Combining Omega-3 Fatty Acids with Home-Based Resistance Exercise to Improve Muscle Health in Older Adults: Associations, Effects, and Engagement

By

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ABSTRACT

It has been predicted that worldwide the percentage of older people, aged 65 and over, globally will increase from 10% in 2024 to approximately 16% in 2050, highlighting a global shift in ageing demographics (Desa, 2019). Indeed, in the UK, from 2019 to 2030, it has been predicted that the number of older adults aged over 65 years will increase by 21.8% (Age UK, 2019). Ageing has many consequences, one of which is the progressive decrease in muscle mass and muscle strength that occurs from approximately 40 years of age and can result in sarcopenia (Dodds et al., 2014, Cruz-Jentoft et al., 2019). Recent data estimates that between 10% and 27% of those over the age of 60 years of age globally have sarcopenia (Petermann-Rocha et al. 2022). Sarcopenia is associated with many adverse outcomes such as cardiac and respiratory diseases, an increase in mortality, falls and fractures and mobility issues which in turn may lead to the decreased quality of life and loss of independence (Cruz-Jentoft et al., 2019). Sarcopenia also has wide economic costs (Mijnarends et al., 2018).

Thus far, there is no effective pharmacological treatment for sarcopenia (Cruz-Jentoft and Sayer, 2019) and so lifestyle changes, such as diet and exercise, are often suggested. There is a wealth of literature that resistance exercise, regardless of age, can increase muscle strength and mass (Fyfe et al., 2022; Manas et al., 2021). However, many older adults in the UK are not actually engaging in resistance-based exercises (Strain et al., 2016). Therefore, a pragmatic and feasible solution is needed to improve participation and adherence to resistance exercise. Home-based resistance exercises with minimal equipment may be a practical solution. On top of this a growing body of literature indicates that supplementation with Long Chain n-3 polyunsaturated fatty acids (LCn-3 PUFA) may be beneficial. There is evidence that LCn-3 PUFA supplementation, via fish and krill oil, can increase muscle strength and muscle mass in healthy older adults (Alkhedhairi et al., 2022; Smith et al., 2015; Timraz et al., 2023). There is also evidence that LCn-3 PUFA supplementation combined with resistance exercise can improve muscle strength and physical function (Cornish et al., 2022). The improvement in muscle strength as a result of LCn-3 PUFA supplementation has been linked to enhancements in neuromuscular function (Gray & Mittendorfer, 2018; Phillips et al., 2024). However, the neuromuscular mechanisms remain unknown.

The aim of chapter 2 was to investigate the associations of n-3 fatty acid intake with handgrip strength and muscle mass indices in older adult participants from the UK biobank study. A secondary aim was to investigate whether these associations differed by physical activity status. A cross-sectional study included 53,170 participants aged 60 years and over from the UK biobank (25,324 men and 27,846 women). Higher n-3 fatty acid intake was positively associated with grip strength index in women. For each additional gram of n-3 fatty acid consumed per day, there was an increase of 0.03 kg/m2 (95% CI: 0.00 to 0.06 kg/m2) in active women and 0.04 kg/m2 (95% CI: 0.00 to 0.07 kg/m2) in inactive women. However, no significant associations were observed in men, whether active (p=0.405) or inactive (p=0.323). Additionally, no significant associations were found between n-3 fatty acid intake and muscle mass index in either active (p=0.858) or inactive (p=0.250) men, or in active (p=0.909) or inactive (p=0.187) women. Thus, the magnitude of the positive association was very small and unlikely to be clinically relevant, and normal dietary intake of n-3 fatty acid is unlikely to counteract sarcopenia and supplements may be needed.

Following this, the aim of Chapter 3 was to determine whether krill oil supplementation enhances the effects of a pragmatic home resistance exercise programme on adaptations in muscle strength (knee extensor maximal torque and grip strength) and size (vastus lateralis muscle thickness), physical function (chair rise and gait parameters) and motor unit function (firing rate, firing rate variability and neuromuscular junction instability) in healthy older adults through a double-blind RCT. A total of 46 healthy older adults aged 60 years and over participated in the study. Participants were randomised to either krill oil supplements (4g/day) plus home-based resistance exercise or placebo supplements (4g/day) plus home-based resistance exercise for 16 weeks. Knee extensor maximal torque was significantly increased by 7.8 Nm (95%CI: 0.1, 14.3, p=0.04) in the krill group with no change in the control group at 16 weeks. Firing rate variability at 10% MVC was significantly decreased by 0.01% (95%CI: -0.02, -0.00, p=0.010) in the krill group with no change in the control group at 16 weeks. No effects of krill oil were observed for other outcomes. Our data indicated LCn-3 PUFA supplementation (krill oil) can result in small but clinically meaningful improvements in lower limb muscle strength responses to resistance exercise training and that these benefits may relate to concomitant improvements in neuromuscular function. We speculate that the improvement in firing rate variability may result from

the effects of LCn-3 PUFAs on enhancing the strength of common synaptic input and reducing synaptic noise.

The aim of Chapter 4 is to explore the enablers and barriers toward home-based resistance exercise in older adults. A subgroup of 10 participants aged 60 years and over (5 male and 5 female) from the 46 participants in chapter 3 were included. A semi-structured interview was carried out following the 16-week study period, during which participants performed home-based resistance exercise including both body weight and resistance band exercises. Reflexive thematic analysis approach was used to analyse the data. The analysis generated five themes: Flexibility and simplicity of home-based resistance exercise, navigating commitment, and the perceived benefits of home-based exercise were enablers for performing home-based resistance exercises. On the other hand, learning home-based resistance exercise along with indolence and procrastination were barriers. The data from this chapter indicated that physiotherapists and other exercise specialists should focus on combining body weight exercises with resistance bands and providing portable devices, like grip strength measuring devices, when they design or prescribe home-based resistance exercise, to enhance engagement in these exercises.

In conclusion, the current thesis has demonstrated that the magnitude of the association between n-3 fatty acid intake and grip strength index in older women, regardless of their activity status, which was not present in men, was small unlikely to be clinically relevant. Thus, supplementation with LCn-3 PUFAs may be needed, and krill oil, when combined with home-based resistance exercise, may offer small but clinically meaningful improvements in muscle strength and motor unit function. Furthermore, home-based resistance exercise was found to be both feasible and motivating for older adults. These findings supported the implementation of combined LCn-3 PUFA supplementation and home-based resistance exercise as a potential strategy to counteract the adverse effects of sarcopenia, although further work is needed to maximise the effectiveness of this strategy.

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I would like to sincerely thank everyone who supported me throughout this journey. I am deeply grateful to the professors, doctors, lab technicians, my colleagues, participants and all those who assisted me in any way during my PhD.

Finally, I would like to express my heartfelt gratitude to my family, my mother, father, wife, and children. Thank you for always being by my side and for making this PhD journey more enjoyable and manageable.

Thank you.

AUTHOR'S DECLARATION

I declare that this thesis is the result of my own work and investigation, except where otherwise stated. It has not been submitted, either in the same or different form, to this or any other university for a degree. However, these works have subsequently been published in peer-reviewed journals.

1- Conference presentation at Nutrification Society Congress (From 2-5 July 2024) The associations of n-3 fatty acid intake with handgrip strength and muscle mass indices in older adults: A cross-sectional study from UK Biobank.
2- Publication: The associations of n-3 fatty acid intake with handgrip strength and muscle mass indices in older adults: A cross-sectional study from UK Biobank. Abdulrahman T. Alsowail, Marion T. Guerrero Wyss, Frederick K. Ho, Carlos Celis-Morales, Stuart R. Gray (Published in Experimental Gerontology in November 2024)
3- Publication: Enablers and barriers toward home-based resistance exercise among older adults who completed a structured program: qualitative study using reflexive thematic analysis. Abdulrahman T. Alsowail, Dalia Malkova, Gemma C Ryde & Stuart R. Gray (Published in BMC Geriatrics in January 2026)

LIST OF ABBREVIATIONS

CVD	Cardiovascular disease
COPD	Chronic obstructive pulmonary disease
IWGS	International Working Group on Sarcopenia
FNIH	Foundation for the National Institutes of Health
EWGSOP	European Working Group on Sarcopenia in Older People
AWGS	Asian Working Group for Sarcopenia
MVC	Maximum voluntary contraction
NMJ	Neuromuscular junction
NF	Near fibre
RCTs	Randomised controlled trials
TUG	Timed Up and Go
LCn-3PUFAs	Long-chain n-3 polyunsaturated fatty acids
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
DPA	Docosapentaenoic acid
ALA	Alpha-linolenic acid
STROBE	Strengthening of the reporting of observational studies in epidemiology

Oxford WebQ	Web-based 24 -h-recall questionnaire
IPAQ	International Physical Activity Questionnaire
BIA	Bioelectrical impedance analysis
MRI	Magnetic resonance imaging
BMI	Body mass index
VL	Vastus lateralis
RBCs	Red blood cells
iEMG	Intramuscular electromyography
CoV	Average of force variability
DQEMG	Decomposition-based quantitative electromyography
NF	Near-fibre
MUPTs	Motor unit potential trains
NFM	Near-fibre MUP
CIs	Confidence intervals
SD	Standard deviation
FR	Firing rate
FRVAR	Firing rate variability
MCID	Minimal clinically important difference
KOREA	Krill Oil Resistance Exercise Ageing
MVPA	Moderate-to-vigorous physical activity

CHAPTER 1: INTRODUCTION

1.1 Ageing and sarcopenia

In recent years, it has been predicted that the global population will increase, from 7.7 billion in 2019, to 8.5 billion in 2030 and more to 9.7 billion in 2050 (Desa, 2019). This increase in the population is not consistent across the life course with the largest growth projected to occur in older adults. Indeed, the proportion of older adults aged 65 and over is projected to increase from 1 in 11 in 2019 to 1 in 6 by 2050 (Desa, 2019). In Europe, including the UK, the proportion of older adults aged 65 and over is projected to reach 1 in 4 by 2050 (Desa, 2019). Much of this demographic shift is driven by changes in global life expectancy, which at birth was 64.2 years in 1990, increasing to 72.6 years in 2019, and is expected to rise further to 77.1 years by 2050 (Desa, 2019). While this is something to celebrate, it comes with its challenges.

One key disadvantage of ageing is that it can lead to biological and physical changes in muscle structure and function (Hairi et al., 2010). Indeed, ageing will cause a reduction in both muscle mass and strength beginning from around 40 years of age (Aagaard et al., 2010, Dodds et al., 2014, Cruz-Jentoft et al., 2019). This process has been termed sarcopenia, which has been defined as follows: “Sarcopenia is a progressive and generalized skeletal muscle disorder associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality” (Cruz-Jentoft et al., 2019). However, it is important to acknowledge that there is no scientific consensus for the definition or measurement of sarcopenia (McLean, Kiel 2015). The following paragraphs will detail the effects of ageing on the specific outcomes of muscle strength and size, as these outcome measures are critical in the context of the current thesis.

