after adjustment for TH aBMD ($p > 0.08$). No significant relationships were seen between muscle density and falls.

Conclusion: Female sex, older age, and lower BMI were associated with subsequent lower muscle density in older community-dwelling adults. Lower FMD was related to increased risk of previous fracture. Changes in muscle density over time might precede adverse outcomes such as falls and fractures and may be a long-term predictor of frailty. It could be also suggested that muscle density could be a more clinically meaningful surrogate of functional decline and disability than muscle size or mass, but more studies are needed to support this notion.

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1. Introduction

Sarcopenia is associated with a number of adverse health outcomes, including decreased quality of life, functional impairment, disability, increased risk of falls, hospitalisation, and increased mortality [1–7]. Muscle health can be assessed in many ways, and researchers have sought to identify muscle parameters, including muscle quality [8], which has been linked to muscle density [9,10]. Few studies have considered the demographic and lifestyle determinants of muscle density, which has been shown to decrease with age [11]. Furthermore lower muscle density may imply greater fatty infiltration within skeletal muscle and so might link to adiposity [7,12].

Muscle density represents an interesting muscle variable to study further as reduced leg muscle density increases the risk of mobility loss and has been associated with falls [13,14], which may increase future fracture risk. Muscle density has been shown to perform better than bone mineral density or muscle size in discriminating individuals with a history of hip fracture, and has been associated with an increased risk of hospitalisation [13,15–20].

Muscle density can be assessed by peripheral quantitative computed tomography (pQCT), a technique that was developed for bone density and bone strength estimation. This technique produces a cross-sectional image that permits quantification of three-dimensional tissue structure properties of a limb segment, enabling the cross-sectional area (CSA) of soft tissue and muscle density to be estimated. Since fat is calibrated to zero with pQCT, typical muscle density values range from 65 to 90 mg/cm^3 [21]. Recent studies have highlighted the link between muscle density assessed by pQCT, and fracture risk [22], but these data were collected in a large US study of older males only.

Assessment of muscle-bone relationships using pQCT-derived variables has been undertaken previously in the Hertfordshire Cohort Study; muscle size and grip strength were associated with bone size and strength, but relationships between gait speed and bone structure and strength were not apparent in this cohort, supporting a role for the muscle-bone unit [23]; in other work in Hertfordshire, we have shown positive associations between changes in muscle area and cortical area in both men and women [24].

Given the relative paucity of available research on muscle density, our aims were to use a prospective study of community-dwelling adults to: (1) identify determinants of peripheral muscle density (lifestyle and anthropometric characteristics); and (2) to relate peripheral muscle density measures to history of falls and prevalent fractures. In our study, participants had a mean age at baseline of 64.7 years. This is a stage in the lifecourse when identification of individuals at high risk of poor musculoskeletal outcomes later in life might be possible, and if evidence exists that lifestyle modification might be beneficial, this may result in substantial personal and societal benefit.

2. Methods

2.1. The Hertfordshire Cohort Study

The Hertfordshire Cohort Study (HCS) is a population-based cohort of older adults, consisting of 1579 males and 1418 females, born in Hertfordshire, UK, between 1931 and 1939 and still living in the county in 1998–2004. All participants were Caucasian. Following our initial contact in 1998–2004, participants completed a baseline home interview and attended a research clinic for detailed assessment of their socio-demographic, lifestyle and clinical characteristics; the study has previously been described in detail [25,26]. In 2004, of the 966 participants from East Hertfordshire who had a dual-energy X-ray absorptiometry (DXA) scan at the start of the study, 642 were recruited for a musculoskeletal follow-up study (8/966 had died, 74/966 could not be located and 242/966 declined to participate). In 2011–2012, 570/642 participants from East Hertfordshire were invited to take part in a further bone follow-up study which involved measurement of muscle density by peripheral quantitative computed tomography (pQCT); 376/570 agreed to participate.

2.2. Ascertainment of participant characteristics in 1998–2004

A lifestyle questionnaire was administered at the home interview to collect information on physical activity (Dallosso questionnaire [27]), smoking, and alcohol consumption. Participants completed a food-frequency questionnaire from which protein intake was ascertained, and a 'prudent diet' score was derived using principal components analysis; higher scores reflected healthier diets [28]. Social class was coded from the 1990 OPCS Standard Occupational Classification (SOC90) unit group for occupation [29]. Social class was ascertained from current or most recent full-time occupation for all men and also among women who never married, and only from husband's occupation for ever-married women. Details of all prescription and over-the-counter medications currently taken were coded according to the British National Formulary; the number of systems medicated was derived as a marker of comorbidity.

Investigations conducted at the baseline clinic included measurement of standing height (Harpenden pocket stadiometer, Chasmors Ltd, London, UK) and weight (SECA floor scale, Chasmors Ltd, London, UK) which were used to derive body mass index (BMI).

2.3. Ascertainment of characteristics at the 2011–2012 follow-up

Bone density measurements have been described in detail previously [30]. pQCT was performed using a Stratec XCT2000 instrument (software version 6.20, Stratec Medizintechnik, Pfrozheim, Germany); scans were acquired at the 4 and 66 % sites of the radius, and at the 4 and 38 % sites of the tibia. Muscle density was derived at the 66 % site on the non-dominant side using standard thresholds and calculated by dividing mass by volume; muscle mass was obtained by calculating total area at C1P2, threshold −50, 41 mg/cm^3 and muscle mass at a threshold of 100 mg/cm^3, filer F03F05. All scans were checked for motion artefact by a trained observer. Additionally, scans were excluded if extreme outliers were observed. Bone mineral density (BMD) of the total hip was assessed using DXA (Lunar Prodigy Advance DXA scanner GE Medical Systems, Waltham MA); the lowest value from the left and right side was used for analysis. Appendicular lean mass (ALM) was derived using the same DXA scanner and height was measured using a wall mounted SECA stadiometer; these measures were used to derive appendicular lean mass index (ALMi) as ALM (kg) divided by the square of height (m).