Prior reviews have noted that muscle strength declines as a consequence of ageing, with limb muscles (mostly the knee extensors) measured during either isometric or dynamic conditions when comparing healthy young, middle-aged, and older adults (Vandervoort, 2002, Porter, Vandervoort & Lexell, 1995). Most included studies have measured the knee extensor muscles due to the simplicity of measurement and their essential role in physical function (Doherty, 2003). Knee extensor strength in older adults aged 60 to 70 years is approximately 20% to 40% lower and can decline by

50% or more in those aged 80 and above, compared to healthy young adults in their 20s (Doherty, 2003).

Not only does knee extensor strength decline with age but grip strength also declines substantially. Previous work based on 12 general population studies in the UK showed that grip strength in older adults aged 60 to 70 years was lower by approximately 5 to 12 kg compared to values observed in individuals in their 30s (Dodds et al., 2014). Furthermore, longitudinal work in older adults found that grip strength declined by 19% in women and 12% in men over a 4 year period (Bassey, Harries, 1993).

Age related declines in muscle strength result partly from changes in muscle size (Doherty, 2003). Skeletal muscle mass declines in older adults aged 75 years by around 0.80–0.98% per year in men and 0.64–0.70% per year in women, whereas muscle strength declines by 3–4% per year in men and 2.5–3% per year in women at the same age (Mitchell et al., 2012). Thus, declines in muscle strength are 2 to 5 times faster and greater than those of muscle mass (Mitchell et al., 2012). This highlights that mechanisms beyond declines in muscle mass contribute to declines in strength and will be discussed later in the section on possible mechanisms underlying sarcopenia.

To summarise, ageing and sarcopenia are associated with declines in muscle mass and strength; however, the decline in muscle strength is faster and greater than that of muscle mass.

1.1.1 Consequences of sarcopenia

Recent evidence from a cross-sectional study of 312 community-dwelling older adults suggests that older adults identified with sarcopenia had lower physical function such as gait speed and chair rise test (Lima et al., 2025). This study found that better performance in the chair stand and gait speed (the 4-meter walk test) was associated with a lower likelihood of sarcopenia (Lima et al., 2025). Moreover, previous studies indicate that a gradual decline in chair stand performance with age where the decline over a ~14-year age span, from 60 to 74 years, is approximately 2.2 to 2.4 repetitions in older adults, based on the maximum number of repetitions completed in 30 seconds (Macfarlane et al., 2006). In addition, it has been estimated that a decline in gait speed begins at age 65 and becomes more noticeable by ~ 70 years of age. Moreover, there

is an inverse association between age and gait speed (Kirkwood et al., 2018). On average, gait speed declines by 0.31 cm/s with each additional year of age. This decline becomes more pronounced at age ~ 70 years, reaching approximately 1.75 cm/s per year (Kirkwood et al., 2018).

Beyond the negative impact of sarcopenia on physical function, this process has also been associated with multiple comorbidities due to the critical role of muscle in health. For example, in over 500,000 participants, aged 37 to 73 years, from the UK Biobank it was shown that a 5 kg lower handgrip strength was associated with a higher risk of all-cause mortality (HR: 1.20), cardiovascular disease (CVD) mortality (HR: 1.19), respiratory mortality (HR: 1.31), chronic obstructive pulmonary disease (COPD) mortality (HR: 1.24), all cancer mortality (HR: 1.17), colorectal cancer mortality (HR: 1.17), breast cancer mortality (only in women) (HR: 1.24) and lung cancer mortality (HR: 1.17) (Celis-Morales et al., 2018). Furthermore, another study from the UK Biobank included a total of 420,727 men and women with no existing cardiovascular or cancer diseases (Yates et al., 2017). They found that men with the lowest handgrip strength had a 38% higher risk of CVD mortality (Yates et al., 2017). In addition to that, another study from the UK Biobank including a total of 396,283 participants, found that diagnosed sarcopenia was significantly associated with 28 comorbidities (Figure 1.1), with rheumatoid arthritis, chronic bronchitis, osteoporosis, stroke, and psoriasis showing the strongest associations (Petermann-Rocha et al., 2020).

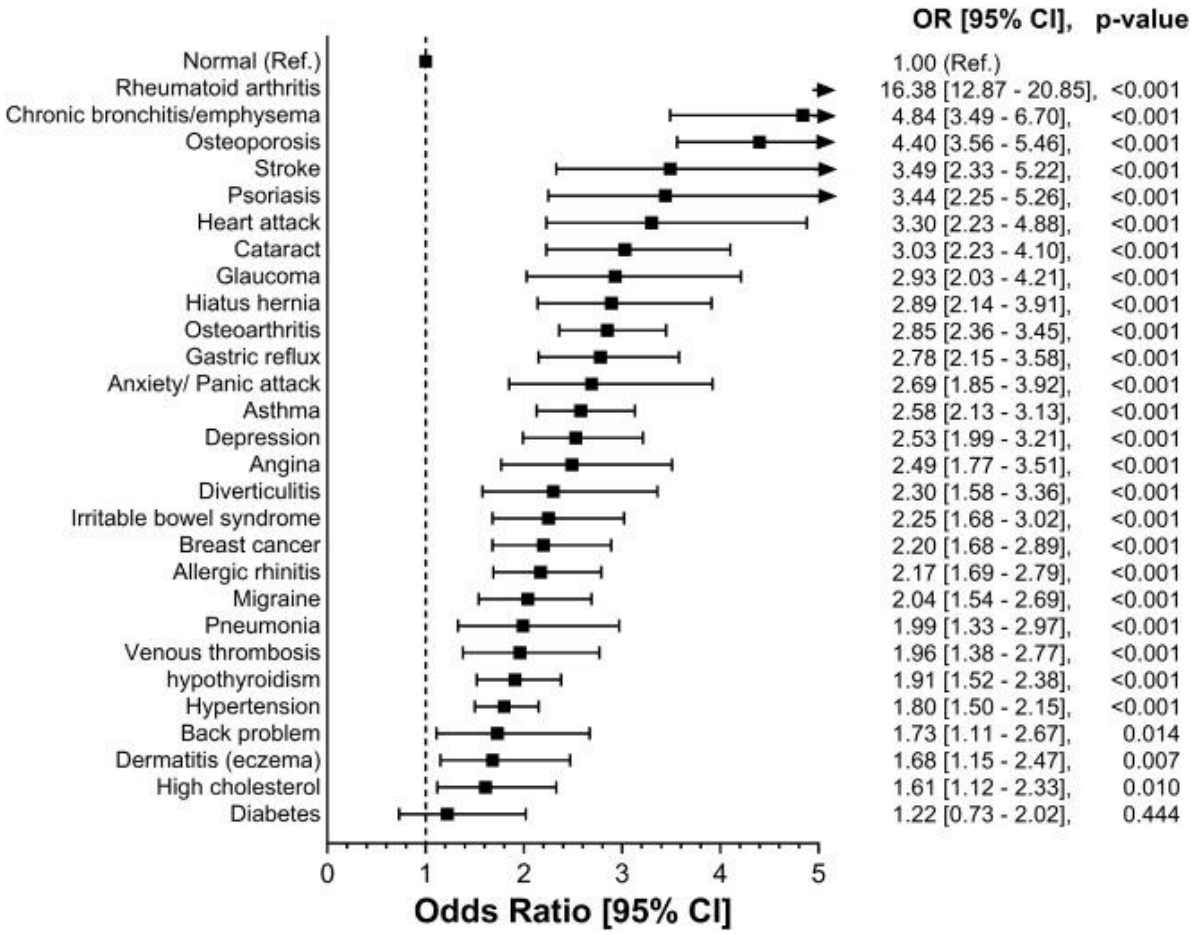

Figure 1.1 Diseases associated with sarcopenia. Data are presented as odds ratios (OR) with their respective 95 % CI. All analyses were adjusted for confounding factors, including age, sex, deprivation and education attainment and waist circumference (Petermann-Rocha et al., 2020).

Moreover, a meta-analysis including 7,022 older adults observed that older adults with sarcopenia had a significantly higher risk of diabetes (OR: 1.51) (Chung, Moon & Chang, 2021). Similarly, in over 700 older adults, aged 60 to 72 years, from a prospective cohort study in Finland it was shown that a lower handgrip strength was significantly associated with higher risk of developing type 2 diabetes (Kunutsor, Voutilainen & Laukkanen, 2020). Interestingly, this association remained robust after adjusting for covariates such as high-density lipoprotein cholesterol, physical activity, smoking, systolic blood pressure, fasting plasma glucose and family history of diabetes (Kunutsor, Voutilainen & Laukkanen, 2020).

A meta-analysis by Zhang et al. (2020), reviewing 10 cohort studies with 10,073 older adults, found that sarcopenia was significantly associated with a higher risk of falls (OR: 1.52). Consistent with this, evidence from an umbrella review including 30 meta-analyses suggests that sarcopenia is associated with a higher risk of falls in older

adults (RR: 1.75). On top of that, sarcopenia was linked to an increased incidence of fractures (HR: 2.25) (Su, Chang & Tsai, 2022). Considering all of the above, it is not surprising that sarcopenia can negatively affect quality of life. Evidence from a meta-analysis including 43 cross-sectional studies with 30,322 older adult participants found that those with sarcopenia, compared to older adults without sarcopenia, had significantly lower quality of life (SMD: −0.76) (Beaudart et al., 2023). Recognizing the consequences of sarcopenia emphasizes the importance of accurately diagnosing and classifying the condition, which will be discussed in the following paragraphs.

1.1.2 Sarcopenia clinical diagnosis and classification

Since the term sarcopenia (from the Greek sarx meaning 'flesh' and penia meaning 'loss') was introduced by Dr. Irwin Rosenberg (Rosenberg, 1997), it has evolved and has been defined as the loss of skeletal muscle mass and strength as a result of ageing (Morley et al., 2001). Expert consensus groups such as the International Working Group on Sarcopenia (IWGS) (Fielding et al., 2011), the Foundation for the National Institutes of Health (FNIH) (Studenski et al., 2014), the first European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2010), the updated EWGSOP2 (Cruz-Jentoft et al., 2019), and the Asian Working Group for Sarcopenia (AWGS) (Chen et al., 2014) have since refined the concept. Table 1.1 shows different recommendations for sarcopenia definition cut-off points for muscle mass, strength and physical performance.

Notably, EWGSOP2 established a widely accepted definition and classification scheme. It considers low muscle strength as the primary parameter of sarcopenia, as it predicts the adverse outcomes of sarcopenia and is the most reliable measure of muscle function (Cruz-Jentoft et al., 2019). Thus, the current clinical classification of sarcopenia based on EWGSOP2 includes probable (pre-sarcopenia), confirmed (sarcopenia), and severe sarcopenia. Individuals are diagnosed with probable sarcopenia if they have low muscle strength; with confirmed sarcopenia if they have both low muscle strength and low muscle quantity or quality; and with severe sarcopenia if they also exhibit low physical performance (Cruz-Jentoft et al., 2019).

Furthermore, EWGSOP2 provides recommendations of sarcopenia cut-off points for muscle strength, mass and physical performance. (Cruz-Jentoft et al., 2019). For example, the cut-off points for muscle strength measured by grip strength are <27 kg

for men and <16 kg for women, whereas if measured by the chair stand test, the cut-off was >15 seconds for five rises (men and women) (Cruz-Jentoft et al., 2019). Figure 1.2 shows the recommendations of cut-off points provided by EWGSOP2.

Table 1.1 Sarcopenia cut-off points for muscle mass, strength, and physical performance proposed by different groups

Working Group	Muscle Mass	Muscle Strength	Physical Performance
IWGS (Fielding et al., 2011)	ALM/height² ≤ 7.23 kg/m² (men) ≤ 5.67 kg/m² (women)	—	Gait speed < 1.0 m/s
FNIH (Studenski et al., 2014)	ALM/BMI < 0.789 (men), < 0.512 (women)	GS < 26 kg (men) GS < 16 kg (women)	Gait speed ≤ 0.8 m/s
EWGSOP (Cruz-Jentoft et al., 2010)	ALM/height² ≤ 7.25 kg/m² (men), ≤ 5.67 kg/m² (women)	GS < 30 kg (men) GS < 20 kg (women)	Gait speed ≤ 0.8 m/s SPPB < 0.8-point score
EWGSOP2 (Cruz-Jentoft et al., 2019)	ASM <20 kg (men) <15 kg (women) ASM/height² <7.0 kg/m² (men) <5.5 kg/m² (women)	GS < 27 kg (men), Grip GS < 16 kg (women) Chair rise > 15 s for 5 rises	Gait speed ≤ 0.8 m/s SPPB ≤ 0.8-point score TUG ≤ 20s 400 m 6 min for completion
AWGS (Chen et al., 2014)	ALM/height² ≤ 7.0 kg/m² (men), ≤ 5.4 kg/m² (women)	GS < 26 kg (men) GS < 18 kg (women)	Gait speed < 0.8 m/s

IWGS: the International Working Group on Sarcopenia, FNIH: the Foundation for the National Institutes of Health, EWGSOP: the first European Working Group on Sarcopenia in Older People, EWGSOP2: the updated European Working Group on Sarcopenia in Older People, AWGS: the Asian Working Group for Sarcopenia, ALM: Appendicular lean Muscle, BMI: Body mass index, ASM: Appendicular Skeletal Muscle Mass. GS: Grip strength, SPPB: Short Physical Performance Battery and TUG: Time up and go.

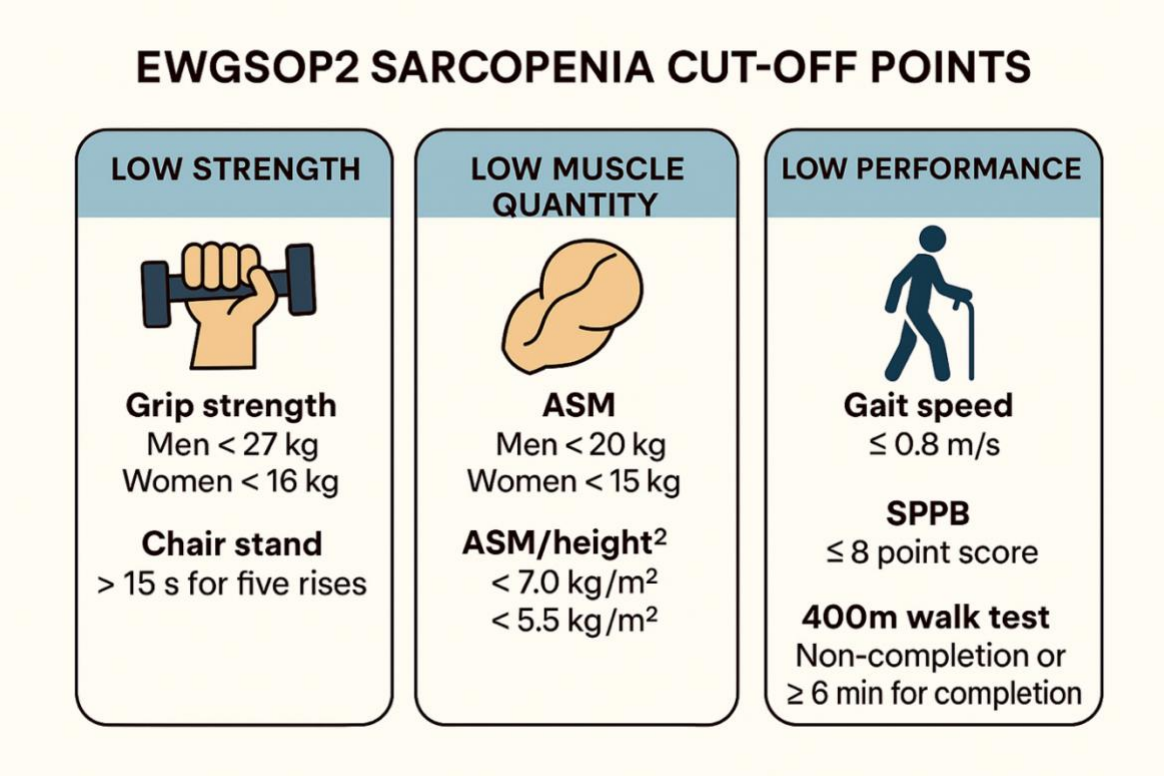

Figure 1.2 EWGSOP2 recommendation of sarcopenia cut-off points for muscle strength, mass and physical performance. ASM: Appendicular Skeletal Muscle Mass and SPPB: Short Physical Performance Battery. This figure was created by the author based on the EWGSOP2 consensus guidelines (Cruz-Jentoft et al., 2019), with assistance from a generative artificial intelligence tool (ChatGPT, OpenAI) for initial figure structuring. All content was reviewed, verified, and finalised by the author.

1.1.3 Prevalence and economic burden of sarcopenia

As stated previously, there is no scientific consensus on the definition or measurement of sarcopenia (McLean & Kiel, 2015). Therefore, accurately estimating the prevalence of sarcopenia remains challenging. Indeed, as detailed in the previous section there are several widely used definitions and measurement criteria for sarcopenia in the literature, including those from IWGS, FNIH, EWGSOP, EWGSOP2 and AWGSA. Accordingly, it is not surprising that the following estimates of sarcopenia prevalence show considerable variation. A systematic review and meta-analysis by Petermann-Rocha et al., (2022) evaluated the global prevalence of sarcopenia including 151 studies from varied countries with 312,804 participants (mean aged 71.5 years). This study observed that the global prevalence of sarcopenia in older adults ranged from 10% to 27%, depending on the classification and cut-off points used, including IWGS,

FNIH, EWGSOP, EWGSOP2, and AWGS (Petermann-Rocha et al., 2022). Additionally, Figure 1.3 showed the prevalence of sarcopenia based on each classification and region of origin (Petermann-Rocha et al., 2022).

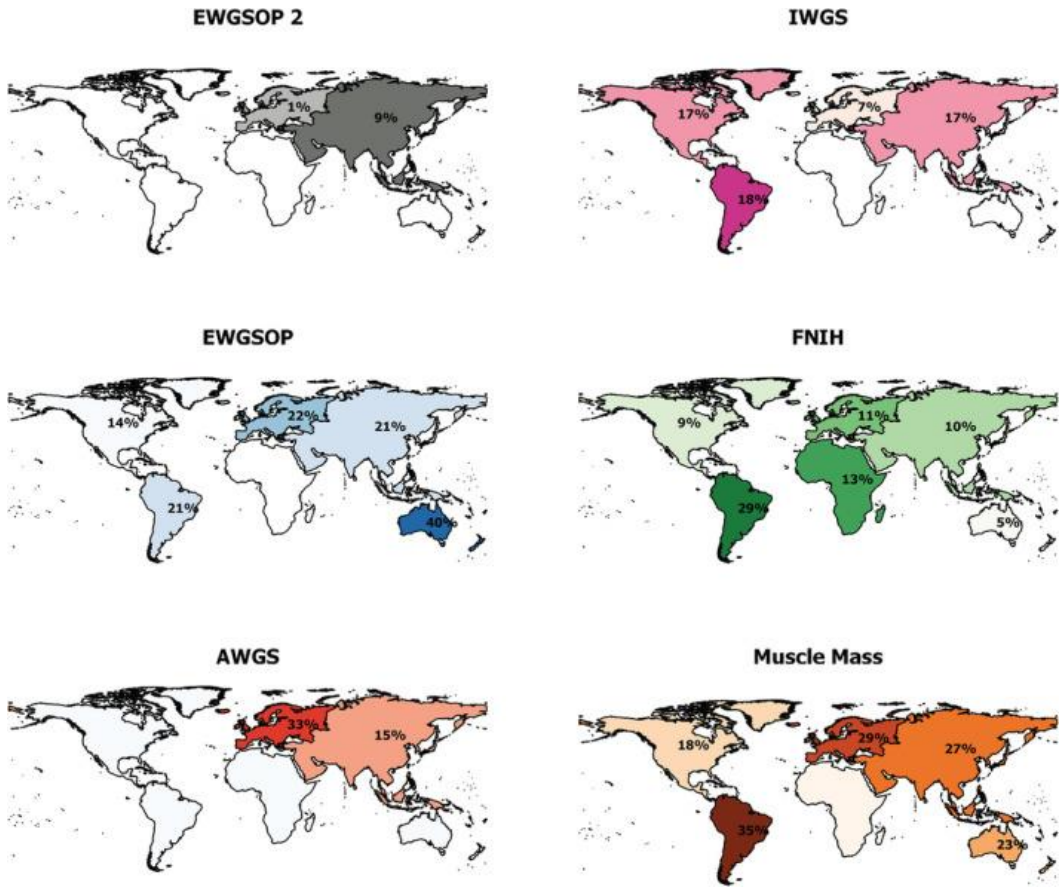

Figure 1.3 Overall prevalence of sarcopenia by classification and region of origin. Data presented as prevalence (%) by classification used. The figure is obtained from (Petermann-Rocha et al., 2022)

Furthermore, the prevalence of sarcopenia among older adults in Europe (28 countries) is projected to increase from approximately 10.9 million in 2016 to 18.7 million by 2045 (72.4% increase), based on the EWGSOP classification and cut-off points (Kilgour et al., 2020). Focusing on the UK, the prevalence of sarcopenia in older adults has been estimated to be 7.4% in men and 11.0% in women, based on EWGSOP classification and cut-off points (Patel et al., 2013). Consequently, as the number of older adults diagnosed with sarcopenia rises, the current and future economic burden of the condition is likely to place increasing pressure on public healthcare systems.