Grip strength (kg) was measured three times for each hand using a Jamar dynamometer (Promedics, Blackburn); the highest measurement was used for analysis. Mean customary gait speed in metres per second was calculated after two 8 ft. walking exercises.

Participants were asked the following through nurse-administered questionnaires: 'Have you had any falls since the age of 45 years?' and 'Have you broken any bones since the age of 45 years?'. Morphometric vertebral fractures were diagnosed from a lateral spine view imaged using the Prodigy DXA scanner and graded based on the Genant semi-quantitative method of vertebral fracture assessment by two trained independent observers [31]. Participants with a vertebral fracture or a self-reported fracture since age 45 years were regarded as having had a previous fracture.

2.4. Statistical analysis

Participant characteristics were described using summary statistics. Standard deviation (SD) scores were derived for continuous baseline characteristics and the muscle density measures to enable comparison of effect sizes. For each participant, follow-up time was calculated as the duration from the study baseline (1998–2004) to when the muscle density measures were ascertained at the 2011–2012 follow-up.

Baseline characteristics in relation to muscle density outcomes at

follow-up were examined separately using linear regression. Sex, baseline age and follow-up time were included as covariates in all models.

Pearson correlations were used to examine muscle density measures in relation to ALM index, grip strength, gait speed and total hip BMD.

Muscle density measures in relation to falls and fractures since age 45 years were examined using logistic regression with adjustment for sex and age and then additionally for total hip BMD.

Analyses were conducted using Stata, release 16.1 (StataCorp, College Station, Texas, USA). The analysis sample comprised the 375 participants who had values for forearm or calf muscle density. To maintain sample size, males and females were pooled for analyses (sex-interaction effects were examined) and analyses were adjusted for sex; $p < 0.05$ was regarded as statistically significant.

3. Results

3.1. Participant characteristics

Characteristics of the 375 participants (197 males, 178 females) who were included in the analysis are presented in Table 1. Mean (SD) age at baseline was 64.7 (2.7) years and median (lower quartile, upper quartile) follow-up time was 11.5 (10.9, 12.3) years. Mean (SD) muscle density values (mg/cm^3) were as follows: forearm [males 79.9 (3.1), females 77.2 (3.2)], calf [males 80.7 (2.6), females 78.5 (2.6)]. Pearson correlations between calf and forearm muscle density were 0.13 ($p = 0.070$) among men and 0.23 ($p = 0.002$) among women (data not shown).

Males, as expected, were taller at baseline (mean [SD] height: males 174.6 [6.7] cm, females 161.9 [5.4] cm) and heavier (mean [SD] weight was 79.9 [10.1] kg among males, 69.6 [12.2] kg among females). Over half of males (n = 115, 58.4 %) and a third of females (n = 62, 34.8 %) were identified as current or previous smokers. Only 48 (24.4 %) males and 3 (1.7 %) females had high alcohol consumption (>21 units per week for males or >14 units per week for females). 55.6 % (n = 105) of males and 56.7 % (n = 101) of females were of manual social class. On average, females had higher diet quality scores compared with males (mean prudent diet score 1.0 vs −0.6) and lower physical activity levels (mean Dallosso activity score was 65.6 in males and 62.1 in females). Overall, 117 (59.4 %) males and 83 (46.6 %) females had less than the recommended protein intake of 1.2 g/kg/day at the HCS baseline stage (1998–2004). This reflects dietary protein intake from food only.

46 (25.7 %) males and 51 (30.9 %) females self-reported fractures since the age of 45 years or had documented vertebral fractures. 103 (56.6 %) males and 119 (72.1 %) females self-reported falls since the age of 45 years.

Sex-interaction effects were not statistically significant in any of the regression models fitted; sex-adjusted analyses were therefore performed among the pooled sample of men and women.

Table 1
Characteristics of the 375 participants who were included in the analysis sample.

Participant characteristic	Mean (SD); median (lower quartile, upper quartile); or n (%)	
	Males (n = 197)	Females (n = 178)
Baseline (1998–2004)		
Age (years)	63.9 (2.5)	65.6 (2.6)
Height (cm)	174.6 (6.7)	161.9 (5.4)
Weight (kg)	79.9 (10.1)	69.6 (12.2)
BMI (kg/m^2)	26.2 (3.1)	26.5 (4.3)
Ever smoked	115 (58.4 %)	62 (34.8 %)
Weekly alcohol units (M: males; F: females)		
Very low (<1 M&F)	21 (10.7 %)	74 (41.6 %)
Low (1-10M, 1-7F)	78 (39.6 %)	81 (45.5 %)
Moderate (11-21M, 8-14F)	50 (25.4 %)	20 (11.2 %)
High (>21M, >14F)	48 (24.4 %)	3 (1.7 %)
Dallosso activity score	65.6 (13.6)	62.1 (13.7)
Prudent diet score	−0.6 (2.0)	1.0 (1.7)
Protein intake (g/day)	93.2 (16.6)	84.3 (19.5)
Occupational social class (manual)	105 (55.6 %)	101 (56.7 %)
Number of systems medicated	1.0 (0.0, 1.0)	1.0 (0.0, 2.0)
Follow-up (2011–2012)		
Age (years)	76.1 (2.5)	76.5 (2.6)
Follow-up time (years)	12.3 (11.8, 12.7)	10.8 (10.5, 11.2)
Calf muscle density (mg/cm^3)	80.7 (2.6)	78.5 (2.6)
Forearm muscle density (mg/cm^3)	79.9 (3.1)	77.2 (3.2)
Appendicular lean mass index (kg/m^2)	8.0 (0.7)	6.4 (0.7)
Grip strength (kg)	36.6 (7.5)	21.8 (6.2)
Gait speed (m/s)	0.79 (0.17)	0.74 (0.18)
Total hip BMD (g/cm^2)	1.03 (0.15)	0.88 (0.14)
Previous fall since age 45 years	103 (56.6 %)	119 (72.1 %)
Self-reported fracture since age 45 years	40 (22.3 %)	45 (27.1 %)
Vertebral fracture	11 (5.6 %)	14 (8.0 %)
Previous fracture since age 45 years	46 (25.7 %)	51 (30.9 %)