Therefore, estimating the accurate economic cost of sarcopenia is of clear importance, however, difficulties in accurately defining sarcopenia remain.

A systematic review including 14 studies from five different countries, such as the USA and China, compared healthcare costs between individuals with sarcopenia and those without (Bruyère et al., 2019). The review found that 11 of the 14 studies reported higher healthcare costs for individuals with sarcopenia compared to those without (Bruyère et al., 2019). In the UK, the annual excess health and social care costs related to muscle weakness in older adults including general practitioner appointments, hospital outpatient and inpatient services, prescribed medications, and both formal (paid) and informal care, were estimated at around £2.5 billion, with the annual excess cost per person being £4,592 (Pinedo-Villanueva et al., 2019).

Furthermore, older adults with sarcopenia were five times more likely to have higher hospital costs compared to those without sarcopenia. (Antunes et al., 2017). Further research demonstrated that, regardless of whether patients with sarcopenia were adults or older adults, hospitalization healthcare costs were significantly higher by €1,240 for adults and €721 for older adults (Sousa et al., 2016). Additionally, in a large community-based study, conducted in the Czech Republic, older adults with sarcopenia incurred more than twice the direct healthcare costs compared to those without sarcopenia (Steffl et al., 2017). Furthermore, lower muscle strength and physical function have been shown to be strongly associated with higher healthcare costs in older adults (Mijnarends et al., 2018). Together, current data indicates that sarcopenia has broad economic implications; thus, understanding the underlying mechanism of sarcopenia is essential to managing it effectively.

1.1.4 Possible mechanisms underlying sarcopenia

The loss of muscle strength and mass with age is multifactorial in origin and this section briefly outlines these mechanisms, with a focus on those most relevant to the current thesis.

1.1.4.1 Protein metabolism

With advancing age, the regulation of protein metabolism becomes disrupted, particularly after meals and following exercise, leading to an imbalance between

anabolic and catabolic processes that contributes to a loss of muscle mass (Cho, Lee & Song, 2022). Muscle mass is maintained through a balance between muscle protein synthesis and muscle protein breakdown (Phillips & Van Loon, 2011; Cuthbertson et al., 2006). Under normal conditions, this balance is tightly regulated. However, protein intake and exercise can stimulate muscle protein synthesis and shift muscle into a positive protein balance, provided that muscle protein breakdown does not increase at the same time (Atherton & Smith, 2012; Cuthbertson et al., 2006). In healthy individuals, nutrient availability following a fasting period, particularly the intake of essential amino acids and leucine, acts as a key stimulus for muscle protein synthesis (Cuthbertson et al., 2006). This response after meals offsets protein losses resulting from muscle protein breakdown during essential processes such as tissue growth and repair, and the synthesis of enzymes and hormones. This process is commonly referred to as the 'fasted-loss/fed-gain' cycle (Cuthbertson et al., 2006).

As mentioned following feeding, muscle protein synthesis increases and exceeds muscle protein breakdown. After this, muscle enters a state in which further increases in protein synthesis do not occur, despite the continued presence of amino acids (Cuthbertson et al., 2006; Atherton and Smith, 2012). Resistance exercise can overcome this response by increasing muscle sensitivity to anabolic stimuli (Cuthbertson et al., 2006; Breen et al., 2011). As a result, muscle protein synthesis can be elevated for several hours following resistance exercise, contributing to increases in muscle mass (Cuthbertson et al., 2006).

An important regulator of muscle protein synthesis is the mechanistic target of rapamycin signalling pathway, which plays an important role in controlling protein synthesis and cell growth (Ruvinsky & Meyuhas, 2006). In skeletal muscle, mechanistic target of rapamycin complex 1 is activated downstream of the Akt pathway through endocrine, paracrine, and autocrine signalling by anabolic hormones including insulin and insulin-like growth factor-1, as well as by amino acid availability and mechanical loading from resistance exercise (Yang et al., 2008; Aguilar-Agon et al., 2019). In mature muscle fibres, where cell number is fixed, mechanistic target of rapamycin signalling is primarily involved in regulating muscle protein synthesis (Atherton and Smith, 2012; Ruvinsky & Meyuhas, 2006). Activation of mechanistic target of rapamycin complex 1 promotes protein synthesis through downstream targets, which are closely linked to mitochondrial energy metabolism to meet the

energetic demands of protein synthesis (Morita et al., 2015; Ruvinsky & Meyuhas, 2006).

Although resting rates of muscle protein synthesis appear to be largely preserved with advancing age, evidence suggests that older adults require a greater availability of amino acids to stimulate muscle protein synthesis compared with younger individuals (Dardevet et al., 2012). This reduced sensitivity to anabolic stimuli is commonly described as anabolic resistance and has been attributed, in part, to age-related reductions in metabolic activity within skeletal muscle and increased insulin resistance (Dardevet et al., 2012; Walrand et al., 2011). It is important to acknowledge that impairments in muscle protein synthesis are more apparent following exercise, where the anabolic response is reduced in older adults (Dardevet et al., 2012). Anabolic resistance is associated with reduced activation of the mammalian target of rapamycin signalling pathway, reduced protein translation, and increased insulin resistance. This frequently occurs alongside chronic low-grade inflammation, termed inflammaging (Walrand et al., 2011; Fulop et al., 2018). Therefore, the expected gains in muscle mass and strength in response to protein intake and resistance exercise are reduced in the context of age-related sarcopenia (Walrand et al., 2011; Fulop et al., 2018).

1.1.4.2 Mitochondrial dysfunction

Mitochondrial dysfunction is widely recognised as a key mechanism underlying sarcopenia, as mitochondria are essential for energy production required for muscle contraction, repair, and protein synthesis (Kumar et al., 2019). Age-related impairments in mitochondrial function may therefore contribute to reduced muscle quality, increased fatigue, and a reduced anabolic response (Kumar et al., 2019). Evidence from studies suggests that declines in mitochondrial function are associated with loss of muscle mass and strength, and that these changes may occur relatively early in the ageing process.

One of the most informative studies in this area is the study conducted by Ibebunjo and colleagues (2013), which examined changes across the lifespan in rats. Rather than comparing separate groups of young and old animals, the same group of rats was assessed at 6, 12, 18, 21, 24, and 27 months of age. This provides a clearer representation of the progression of age-related muscle changes over time. The study

measured mitochondrial enzyme activity in the plantaris muscle and reported that mitochondrial enzyme activity declined with ageing. This decline was consistent with increased muscle fatigue and a reduction in muscle mass and strength (Ibebunjo et al., 2013). These findings support the idea that mitochondrial dysfunction contributes to age-related impairment in muscle function and may represent a key pathway in sarcopenia.

In the same study, mitochondrial dysfunction was linked to reduced expression of gene pathways associated with mitochondrial energy metabolism. It is important to acknowledge that the most pronounced reduction occurred around 21 months in rats, which was suggested to approximate midlife in humans, and this reduction continued with further ageing. This pattern is important because it suggests that mitochondrial deterioration may be established before advanced old age. As mitochondrial energy metabolism provides the energetic support for anabolic processes, reduced mitochondrial capacity may limit the ability of muscle to maintain protein turnover. Consistent with this, mitochondrial dysfunction has been described as being associated with disturbed energy production required for muscle protein synthesis and muscle mass maintenance (Kumar et al., 2019).

The Ibebunjo et al. (2013) study also reported increased expression of pathways related to cell cycle regulation, cell death, immune response, and protein breakdown around a similar age. These changes provide evidence of a shift towards a more catabolic and inflammatory gene expression profile during ageing. It is worth noting that these anabolic and catabolic gene expression patterns were described as being linked to the mammalian target of rapamycin pathway, which is, as detailed previously, central to muscle protein synthesis regulation and is sensitive to both nutrient availability and mechanical loading (Ibebunjo et al., 2013). These findings help to connect mitochondrial dysfunction, disrupted protein metabolism, and inflammatory activation as related mechanisms in sarcopenia.

Beyond mitochondrial metabolism, ageing also affects the function of contractile proteins. Studies in aged rats reported a 24 to 30% decline in the fraction of myosin heads in a strong-binding state, alongside a 24 to 27% decline in tension, compared with younger rats (Lowe et al., 2002). This finding suggests that ageing reduces the

proportion of force-generating cross-bridges, which would impair muscle contractility. Lowe et al. (2004) further suggested that this weakened contractility may reflect a slowing of the actomyosin ATPase cycle, with similarities to mechanisms seen in muscular dystrophy. These findings support the concept that sarcopenia is not simply a loss of muscle quantity but also involves declines in muscle quality, including reduced contractile efficiency.

Overall, the evidence suggests that mitochondrial dysfunction and energy limitations are central to the development of sarcopenia. Declining mitochondrial oxidative capacity may impair both endurance and strength-related functions, reduce the capacity for muscle repair, and limit anabolic responses. When combined with changes in contractile protein function, these energetic limitations likely contribute to functional decline in ageing muscle and may play a role in the progression of sarcopenia.

1.1.4.3 Inflammation

Chronic low-grade inflammation is a hallmark of ageing and has been implicated as a key mechanism contributing to sarcopenia (Ferrucci & Fabbri, 2018). This age-related inflammatory state is commonly referred to as inflammaging and is characterised by elevated circulating inflammatory mediators in the absence of an acute infection or injury (Beyer, Mets & Bautmans, 2012). Evidence suggests that inflammaging may contribute to muscle loss by promoting catabolic processes, impairing anabolic signalling, and negatively affecting muscle repair and regeneration (Beyer, Mets & Bautmans, 2012; Ferrucci & Fabbri, 2018). A number of studies have investigated age-related changes in inflammatory mediators. An age-related increase in plasma levels of pro-inflammatory markers, including tumour necrosis factor alpha, C-reactive protein, interleukin-6, and interleukin-1 beta, alongside a reduction in anti-inflammatory mediators such as interleukin-10, provides evidence for chronic low-grade inflammation with age (Daussin et al., 2021). This inflammatory environment is also linked to increased susceptibility to infection, cancer, and chronic diseases in older adults. Although ageing is considered the primary driver of inflammaging, other factors may contribute to earlier onset or greater inflammatory burden, including physical inactivity, low intake of protein and micronutrients, smoking, and stress (Fulop et al., 2018).