Previous fractures included self-reported and vertebral fractures.

3.2. Associations between baseline characteristics and muscle density

Associations between baseline characteristics and muscle density measures at follow-up are presented in Table 2. Sex, baseline age and follow-up time were included as covariates in all models. Female sex, lower weight, and lower BMI were associated with both lower forearm and calf muscle density. SD differences in calf muscle density for females compared to males, and per SD lower weight and BMI were −0.84 [95 % CI: −1.13, −0.54], −0.37 [−0.46, −0.27] and −0.31 [−0.40, −0.23] respectively. Additional correlates of lower calf muscle density included older age (SD difference per SD younger age: 0.20 [0.10, 0.30], $p < 0.001$) and shorter stature (SD difference per SD shorter height: −0.16

Table 2
SD difference in forearm and calf muscle density (2011/2012) per SD lower level of characteristic at HCS baseline (1998–2004).

Participant characteristic	Forearm muscle density		Calf muscle density	
	Estimate (95 % CI)	p-Value	Estimate (95 % CI)	p-Value
Age	0.09 (−0.01, 0.19)	0.082	*0.20 (0.10, 0.30)*	*<0.001*
Sex (female vs male)	*−1.04 (−1.33, −0.74)*	*<0.001*	*−0.84 (−1.13, −0.54)*	*<0.001*
Height	−0.11 (−0.24, 0.02)	0.109	*−0.16 (−0.30, −0.03)*	*0.018*
Weight	*−0.16 (−0.26, −0.06)*	*0.002*	*−0.37 (−0.46, −0.27)*	*<0.001*
BMI	*−0.12 (−0.21, −0.03)*	*0.012*	*−0.31 (−0.40, −0.23)*	*<0.001*
Smoking (ever vs never)	0.01 (−0.18, 0.20)	0.908	0.00 (−0.19, 0.19)	0.997
Alcohol consumption (per lower band)	0.05 (−0.06, 0.15)	0.374	0.04 (−0.07, 0.14)	0.507
Dallosso activity score	0.05 (−0.04, 0.14)	0.284	−0.04 (−0.13, 0.06)	0.469
Prudent diet score	0.03 (−0.07, 0.13)	0.612	−0.10 (−0.20, 0.00)	0.052
Protein intake	0.04 (−0.05, 0.14)	0.398	0.04 (−0.06, 0.13)	0.422
Social class (manual vs non-manual)	0.10 (−0.08, 0.28)	0.278	−0.03 (−0.22, 0.16)	0.743
Comorbidity (per fewer system medicated)	−0.00 (−0.08, 0.08)	0.983	0.06 (−0.02, 0.15)	0.139

SD: standard deviation.
CI: confidence interval.
Each regression model included the individual participant characteristic of interest along with sex, baseline age and follow-up time.
Significant associations ($p < 0.05$) are shown in italic.

[−0.30, −0.03], p = 0.018). Lifestyle factors, social class and comorbidity were not associated with either of the muscle density measures.

3.3. Muscle density in relation to musculoskeletal parameters and clinical outcomes

Forearm and calf muscle density were weakly correlated with total hip BMD (males: r = 0.13 (p = 0.089) and r = 0.20 (p = 0.006), females: r = 0.19 (p = 0.011) and r = 0.29 (p < 0.001) respectively) (Table 3). Calf muscle density was moderately correlated with ALM index among both males (r = 0.41, p < 0.001) and females (r = 0.38, p < 0.001); calf muscle density was also correlated with grip strength among males (r = 0.23, p = 0.002). In general, correlations between musculoskeletal parameters and forearm muscle density were weaker than the correlations with calf muscle density (Table 3).

After adjustment for sex and age, lower forearm muscle density was related to increased risk of previous fracture (odds ratio (95 % CI) per SD lower forearm muscle density: 1.42 (1.07, 1.89), p = 0.015) (Table 4). This association was attenuated after adjustment for total hip BMD (p > 0.08). By contrast, no significant relationships were seen between calf or forearm muscle density and previous falls. However, a trend was observed between lower calf muscle density and increased risk of previous fracture after adjustment for sex and age (odds ratio (95 % CI) per SD lower calf muscle density: 1.23 (0.94, 1.62), p = 0.131). Similarly, lower values of each muscle density measure were associated with greater risk of vertebral fracture after adjustment for sex and age, but these associations were not statistically significant.