The relationship between inflammation and sarcopenia is supported by observational evidence, although findings are not consistent across studies. Some studies have reported higher C-reactive protein levels in older adults with sarcopenia compared with controls (Kim et al., 2013; El Maghraoui et al., 2016; Ishihara et al., 2016). However, these studies did not report differences in interleukin-6 or tumour necrosis factor alpha between individuals with and without sarcopenia, highlighting that the inflammatory signature of sarcopenia may not be uniform across populations. In contrast, other studies have reported elevated interleukin-6 and tumour necrosis factor alpha in older adults with sarcopenia, with these markers identified as predictors of sarcopenia and its severity (Rong et al., 2018). Taken together, these findings suggest that inflammation is likely involved in sarcopenia, but the specific mediators and the strength of association may vary by study design, population, and diagnostic criteria.
Evidence from the literature also supports a link between inflammatory burden and physical function. Grosicki et al. (2020) conducted an RCT including older adults aged 70 years and above from the United States and Sweden and reported that interleukin-6 levels were inversely related to muscle mass and strength and were associated with poorer mobility outcomes, including slower stair climb time. It is important to acknowledge that in participants assigned to a physical training programme three times per week for six months, reductions in interleukin-6 were associated with improvements in gait speed and muscle mass. This supports the idea that regular physical activity may reduce inflammatory burden and may therefore contribute to the maintenance of muscle function with age.

Large cohort evidence provides further support. The Health ABC Study reported that higher interleukin-6 levels were associated with weaker handgrip strength across sexes and ethnic groups, and higher interleukin-6 and tumour necrosis factor alpha were associated with lower muscle mass in specific subgroups (Visser et al., 2002). In addition, several studies across different populations have reported relationships between elevated inflammatory mediators and poorer muscle outcomes (Pedersen et al., 2003; Penninx et al., 2004; Toth et al., 2005). Whilst these studies support an association, the underlying biological pathway remains complex. From a mechanistic perspective, inflammaging may accelerate muscle loss by influencing anabolic and catabolic signalling pathways (Dalle, Rossmeislova & Koppo, 2017). It has been suggested that chronic inflammation may act on the mammalian target of rapamycin

signalling pathway to inhibit anabolic signalling, thereby accelerating muscle loss with ageing (Dalle, Rossmeislova & Koppo, 2017). However, evidence also suggests that the relationship may be bidirectional. For example, Weichhart (2018) proposed that mammalian target of rapamycin signalling may also promote the production of pro-inflammatory mediators, suggesting a relationship between impaired anabolic signalling and chronic inflammation. In addition, inflammatory mediators such as tumour necrosis factor alpha have been associated with alterations in calcium handling, including reductions in calcium function, which is an early change in muscle metabolism linked to reduced muscle function (Lowe et al., 2004). Therefore, whilst the association between inflammation and sarcopenia is supported by multiple studies, the causal pathways and interactions with protein metabolism, mitochondrial function, and neuromuscular mechanisms remain to be fully established.

Overall, inflammaging represents an important contributor to sarcopenia, both through direct effects on muscle metabolism and through interactions with other age-related mechanisms.

1.1.4.4 Neuromuscular dysfunction

With ageing there is a reduction in both number and size of muscle fibres, mainly type 2 fibres, alongside increases in fat infiltration, with the loss of fibres to some extent caused by a slowly progressive neurogenic process (Ciciliot et al., 2013, Cho, Lee & Song, 2022). Furthermore, satellite cells, which are responsible for muscle repair and regeneration (Verdijk et al., 2014), decrease in number and function with age, reducing muscles potential for hypertrophy (Cho, Lee & Song, 2022). In addition, mitochondrial dysfunction, insulin resistance, chronic inflammation, and oxidative stress may contribute to the loss of muscle during sarcopenia (Ji, 2001, Huang, Hood, 2009, Walrand et al., 2011, Fulop et al., 2018).

As mentioned previously, there is evidence that the loss of strength is driven by factors other than the loss of muscle mass and there is evidence that these are neural in origin. Emerging evidence suggests that force steadiness of knee extensors was significantly lower in older adults when compared to younger adults at low-level force such as 10% maximum voluntary contraction (MVC) (Tracy, Enoka, 2002). This is supported by a recent literature review and meta-analysis by Oomen and van Dieën

(2017), which found that force steadiness of the knee extensors significantly declined with ageing, with a large, pooled effect size (r = 0.72; 95% CI: 0.62–0.79). This may indicate that variability in force steadiness due to ageing can limit motor control which in turn may negatively affect physical performance in older adults (Oomen and van Dieën 2017).

Evidence from several studies has established that ageing and sarcopenia are associated with a number of neuromuscular system changes, including a decrease in motor unit (MU) number with remaining MUs becoming larger in their size, increased denervation, individual fibre dysfunction, impaired motor unit remodelling, and eventual permanent muscle fibre loss. These changes may affect neuromuscular function, such as motor unit firing rate, firing rate variability, and neuromuscular junction (NMJ) transmission stability (Jones et al., 2022; Hepple & Rice, 2016; Anagnostou & Hepple, 2020; McNeil et al., 2005).

Indeed, a systematic review and meta-analysis of 30 studies comparing firing rate between older and younger adults observed that firing rate during isometric contractions was lower in older adults which could explain the age-related decline in muscle strength (Orssatto et al., 2022). For firing rate variability, a number of studies have investigated differences in firing rate variability in healthy older adults compared to young. These studies observed that firing rate variability is significantly greater in healthy older adults than younger adults (Laidlaw, Bilodeau & Enoka, 2000, Tracy et al., 2005). With regard to NMJ transmission instability, a couple of studies have assessed it by quantification of near fibre (NF) jiggle. Both studies found that NF jiggle was significantly higher in healthy older adults compared to young participants, indicating an age-related deterioration of NMJ transmission stability (Piasecki et al., 2016, Hourigan et al., 2015).

Understanding the age-related declines, adverse outcomes, prevalence and economic burden of sarcopenia, it is therefore essential to manage, prevent, and treat the condition.

1.2 Resistance exercise as an intervention for sarcopenia

Currently, there is no effective pharmacological treatment for sarcopenia (Cruz-Jentoft and Sayer, 2019). Therefore, the most applicable and effective intervention to

counteract the adverse outcomes of sarcopenia is non-pharmacological treatment such as physical activity (Dent et al., 2018). Indeed, a systematic review and meta-analysis, including 124 studies with 230,174 older adults, found that lower risk of sarcopenia was associated with participating in physical activity in older adults, from both cross-sectional and longitudinal studies with moderate-to-vigorous physical activity (MVPA) showing the most robust association (Sánchez-Sánchez et al., 2024). Likewise, a cross-sectional study from the Hertfordshire Sarcopenia Study including 131 older adults who aged from 74 to 84 years, physical activity measured by accelerometer was associated with lower risk of sarcopenia (measured by EWGSOP2 sarcopenia cut-off points for muscle strength, mass and physical performance) and improved gait speed (Westbury et al., 2018). However, physical activity was not associated with improvements in handgrip strength (Westbury et al., 2018).

Furthermore, a 4-year longitudinal study from the China Health and Retirement Longitudinal Study between 2011 and 2015 included a total of 3,760 participants aged 40 years and above (Zhao et al., 2024). Sarcopenia was identified based on muscle mass, strength, and physical performance using the AWGS classification. The results indicate an association between participation in MVPA and a lower risk of sarcopenia compared to sedentary individuals in a cohort of middle-aged and older adults (Zhao et al., 2024).

From the broad range of physical activities, resistance exercise is the most promising intervention to enhance muscle strength and size in older adults (Giallauria et al., 2015). Specifically, a progressive resistance exercise program, meaning that the intensity and difficulty level of the exercise increased, showed a positive effect on muscle strength and physical function in older adults (Liu, Latham, 2009). Indeed, a systematic review and meta-analysis with aim to investigate different non-pharmacological treatment such as whole-body vibration training, resistance exercise and mixed training (including resistance exercise in conjunction with aerobic exercise, endurance and balance) on muscle strength and physical function in older adults with sarcopenia (Lu et al., 2021). A total of 26 studies (25 randomised controlled trials RCTs) involving 1,191 older adults diagnosed with sarcopenia (most of which used EWGSOP or AWGS criteria) were included (Lu et al., 2021). The findings showed that resistance exercise and mixed training significantly improved knee extension strength, handgrip strength, gait speed, and Timed Up and Go (TUG) performance but not chair

rise test performance compared to control groups. In contrast, whole-body vibration training showed a statistically significant improvement only in TUG performance, with a small effect size (SMD = –0.30, 95% CI: –0.60 to 0.00, p=0.05) (Lu et al., 2021). Although both resistance exercise and mixed training had positive effects on muscle strength and physical function, resistance exercise was superior to mixed training in improving these outcomes (Lu et al., 2021). Similarly, a systematic review and meta-analysis with a total of 14 studies of RCTs, involving 561 older adults diagnosed with sarcopenia (half of the studies used EWGSOP or AWGS criteria), were included. (Giallauria et al., 2015). The findings showed that resistance exercise significantly improved knee extension strength, handgrip strength and gait speed (Giallauria et al., 2015).

Therefore, the International Clinical Practice Guidelines for Sarcopenia strongly recommend, with moderate certainty of evidence, that prescribing resistance exercise interventions can effectively improve muscle strength, muscle mass, and physical function in older adults (Dent et al., 2018). Furthermore, the World Health Organization recommends that older adults engage in moderate to high intensity muscle-strengthening activities, such as resistance exercises, at least twice a week to improve physical function (World Health Organization, 2020). In addition, the UK Chief Medical Officers' Physical Activity Guidelines published in 2019 clearly recommend that older adults should engage in moderate intensity physical activity, such as swimming, brisk walking, or cycling, for at least 150 minutes per week, or in vigorous intensity activities, such as running, stair climbing, or sports, for at least 75 minutes per week, or a combination of both intensities (Davies et al., 2019). They also recommended that older adults engage in strengthening activities, such as resistance exercise, at least two days per week, and minimize sedentary time as much as possible (Davies et al., 2019). More specifically, the Scottish Physical Activity Guidelines (2011) recommended that older adults aged 65 and over, particularly those at risk of falls, engage in muscle-strengthening, balance, and coordination exercises. Prior to this update, the guidelines had focused solely on aerobic activity for older adults (Strain et al., 2016).

However, many older adults do not meet these guidelines. Indeed, data from the Scottish Health Survey (2023) showed that many older adults, particularly women, did not meet the recommended physical activity guidelines of engaging in moderate-intensity physical activity for at least 150 minutes per week, vigorous-intensity activity for at least 75 minutes per week, or a combination of both (Figure 1.4) (Scottish Health Survey, 2023). Only 52% of older adults aged between 65 and 74 years met the guidelines, while just 36% of those aged 75 and over did so (Scottish Health Survey, 2023).

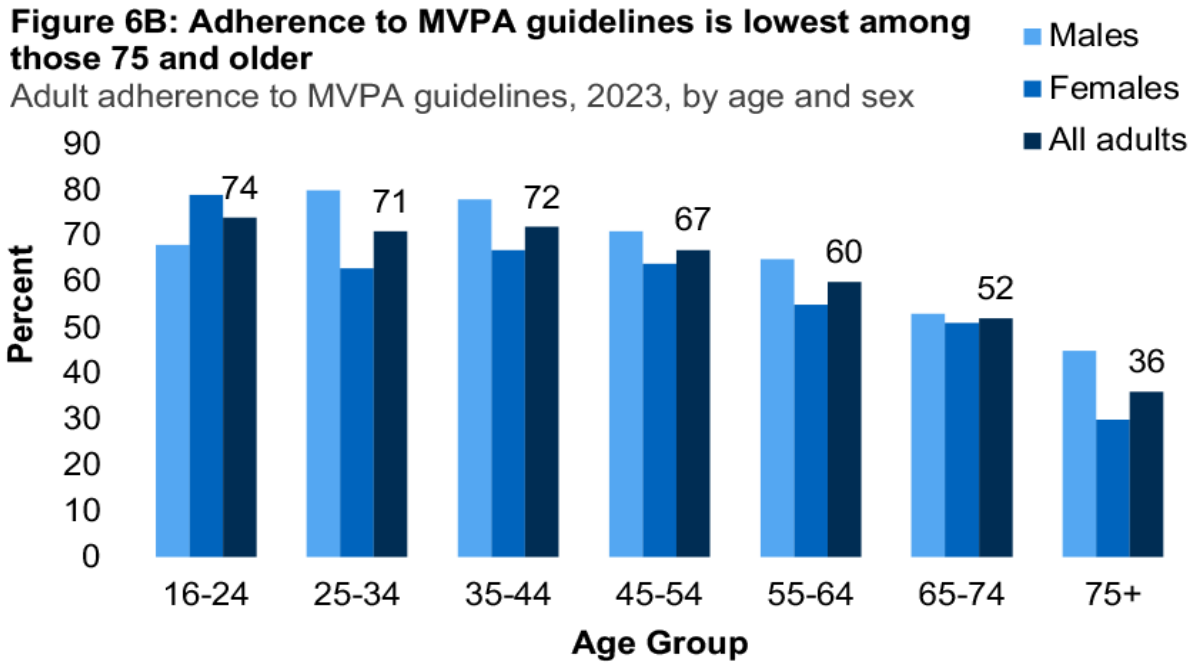

Figure 1.4 This figure provided by Scottish Health Survey, (2023) It illustrates the adherence to moderate-to-vigorous physical activity (MVPA) guidelines among adults and older adults in Scotland by age and sex in 2023. Engaging in physical activity progressively decline with age.

In regard to the recommendation of moderate to vigorous physical activity and muscle strengthening such as resistance exercise guidelines, data from the Scottish Health Survey (2023) (Figure 1.5) showed that engaging in physical activity and strengthening activities progressively decline with age. With only 15% of older adults aged between 65 and 74 years meeting the guidelines, while just 9% of those aged 75 and over did so (Scottish Health Survey, 2023).

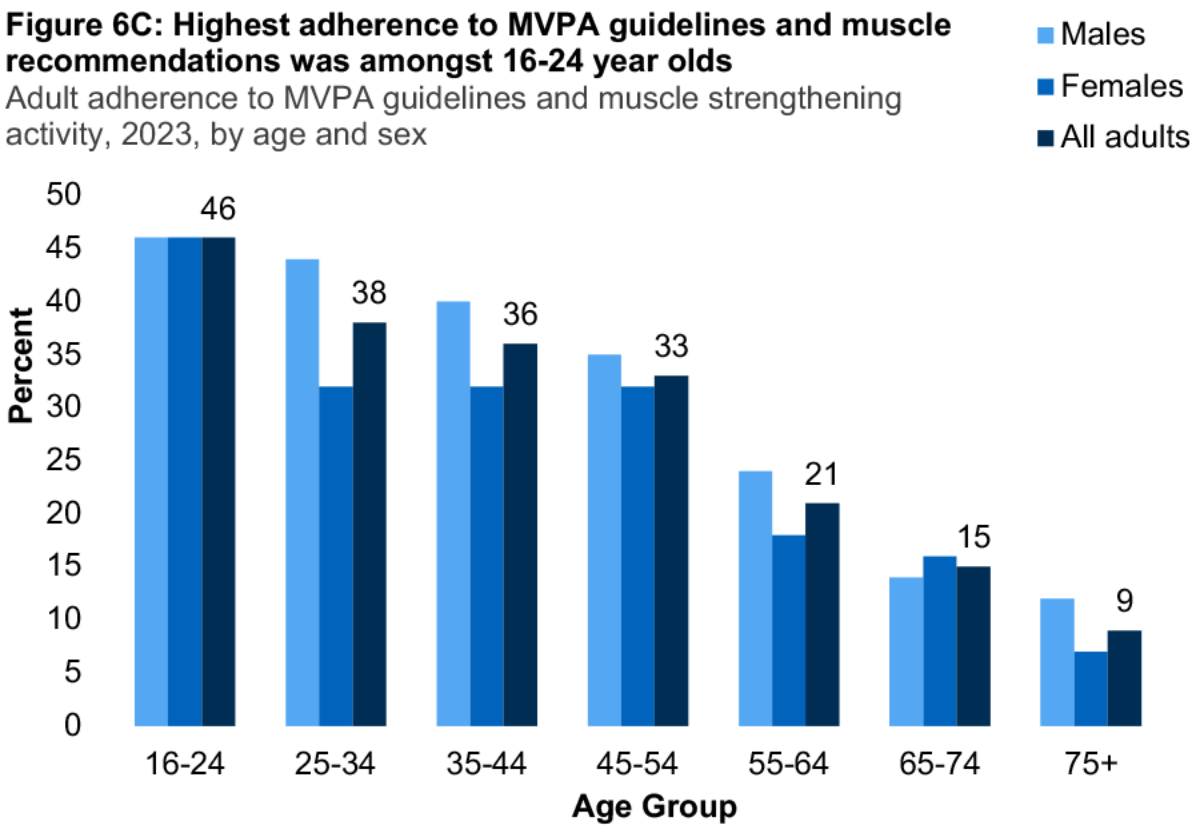

Figure 1.5 This figure provided by Scottish Health Survey, (2023) It illustrates the adherence to moderate-to-vigorous physical activity (MVPA) and muscle strengthening activity guidelines among adults and older adults in Scotland by age and sex in 2023.

Furthermore, another study conducted in Scotland (Figure 1.6) found that only 12% of women and 14% of men aged 65–74 met the UK's recommendation to perform muscle-strengthening exercises at least twice per week (Strain et al., 2016). Among adults aged 75 and over, adherence was even lower, with only 4% of women and 9% of men meeting the guidelines (Strain et al., 2016). Even among those who did meet the recommendation for muscle-strengthening activity, many were not actually engaging in resistance-based exercises (Table 1.2) (Strain et al., 2016). For example, only 6% of men and 4% of women aged between 65 and 74 reported participating in gym-based training. More specifically, just 4% of men and 3% of women aged between 65 and 74, and 3% of men and 1% of women aged 75 and over, engaged in such exercises (Strain et al., 2016).

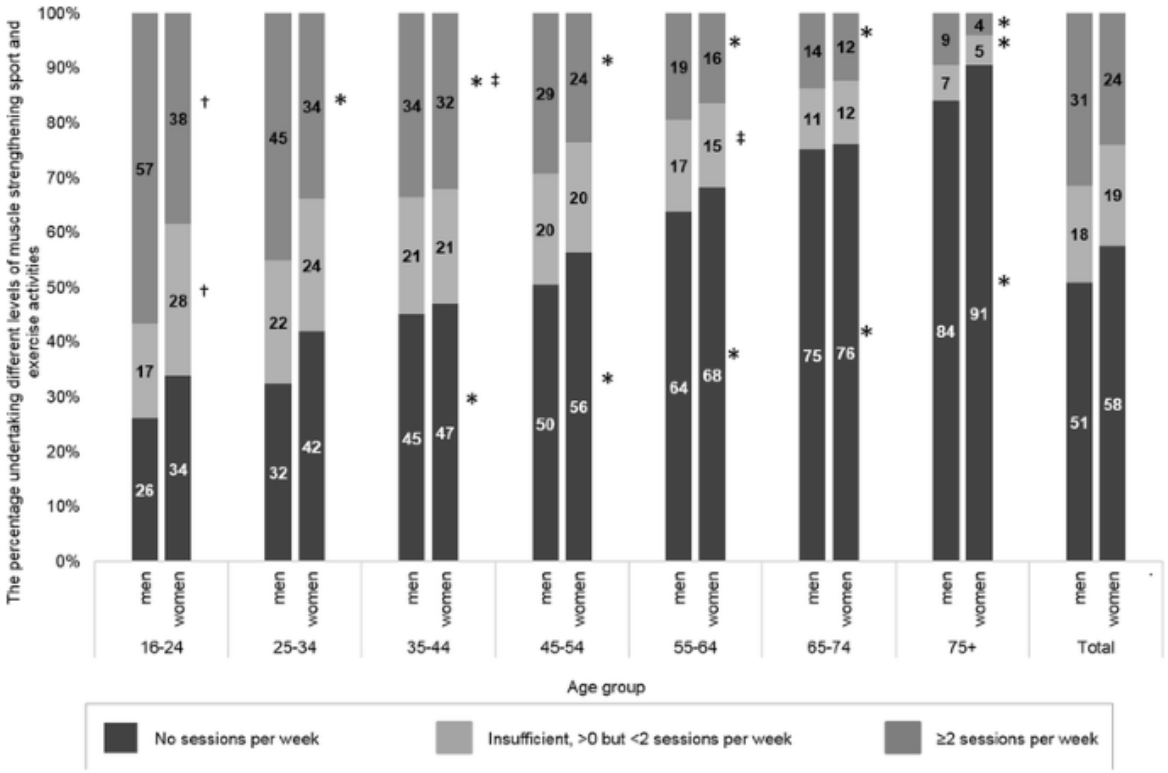

Figure 1.6 This figure provided (Strain et al., 2016). It illustrates the adherence to the muscle strengthening guidelines among adults and older adults in Scotland by age and sex in 2012.

Table 1.2 Participation in the top five muscle strengthening activities, by age group, stratified by gender provided by (Strain et al., 2016).