4. Discussion

In this study we reported muscle density values for community-dwelling Caucasian UK males and females in older age, and explored the demographic, anthropometric and lifestyle determinants of muscle density. We also considered the relationships of muscle density measures to the clinical outcomes of falls and fractures. Our study demonstrated that demographic and anthropometric characteristics (female sex, older age, and lower adiposity), rather than lifestyle factors examined such as physical activity and diet, were associated with lower muscle density, approximately 11 years later. We have also demonstrated that forearm muscle density was associated with previous fracture, rather than falls history.

These findings complement earlier evidence linking lower muscle density/attenuation with adverse clinical outcomes including falls, fractures, poor physical performance, reduced muscle strength, frailty, and poor prognosis [10,18,19,32–45]. We found that only forearm, and not calf muscle density, was significantly associated with previous fracture in our cohort; we examined these associations with previous fractures at any site. Additional information on fractures since age 45 years, such as their type, date, and total number, was unavailable. However, it seems likely that a high proportion of fractures were upper limb distal forearm fractures, as the majority occurred in women in midlife. We suspect that the lack of association of calf muscle density with prior fracture reflects a health survivor bias in this cohort making calf muscle density less reflective of functional limitations, whereas forearm muscle density may be more reflective of general fragility contrary to lower limbs which are load bearing sites. In other studies, fat infiltration at mid femur, a measure of reduced muscle quality likely through reduction in force generating capacity through loss of type II fibers, was independently associated with a modest increase risk of incident clinical fracture in the Health, Aging, and Body Composition Study [46]. As lower extremity muscle attenuation and pQCT-derived muscle density is associated with poor physical performance, this might explain the relative higher reported risk of hip fractures in those individuals [20,32,34,47–49].

Table 3
Cross-sectional Pearson correlations between musculoskeletal parameters and muscle density at the forearm and calf (2011/2012) stratified by sex.

Parameter	Forearm muscle density	Calf muscle density
Males		
ALM index	r = 0.16 (p = 0.033)	r = 0.41 (p < 0.001)
Grip strength	r = 0.08 (p = 0.262)	r = 0.23 (p = 0.002)
Gait speed	r = 0.00 (p = 0.980)	r = 0.08 (p = 0.331)
Total hip BMD	r = 0.13 (p = 0.089)	r = 0.20 (p = 0.006)
Females		
ALM index	r = 0.14 (p = 0.073)	r = 0.38 (p < 0.001)
Grip strength	r = −0.02 (p = 0.832)	r = 0.04 (p = 0.603)
Gait speed	r = 0.02 (p = 0.845)	r = 0.07 (p = 0.369)
Total hip BMD	r = 0.19 (p = 0.011)	r = 0.29 (p < 0.001)

ALM index: appendicular lean mass index.
BMD: bone mineral density.

The lack of association between grip strength and forearm muscle density among both males and females was surprising. However, a possible reason for the lack of association is that muscle density was only assessed on the non-dominant side whereas the highest out of six grip strength measurements (three on each side) was used for analysis. We also reported no association between forearm or calf muscle density with falls which was somewhat unexpected. Muscle density has previously been shown to be associated with falls status, and this association is independent of functional mobility [13,34]. Again, this may reflect our use of retrospective questionnaires, which may be limited by recall bias.

Our other findings are certainly consistent with what is currently known. Older age was associated with lower calf muscle density in our cohort after adjustment for sex and follow-up time; this association was also robust when additionally adjusted for weight (data not shown). Skeletal muscle fibre changes have been reported in ageing humans [50], and changes in muscle fibre morphology, infiltration of fat and other non-contractile proteins, altered gene expression, and innervation can all affect muscle quality [51–53]. Previous cross sectional and longitudinal cohorts have suggested that muscle density changes over time are also age-related [10,54–56] supporting our findings, while female sex and poor quality of life (according to Health Assessment Questionnaire scores) were associated with declines in muscle density in a study of patients with rheumatoid arthritis [45]. Therefore, changes in muscle density over time might precede adverse outcomes such as falls and fractures and may be a long-term predictor of frailty. It could be also suggested that muscle density could be a more clinically meaningful surrogate of functional decline and disability than muscle size or mass but more studies are needed to support this notion [20,57].

In our cohort, lifestyle factors such as physical activity, diet, smoking, and alcohol consumption were not associated with future muscle density. Previous studies have examined the effect of smoking on muscle mass and strength in older adults, but not muscle density in the general population [58,59], though one study examining factors associated with declines in pQCT derived-muscle density in rheumatoid arthritis patients showed that active smoking was associated with lower muscle density [60]. In addition, the toxic effects of excess alcohol on skeletal muscle are recognised as important [61,62]; however, a recent meta-analysis did not show alcohol as a risk factor for sarcopenia [63] and studies examining the associations of alcohol specifically with muscle density are absent, so our observations here (where few participants drank to excess, or were current smokers) are perhaps unsurprising. Nutrition intake, specifically dietary protein, alone and/or resistance exercise are recognised as important for muscle health [64,65]. In contrast, dietary protein intake was not related to subsequent muscle density in our cohort possibly because the proportion of adults not consuming recommended levels was lower than in other samples [66]. Information on resistance exercises was not available in our cohort at baseline; however, carrying loads of 10 lb. more frequently was related (p = 0.038) to greater subsequent calf muscle density at follow-up after

Table 4
Odds ratios for previous falls and fractures since age 45 years per SD decrease in parameter in 2011/2012.