Men							
45–54		**55–64**		**65–74**		**75+**	
Workout at gym	**16**	**Swimming**	**10**	**Swimming**	**7**	**Swimming**	**4**
Swimming	**15**	**Workout at gym**	**9**	**Workout at gym**	**6**	**Workout at gym**	**3**
Cycling	**15**	**Hillwalking**	**8**	**Hillwalking**	**5**	**Exercises**	**3**
Running	**11**	**Cycling**	**7**	**Exercises**	**4**	**Golf**	**3**
Hillwalking	**10**	**Exercises**	**7**	**Golf**	**4**	**Hillwalking**	**2**
45–54		**55–64**		**65–74**		**75+**	
Swimming	**14**	**Swimming**	**12**	**Swimming**	**8**	**Aerobics**	**4**
Workout at gym	**12**	**Aerobics**	**7**	**Aerobics**	**6***	**Swimming**	**2**
Aerobics	**11**	**Workout at gym**	**6**	**Workout at gym**	**4**	**Exercises**	**1**
Exercises	**8**	**Hillwalking**	**6**	**Hillwalking**	**4**	**Dancing**	**1**
Hillwalking	**8**	**Exercises**	**4**	**Exercises**	**3**	**Hillwalking**	**1**

Data are presented as the percentage (%) of participants reporting engagement in each activity within age and sex categories. The data were obtained from the Scottish Health Survey and reported by Strain et al. (2016). Activities reflect self-reported participation in muscle-strengthening exercises.

Building upon previous findings, it is very important to understand why older adults do not participate in such exercises. Thus, results from studies that investigate the motivators and barriers to resistance exercises in older adults are needed. A previous systematic review suggests that the barriers for older adults to participate in resistance exercise included lack of equipment, available exercise programs, access to exercise facilities, and family and work obligations (Burton et al., 2017). In addition, a lack of understanding and awareness of the importance of resistance exercise, physical and psychological challenges such as the inability to perform resistance exercise due to the decline in physical strength associated with ageing, are also reported barriers by older adults toward resistance exercise (Hurst et al., 2023). Furthermore, a dislike of the gym environment and a fear of self-injury in the gym are other barriers for older adults preventing participation in resistance exercises (Dismore et al., 2020). Therefore, establishing an appropriate resistance exercise program that considers and addresses these common barriers is essential. Furthermore, a pragmatic and feasible solution is also needed to improve participation and adherence to resistance training. Therefore, home-based resistance exercise with minimal equipment may offer a practical approach to overcoming these barriers.

1.2.1 Home-based resistance exercise

Indeed, previous work by Simek et al. (2015) found that older adults prefer home-based resistance exercise due to the structure of such programs, which allows them to be performed at home. This may help overcome previously mentioned barriers such as limited access, dislike of the gym environment, lack of exercise facilities, and absence of equipment. In addition, older adults reported physical health benefits from home-based resistance exercise, including increased muscle strength, injury prevention, and improved balance. Furthermore, home-based resistance exercises were seen as time-efficient, as they do not take long to complete, which may also help address common barriers such as family and work obligations (Jansons, Paul et al., 2023).

As previously mentioned, resistance exercise can improve muscle strength and physical function in older adults. However, it is important to specifically examine the effects of home-based resistance exercise on muscle strength and physical function. A systematic review and meta-analysis of Manas et al. (2021) found that home-based resistance exercise training, in older adults, can improve lower muscle strength,

physical function, balance and can be performed safely with no major adverse events reported. Furthermore, the adherence rate for home-based resistance exercise was 67% (Manas et al., 2021). In addition, home-based resistance training not only improved muscle strength, physical function, and balance, and was performed safely, but also enhanced overall quality of life and exercise-related self-efficacy, while reducing fear of falling in older adults (Zhang et al., 2022).

To design an effective home-based resistance exercise program that older adults are likely to adhere to, it is important to understand the factors they find most preferable about home-based resistance exercise. A valuable study by Simek et al. (2015) investigated the aspects of home-based resistance exercise programs that older adults like (Figure 1.7). A key aspect was participants' autonomy, where they had the ability to choose when, how long, and which exercises to perform. Furthermore, older adults preferred the structure of home-based exercise programs to be time-efficient, simple, include easy exercises, and fit into daily routine activities.

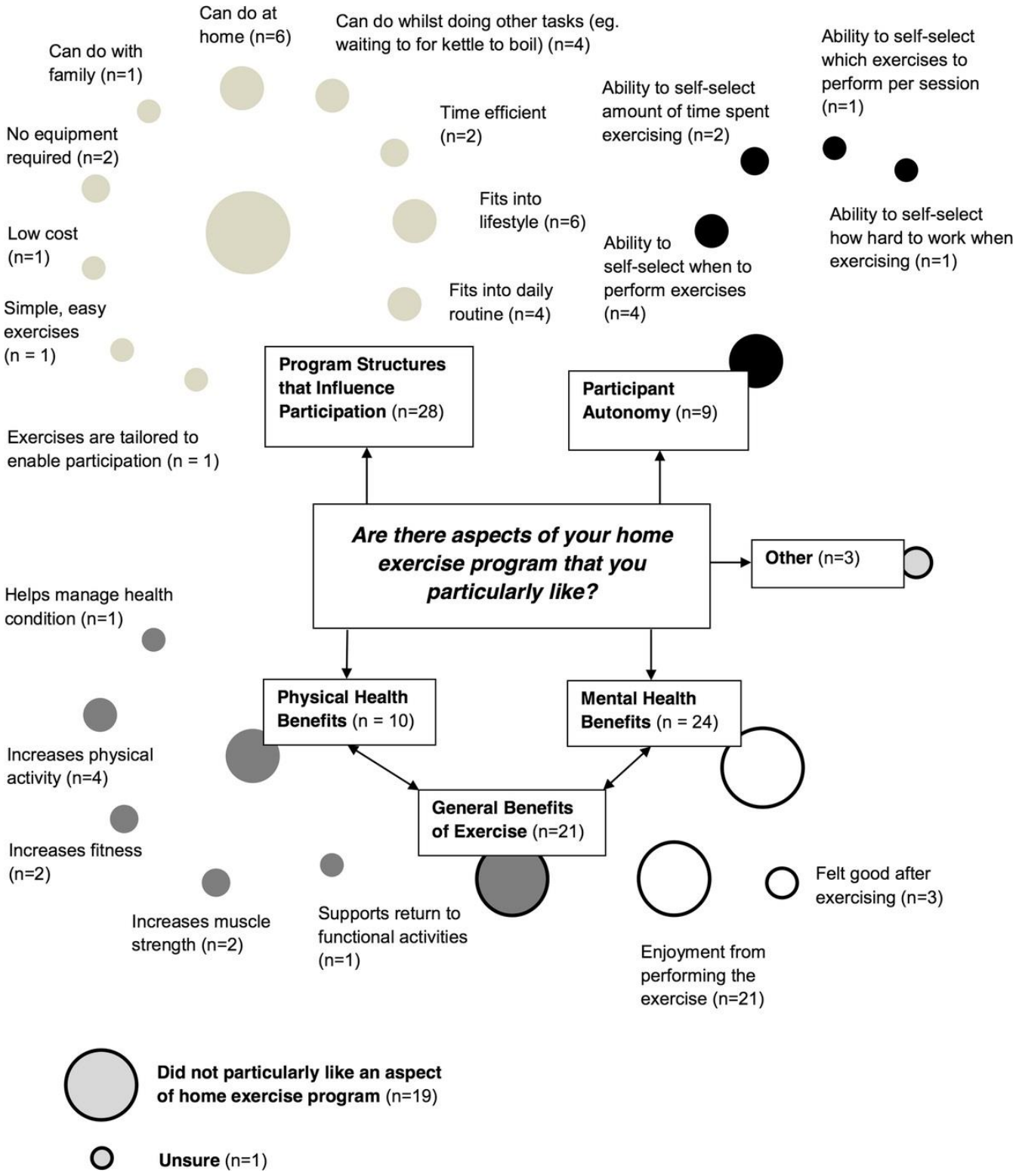

Figure 1.7 An illustration of the aspects of home-based resistance exercise that older adults like. This figure provided by Simek et al., (2015).

Resistance exercise is not the only intervention used to counteract the adverse outcomes of sarcopenia; nutritional supplementation, such as long-chain n-3 polyunsaturated fatty acids (LCn-3PUFAs), has shown a promising effect.

1.3 Role of (LCn-3PUFAs) as intervention for sarcopenia

Long-chain polyunsaturated fatty acids (LC-PUFAs), defined as fatty acids containing 20 to 22 carbon atoms and 5 to 6 double bonds, and LCn-3 PUFAs are a subgroup of these (Calder, 2018). There are three main types of LCn-3 PUFAs: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) (Calder, 2018). Figure 1.8 shows the structure of the main types of LCn-3 PUFAs. Moreover, EPA and DHA are the most common types of LCn-3 PUFAs used in supplements and have been widely studied (Witard, Combet & Gray, 2020). Although less well-known, DPA has recently emerged as an area of interest (Kaur et al., 2011). Furthermore, alpha-linolenic acid (ALA) is a subgroup of n-3 PUFAs (short-chain) (Calder, 2018) and can be converted to EPA and DHA, however, the conversion rate is limited at approximately less than 15% (Harris 2010). ALA can be found in plant oils like flaxseed, soybean, and canola oils, while EPA and DHA are primarily found in fish and seafood (Harris 2010).

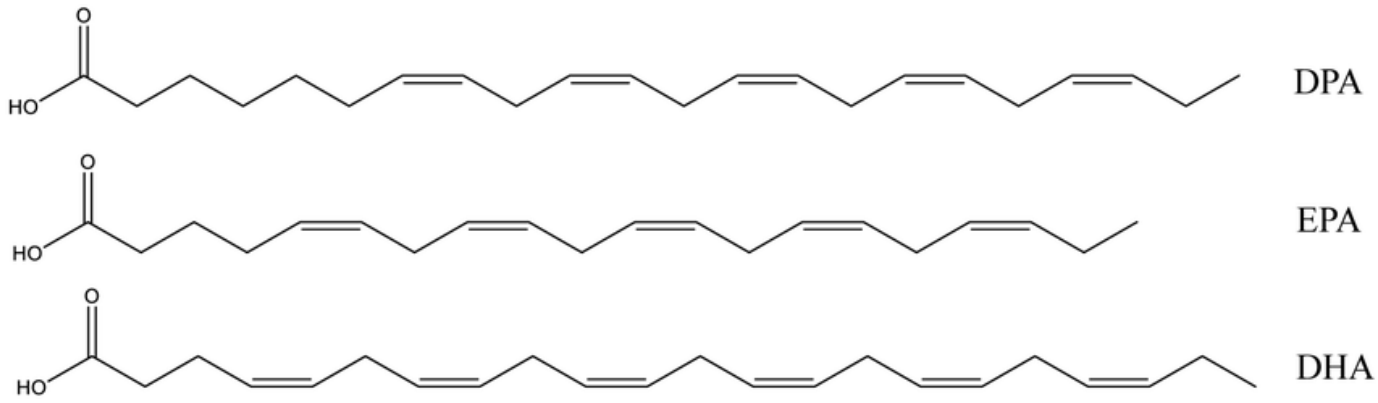

Figure 1.8 illustrated the structure of main type LCn-3 PUFAs: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) (Li et al., 2018).