Parameter	Adjustments	Previous fall		Previous fracture		Previous vertebral fracture	
		Odds ratio (95 % CI)	p-Value	Odds ratio (95 % CI)	p-Value	Odds ratio (95 % CI)	p-Value
Forearm muscle density	Sex, age	0.90 (0.70, 1.17)	0.439	*1.42 (1.07, 1.89)*	*0.015*	1.44 (0.88, 2.37)	0.151
	Sex, age, total hip BMD	0.88 (0.67, 1.14)	0.330	1.30 (0.97, 1.75)	0.081	1.23 (0.73, 2.06)	0.431
Calf muscle density	Sex, age	1.01 (0.78, 1.30)	0.938	1.23 (0.94, 1.62)	0.131	1.53 (0.95, 2.44)	0.077
	Sex, age, total hip BMD	0.98 (0.75, 1.27)	0.866	1.10 (0.82, 1.47)	0.527	1.15 (0.70, 1.90)	0.574

Previous fractures include self-reported and vertebral fractures.
Significant associations ($p < 0.05$) are shown in italic.

adjustment for sex, age, and follow-up time (data not shown).

There are strengths and limitations of the current study, some of which have been discussed previously. The determinants of future muscle density have not been previously explored in a community or hospital-based cohort. The literature on pQCT analyses in older adults is limited and previous studies have focused on associations between pQCT derived muscle data and outcomes but not determinants of future muscle density [35,67–69]. Peripheral QCT is proving to be a useful tool for the measurement of muscle density and has been found to be highly correlated with MRI-derived measures of muscle cross-sectional area [70]. HCS is a well characterised cohort that has been extensively phenotyped according to strict protocols by highly-trained fieldworkers [26]. Individuals recruited were selected because they had been born in Hertfordshire and continued to live there in 1998–2004, as in previous studies. Although our cohort might be expected to demonstrate a healthy cohort effect (as evidenced by low rates of smoking and high dietary calcium intakes), we have previously demonstrated that the Hertfordshire population studied have similar smoking characteristics and bone density to national figures [25]. This healthy cohort effect might have contributed to the absence of associations between lifestyle factors and future muscle density in our cohort and the fairly high mean values of muscle density observed. Drop out at each stage of the study occurred due to participants moving away or becoming unwilling to participate in further studies; this has contributed to the relatively small number of participants examined. We also recognise the limitations associated with self-reported information, and the lack of phenotypic data around time spent participating in resistance exercises at baseline. Another limitation is the potential for recall bias from participants self-reporting previous fractures and falls which may have occurred decades ago. Furthermore, additional information on falls and fractures since age 45 years, such as their type, date and total number, was unavailable. A key limitation is that only falls and fractures ascertained prior to the muscle density measures were available; determining whether muscle density influences risk of adverse outcomes or vice versa is limited without also having incident outcomes assessed after the muscle density measures. Finally, the narrow age range of the analysis sample prevents a detailed characterisation of how muscle density varies over the lifecourse.

5. Conclusion

This study provides further insights into the determinants of future muscle density and the associations of muscle density with clinical outcomes such as falls and fractures in a well characterised community-dwelling cohort of older adults. pQCT-derived muscle density could provide a biomarker to further complement the musculoskeletal health assessment in older adults and further studies are now warranted.

CRediT authorship contribution statement

FL, NF, NCH, HPP, CC, KW and ED participated in the conception, design and conduct of the study. LW conducted the statistical analyses. FL drafted the first version of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

ED declares consultancy and speaker fees from Viatris, Pfizer, UCB and Lilly.

CC has received lecture fees and honoraria from Amgen, Danone, Eli Lilly, GSK, Kyowa Kirin, Medtronic, Merck, Nestlé, Novartis, Pfizer, Roche, Servier, Shire, Takeda and UCB outside of the submitted work.

NF declares travel bursaries from Pfizer and Eli Lilly.

HPP has received lecture fees from Abbott, Pfizer, and HC-UK conferences outside of the submitted work.

The remaining authors declare that they have no conflicts of interest.

Data availability

Hertfordshire Cohort Study data are accessible via collaboration. Initial enquires should be made to CC (Principal Investigator). Potential collaborators will be sent a collaborators' pack and asked to submit a detailed study proposal to the HCS Steering Group.

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Ethical approval

All study participants provided written informed consent and ethical approval was obtained from the Hertfordshire Research Ethics Committee (reference 07/MRE01/30). The baseline Hertfordshire Cohort Study had ethical approval from the Hertfordshire and Bedfordshire Local Research Ethics Committee and the follow-up had ethical approval from the East and North Hertfordshire Ethical Committees.

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Appendix M Relationships between muscle parameters, and history of falls and fractures in the Hertfordshire Cohort Study: Do all muscle components relate equally to clinical outcomes?

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ORIGINAL RESEARCH

Relationships Between Muscle Parameters and History of Falls and Fractures in the Hertfordshire Cohort Study: Do All Muscle Components Relate Equally to Clinical Outcomes?

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Abstract

In previous work, relationships between muscle and bone size and strength have been demonstrated and were stronger in females, suggesting possible sexual dimorphism. Here we examine sex-specific associations between individual muscle sarcopenia components with clinical outcomes (falls and fractures). 641 participants were recruited. Muscle mass was assessed as cross-sectional area (CSA) by peripheral quantitative computed tomography of the calf, grip strength (GpS) by Jamar dynamometry and function by gait speed (GtS). Falls and fractures were self-reported. Ordinal and logistic regression were used to examine the associations between muscle measurements and outcomes with and without adjustment for confounders. Mean (SD) age was 69.3 (2.6) years. CSA, GpS, and GtS were greater among males ($p < 0.002$). A higher proportion of females had fallen since age 45 (61.3% vs 40.2%, $p < 0.001$); in the last year (19.9% vs 14.1%, $p = 0.053$); and reported a previous fracture since age 45 (21.8% vs 18.5%, $p = 0.302$), than males. Among females, greater CSA was related to reduced risk of falling and fewer falls in the previous year in fully adjusted analysis only ($p < 0.05$); higher GpS was related to lower risk of falls since age 45 in unadjusted analysis ($p = 0.045$) and lower risk of fracture since age 45 in both unadjusted and fully adjusted analysis ($p < 0.045$). No statistically significant associations were observed for GtS among either sex for any relationships between muscle measurements and clinical outcomes studied. We observed relationships between muscle mass and strength but not function with falls and fractures in females only; further longitudinal studies are required to reproduce these results.

Keywords Sarcopenia · Falls · Fractures · Muscle mass · Muscle strength · Gait speed

Introduction

Falls constitute a major risk factor for fracture and associated morbidity, mortality and economic costs [1]. Sarcopenia is an important contributor to falls risk, and hence fractures [2]. We have previously demonstrated relationships between muscle size and grip strength, and bone size and strength, supporting a role for the muscle-bone unit [3], with stronger relationships in females as it has been observed elsewhere [4, 5]. In 2019, the revised European Working Group on Sarcopenia in Older People 2 guidelines were published emphasising muscle strength, relative to muscle mass and function [6]. The aim of this study was to examine the strength of sex-specific associations between each of the key individual sarcopenia components (muscle mass, strength, and function) with the clinically important outcomes of falls and fractures in a population-based cohort of older adults.

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Materials and Methods

The Hertfordshire Cohort Study

The Hertfordshire Cohort Study (HCS) comprises 2997 individuals born in Hertfordshire from 1931 to 1939 who lived there in 1998–2004 where they completed a home interview and clinic visit for a detailed health assessment. In 2004, of the 966 participants from the geographic region of East Hertfordshire who formed the in-depth musculoskeletal subgroup, 642 attended a clinic visit as part of a musculoskeletal follow-up study. The HCS baseline investigations had ethical approval from the Hertfordshire and Bedfordshire Local Research Ethics Committee and all participants provided written informed consent [7]; ethical approval was also obtained for all HCS follow-up studies. Further details of HCS have been described previously [7].

Ascertainment of Participant Information in 1998–2004

Physical activity (Dallosso questionnaire) was ascertained by a nurse-administered questionnaire [8]. Dietary calcium intake was determined using a food-frequency questionnaire [9]. Current or most recent full-time occupation (husband's for ever-married females) was ascertained. Social class was coded from the 1990 OPCS Standard Occupational Classification (SOC90) unit group for occupation [10], using computer-assisted standard occupational coding to generate the following occupational classes: I (Professional); II (Managerial and technical); IIINM (Skilled non-manual); IIIM (Skilled manual); IV (Partly skilled); V (Unskilled) [11]. These were dichotomised as follows: 'Non-manual' (I, II and IIINM) and 'Manual' (IIIM, IV and V). Fractures since age 45 years were self-reported. Among females, information on hormone replacement therapy (HRT) use, the age at which they had their last menstrual cycle and whether they had undergone a hysterectomy was also collected.

Ascertainment of Participant Information in 2004–2005

Information on fractures since baseline, whether participants had fallen since age 45 years, the number of falls in the last year, smoking status and alcohol consumption was ascertained by a nurse-administered questionnaire. History of fracture since age 45 was determined from questionnaire data here and at baseline. Among females, information on HRT use was updated. Height was measured (Harpenden pocket stadiometer, Chasmors Ltd, London, UK) along with weight (SECA floor scale, Chasmors Ltd, London, UK) and used to derive BMI (kg/m^2). Grip strength was measured three times for each hand using a Jamar dynamometer; the highest measurement was used for analysis. Customary gait speed in metres per second was calculated using a 3 m walk test. Radial and tibial (non-dominant side) peripheral qualitative computed tomography (pQCT) scans (Stratec 2000XL instrument, version 6.00) were performed; the other side was scanned if the non-dominant side had sustained a fracture. Calf muscle area was derived using default procedures, thresholds, and edge tracking settings to segment muscle from subcutaneous fat. Additional details relating to the pQCT scans have been published previously [12]. At time of assessment of the muscle size, strength, and function measures in this study (2004–2005), 33 (5%) participants were taking bisphosphonates and 113 (18%) were taking medications for the endocrine system. Associations of interest were similar if binary variables for current use of bisphosphonates and medications for the endocrine system were included as additional adjustments as shown in Table 2.

Statistical Methods

Participant characteristics were described using summary statistics. Associations between calf muscle area, grip strength and gait speed in relation to binary outcomes were examined using logistic regression with and without adjustment for age, BMI, social class, smoker status, alcohol consumption, physical activity, dietary calcium intake, hormone replacement therapy use (females only) and time since menopause (females only), use of bisphosphonates and use of medications for the endocrine system. Relationships between predictors and number of falls in the last year (0, 1, > 1) were examined using ordinal regression with the same set of adjustments. Sex-stratified analyses were performed; $p < 0.05$ was regarded as statistically significant. Analyses were conducted using Stata, release 17.0. The analysis sample comprised 641 participants with data on at least one predictor and at least one outcome; of the 642 participants who attended the 2004–2005 follow-up stage, one participant had missing values for grip strength, gait speed and calf muscle area so they were excluded from the analysis sample.

Results

Descriptive Statistics

Participant characteristics of the analysis sample are presented in Table 1. Mean (SD) age was 69.3 (2.6) years. Calf muscle area, grip strength and gait speed were greater among males than females ($p < 0.002$ for all associations). Compared to males, a greater proportion of females had

Table 1 Participant characteristics of the analysis sample

Characteristic	Males ($n=322$)			Females ($n=319$)			*P*-value
	Total N	Mean	SD	Total N	Mean	SD	
Age (years)	322	69.2	2.5	319	69.5	2.6	0.127
Height (cm)	322	173.7	6.7	319	160.5	6.1	< 0.001
Weight (kg)	322	82.3	12.4	319	71.7	13.8	< 0.001
BMI (kg/m^2)	322	27.3	3.8	319	27.8	4.9	0.106
Dallosso activity score[a]	322	63.9	14.3	319	61.8	14.3	0.060
Calf muscle area (mm^2)	293	8035	1204	295	6212	981	< 0.001
Grip strength (kg)	321	42.2	7.6	318	24.9	5.8	< 0.001
Gait speed (m/s)	320	0.92	0.17	317	0.88	0.16	0.001
	Total N	Median	IQR	Total N	Median	IQR	
Dietary calcium (g/day)[a]	322	1.2	1.0, 1.4	319	1.1	0.9, 1.3	< 0.001
Alcohol intake (units/week)	322	7.6	1.5, 16.5	317	1.3	0.0, 4.8	< 0.001
	Total N	N	%	Total N	N	%	
Smoker status	322			316			< 0.001
Never		121	37.6		200	63.3	
Ex		174	54		99	31.3	
Current		27	8.4		17	5.4	
Social class (manual)[b]	306	175	57.2	319	182	57.1	0.973
HRT use				319			N/A
Never					185	58	
At least 5 years ago					74	23.2	
Within last 5 years					47	14.7	
Current					13	4.1	
Years since menopause				316			N/A
< 10 years					11	3.5	
≥ 10 and < 15 years					49	15.5	
≥ 15 and < 20 years					75	23.7	
≥ 20 and < 25 years					60	19	
≥ 25 and < 30 years					33	10.4	
≥ 30 years					9	2.8	
Hysterectomy					79	25	
Fallen since age 45 years	321	129	40.2	318	195	61.3	< 0.001
Fallen in last year	319	45	14.1	317	63	19.9	0.053
Number of falls in last year	318			317			0.112
0		274	86.2		254	80.1	
1		36	11.3		49	15.5	
2 or more		8	2.5		14	4.4	
Fracture since age 45 years	314	58	18.5	317	69	21.8	0.302

[a]Ascertained at HCS baseline (1998–2004); all other characteristics were ascertained in 2004–2005

[b]Manual occupations comprise IIIM (Skilled manual), IV (Partly skilled) and V (Unskilled) from the 1990 OPCS Standard Occupational Classification (SOC90) unit group for occupation

P-values for sex-differences in characteristics were calculated using *t* tests, Wilcoxon rank-sum tests, or chi-squared tests as appropriate

fallen since age 45 years (61.3% vs 40.2%, $p < 0.001$); fallen in the last year (19.9% vs 14.1%, $p = 0.053$); and had a previous fracture since age 45 years (21.8% vs 18.5%, $p = 0.302$). However, these latter two sex-differences were not statistically significant.

Relationships Between Muscle Size, Strength, and Function In Relation tTo Falls and Fractures

Associations between predictors (calf muscle area, grip strength, gait speed) and outcomes (fallen since age 45,

Table 2 Odds ratios for outcomes per SD increase in predictors among males and females

P-ValuePredictor	Outcome	Males							*P*-Value
		Unadjusted		Adjusted*		Unadjusted			
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	
Calf muscle area	Fallen since 45	0.97 (0.77, 1.23)	0.798	1.06 (0.79, 1.44)	0.691	0.93 (0.73, 1.17)	0.534	0.79 (0.58, 1.06)	0.119
	Fallen in last year	1.01 (0.72, 1.42)	0.941	1.13 (0.74, 1.72)	0.586	0.79 (0.59, 1.06)	0.120	**0.66 (0.44, 0.97)**	**0.037**
	No. falls in last year	1.04 (0.74, 1.47)	0.823	1.11 (0.72, 1.69)	0.643	0.79 (0.59, 1.06)	0.112	**0.64 (0.43, 0.95)**	**0.025**
	Fracture since 45	0.95 (0.70, 1.28)	0.722	0.96 (0.65, 1.42)	0.840	1.03 (0.78, 1.36)	0.838	1.11 (0.78, 1.58)	0.552
Muscle (Grip) strength	Fallen since 45	0.85 (0.68, 1.07)	0.167	0.87 (0.67, 1.12)	0.273	**0.79 (0.63, 0.99)**	**0.045**	0.79 (0.61, 1.01)	0.060
	Fallen in last year	0.75 (0.55, 1.03)	0.078	0.76 (0.54, 1.08)	0.129	0.88 (0.67, 1.17)	0.382	0.82 (0.60, 1.11)	0.198
	No. falls in last year	0.77 (0.56, 1.06)	0.105	0.78 (0.55, 1.11)	0.175	0.85 (0.64, 1.13)	0.273	0.77 (0.57, 1.06)	0.109
	Fracture since 45	1.33 (0.98, 1.81)	0.070	1.35 (0.95, 1.92)	0.098	**0.74 (0.56, 0.97)**	**0.030**	**0.74 (0.55, 0.99)**	**0.042**
Gait speed	Fallen since 45	0.99 (0.79, 1.23)	0.902	1.00 (0.78, 1.28)	0.988	0.85 (0.68, 1.07)	0.173	0.87 (0.67, 1.13)	0.309
	Fallen in last year	0.76 (0.55, 1.05)	0.100	0.83 (0.58, 1.17)	0.287	0.88 (0.67, 1.16)	0.352	0.87 (0.63, 1.19)	0.374
	No. falls in last year	0.77 (0.55, 1.07)	0.124	0.83 (0.58, 1.18)	0.294	0.84 (0.64, 1.12)	0.232	0.84 (0.61, 1.16)	0.289
	Fracture since 45	1.16 (0.87, 1.54)	0.301	1.10 (0.80, 1.52)	0.547	1.06 (0.81, 1.39)	0.688	1.09 (0.80, 1.47)	0.593

OR Odds ratio; *CI* confidence interval; *SD* standard deviation

Sex-specific z-scores were derived for calf muscle area, grip strength and gait speed to enable the comparison of effect sizes

*Adjusted for age, BMI, social class, smoker status, alcohol consumption, physical activity (ascertained from 1998 to 2004), dietary calcium intake (ascertained from 1998–2004), hormone replacement therapy use (females only), time since menopause (females only), use of bisphosphonates and use of medications for the endocrine system

Odds ratios for being in a higher category for number of falls in the last year (0, 1 or > 1) were estimated using ordinal regression; logistic regression was used for the other outcomes

All participant characteristics were ascertained from 2004 to 2005 unless stated otherwise

fallen in last year, number of falls in last year, fracture since age 45) are presented in Table 2. Among females, greater calf muscle area was related to reduced risk of falling in the previous year and fewer falls in the previous year ($p < 0.05$) but only in fully adjusted analysis; higher grip strength was related to lower risk of falls since age 45 in unadjusted analysis only (odds ratio per SD greater grip strength: 0.79 (0.63, 0.99), $p = 0.045$) and lower risk of fracture since age 45 in both unadjusted (0.74 (0.56, 0.97), $p = 0.030$) and fully adjusted analysis (0.74 (0.56, 0.99), $p = 0.044$). No statistically significant associations were observed for gait speed among females, or among males for any of the predictors in relation to any of the outcomes.

Discussion

In this study, higher grip strength was related to lower risk of falls and fractures since age 45 years and greater muscle size was associated with both reduced risk of falling and fewer falls in the previous year. The association between muscle strength and risk of fractures remained robust after adjustments. Conversely, associations regarding muscle size were only significant in adjusted models. Our findings support previous evidence that muscle strength is a key characteristic in detecting older adults at risk of adverse outcomes including falls and fractures [6]. Our study once again demonstrated sexual dimorphism in relationships observed and in general accord with previous

literature, although previous studies have also suggested important relationships between muscle measures and bone outcomes in men [5].

Gait speed was not associated with prevalent falls and fractures in this study. Gait speed has been shown to reflect health and functional status, and to be associated with survival in older adults [13–15]. We previously found no associations of gait speed with measures of bone size, strength and density in the same cohort [3]. Amongst other physical performance tests, gait speed has previously been shown to be weakly associated with risk of hip fractures in participants without walking difficulties [16]. Gait speed is suitable for screening of poor physical performance and is used to identify cases of severe sarcopenia, as defined by the European Working Group on Sarcopenia in older adults (EWSGOP2) [6], but it is possible that it is more adversely affected by gait ability and/or severe weakness that leads to falls and fractures [17]. Two main types of gait speed assessment exist: the short-and long-distance gait test. Some groups favour the use of long-distance gait speed for its established relationship to mobility disability and public health relevance [18, 19]. Conversely, short gait tests can be used as surrogates for long-distance speed tests for the assessment of functional status in older adults, and are easily implemented into clinical practice [6, 20]. Thus, we suggest that gait speed combined with other physical performance measures, such as chair stand test, might perform better as a predictor of falls and fractures when assessing community-dwelling older adults [16].

There are several strengths and limitations to this work which was undertaken in a very well-characterised cohort that has previously been shown to be representative of the UK population [7]. While the sex differences noted in our study insights into potential differential sex-specific mechanisms, a healthy bias in males, as indicated by the relatively higher mean of grip strength and gait speed, and the use of specific cut-off points to define each sarcopenia components should also be considered as a contributing factor to the absence of associations between sarcopenia and falls and/or fractures in males. However, since the cohort is made up of community-dwelling individuals, generalisability of these findings to less healthy or institutionalized groups may be limited. Specifically, we also acknowledge the limitations associated with self-reported outcomes and the need for prospective data.

Conclusion

In conclusion we have observed relationships between muscle mass and strength but not function with falls and fractures in females but not males. Large prospective studies are needed to confirm the above-mentioned relationships, and to further explore the sexual dimorphism observed.

Author Contributions FL, NRF, MHE, CC, and EMD participated in the conception, design and conduct of the study. LDW conducted the statistical analyses. FL drafted the first version of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest EMD declares consultancy and speaker fees from Pfizer, UCB, Viatris and Lilly. CC has received lecture fees and honoraria from Amgen, Danone, Eli Lilly, GSK, Kyowa Kirin, Medtronic, Merck, Nestlé, Novartis, Pfizer, Roche, Servier, Shire, Takeda and UCB outside of the submitted work. MHE declares conference and course attendance funding from Eli Lilly, other from UCB, other from Pfizer, other from Chugai, other from AbbVie and an unrestricted project grant from Servier. NRF declares travel bursaries from Pfizer and Eli Lilly. LDW and LF declare no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and /or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All study participants provided written informed consent and Ethical approval was obtained from the Hertfordshire and Bedfordshire Local Research Ethics Committee.

Informed Consent Informed consent was obtained from all participants included in the study.

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