There are many natural sources of LCn-3 PUFAs, including oily fish such as tuna, cod, salmon, anchovies, herring, and mackerel. LCn-3 PUFAs are also found in crustaceans such as krill, prawns, shrimp, shellfish, and crabs. In addition to seafood, smaller amounts of LCn-3 PUFAs can be found in various other foods, including most meats, yogurt, milk, egg yolks, olives and olive oil. Furthermore, there are supplementation sources of LCn-3 PUFAs such as fish and krill oil.

1.3.1 General effects of LCn-3 PUFAs

Extensive research has shown that LCn-3 PUFAs have a potential benefit for health. For example, a number of systematic reviews and meta-analyses showed that higher consumption of LCn-3 PUFAs was associated with lower risk of fatal coronary heart disease, heart failure and coronary disease (Djoussé et al., 2012, Del Gobbo et al., 2016). A possible explanation is that blood viscosity and platelet aggregation can be regulated by prostaglandins and thromboxane, which are synthesised from EPA and DHA, thus supporting cardiovascular health and reducing the risk of CVD. Furthermore, a meta-analysis of 17 RCTs found that the consumption of LCn-3 PUFAs can reduce blood pressure (Miller, Van Elswyk & Alexander, 2014). Moreover, LCn-3 PUFAs have been found to reduce uterine contractions thus, preventing preterm birth by reducing prostaglandin production (Yamashita et al., 2013). In addition to that LCn-3 PUFAs have a positive impact on inflammation by decreasing the secretion of pro-inflammatory cytokines (Kavyani et al., 2022, Horia, Watkins, 2007).

Furthermore, evidence from a number of studies has shown that LCn-3 PUFAs have positive effects in preventing or treating a number of conditions, for example diabetes, inflammatory diseases such as rheumatoid arthritis, atherosclerosis, and neurological diseases such as dementia (Lewis et al., 2021, Samieri et al., 2008, Thies et al., 2003, Goldberg, Katz, 2007, Nettleton, Katz, 2005, Lemaitre et al., 2003). This positive effect may be explained by the ability of LCn-3 PUFAs to reduce inflammation through their anti-inflammatory properties, as previously discussed and lower oxidative stress by decreasing the formation of reactive oxygen species. This, in turn, enhances mitochondrial efficiency and improves its metabolic function. (Lalia et al., 2017, Ibebunjo et al., 2013).

Ultimately, ageing is associated with inflammation and oxidative stress, both of which may contribute to the progressive loss of muscle. The following section will discuss evidence from the literature regarding the potential role of LCn-3 PUFAs in improving muscle health.

1.3.2 Effects of LCn-3 PUFA supplementation on muscle

Extensive research has been carried out on the effect of LCn-3 PUFAs on muscle health, including epidemiological, animal, and cell-based studies. While these provide valuable insights, the focus of this section is on human intervention studies.

Although krill oil supplementation has shown a promising effect in counteracting the adverse outcome of sarcopenia (Alkhedhairi et al. 2022). However, it has not been explored in the literature as extensively as fish oil supplementation. For example, a systematic review and meta-analysis by Esteves et al. (2023), which included 14 studies most of which used fish oil as the supplement, found that LCn-3 PUFAs produced small improvements in muscle strength but had no significant effect on muscle mass or physical function in healthy older adults and younger adults. Similarly, another systematic review and meta-analysis by Bird et al. (2021), which included 66 studies (also primarily using fish oil), reported improvements in both muscle size and strength in adults and older adults. In addition, a systematic review and meta-analysis by Rondanelli et al. (2021), which included seven studies, found that LCn-3 PUFAs derived from fish oil improved muscle size and physical function in middle aged and older adults.

The differences in these findings may be due to varying inclusion criteria across studies. For instance, Bird et al. (2021) and Rondanelli et al. (2021) included participants with chronic conditions such as COPD or cancer, while Esteves et al. (2023) focused on healthy participants. Furthermore, the methods used to assess muscle size, strength, and function differed between studies.

As mentioned earlier, most existing research in this field has used fish oil as the primary LCn-3 PUFA source. However, krill oil is an alternative that also contains LCn-3 PUFAs. Studies show that krill oil supplementation can achieve similar increases in plasma EPA and DHA levels compared to fish oil, but at a lower dose (Ulven et al., 2011). Additionally, when krill oil and fish oil were compared at equivalent doses of EPA and DHA, krill oil led to a greater increase in the omega-3 index (Ramprasath et al., 2013). Notably, krill oil contains additional bioactive components that may benefit muscle health, such as astaxanthin and choline (Moretti et al., 2020; Liu et al., 2018). A recent double-blinded RCT by Alkhedhairi et al. (2022) observed that krill oil supplementation can improve muscle size, strength and neuromuscular function, as indicated by a 17% increase in M-wave amplitude which may enhance muscle

excitability in healthy older adults. However, further studies are needed to confirm the effect of krill oil supplements.

1.3.3 LCn-3 PUFAs supplementation and resistance exercise

The combination of resistance exercise and LCn-3 PUFA supplementation has been studied in the literature as an intervention to manage sarcopenia. A recent meta-analysis by Cornish et al. (2022), which included 10 studies, found that LCn-3 PUFA supplementation combined with resistance exercise can improve lower-body muscle strength and physical function, such as TUG and chair rise tests, but not muscle mass or gait speed in older adults. Conversely, a meta-analysis by Dam et al. (2025), which included 9 studies, observed that LCn-3 PUFA supplementation combined with resistance exercise improved only physical function, specifically chair rise performance, but not muscle strength or mass.

The discrepancies between these two meta-analyses may be attributed to differences in inclusion criteria. For instance, Dam et al. (2025) included only older adults aged ≥ 65 years, whereas Cornish et al. (2022) included participants aged ≥55 years. Furthermore, Dam et al. (2025) included studies that used either n-3 PUFAs or n-3-6-9 blends, which may have influenced the outcomes. As a result, the two meta-analyses included different sets of studies, potentially accounting for the variation in findings.
It is important to note that none of the studies included in either meta-analysis used krill oil supplementation in conjunction with resistance exercise, nor did they assess motor unit function using advanced techniques such as Intramuscular electromyography (iEMG), which could help explore the neuromuscular mechanisms underlying improvements in muscle strength. Furthermore, only one study in the meta-analysis by Dam et al. (2025) employed a home-based resistance exercise intervention. These gaps highlight the need for further research to investigate the effects of krill oil combined with home-based resistance exercise, with a particular focus on the neuromuscular mechanisms underlying strength improvements.

1.3.4 Possible mechanisms responsible for the beneficial effects of LCn-3 PUFAs

As mentioned previously there is evidence that LCn-3 PUFAs, particularly EPA and DHA supplementation via fish and krill oil, can increase muscle strength and muscle

mass in healthy older adults (Alkhedhairi et al. 2022, Smith et al. 2015, Timraz et al. 2023, Ma et al. 2021). However, the mechanisms underlying the effects of LCn-3 PUFAs on muscle mass and function (strength and endurance) in older adults, is not fully understood yet. Nevertheless, it is possibly multifactorial, involving some or all of the mechanisms illustrated in Figure 1.9.

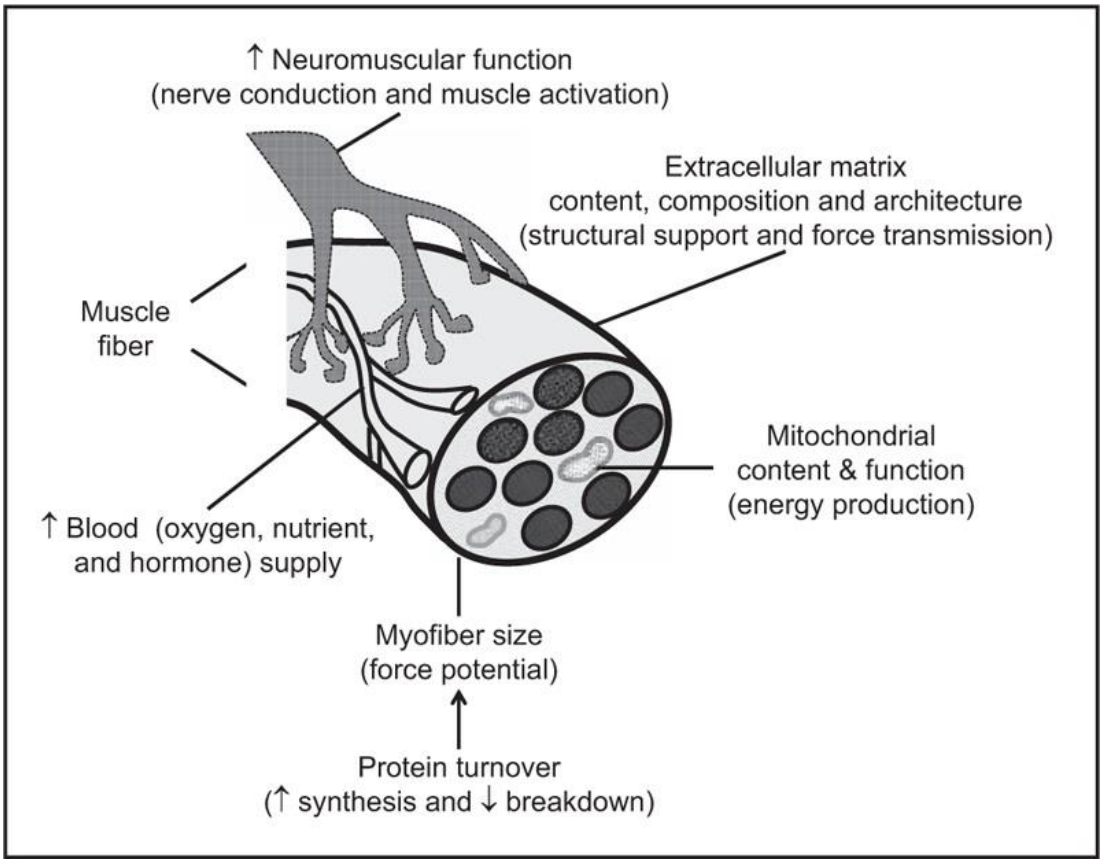

Figure 1.9 Possible mechanisms responsible for the beneficial effects of LCn-3 PUFAs on muscle mass and strength. This figure provided by (Gray, Mittendorfer, 2018).

Two primary mechanisms may explain the beneficial effects of LCn-3 PUFAs on muscle mass. The first involves changes in muscle protein turnover, referring to the balance between protein synthesis and breakdown (Gray, Mittendorfer, 2018). Indeed, a number of studies have shown that supplementation of LCn-3 PUFAs (particularly fish oil) can improve the rate of muscle protein synthesis in young and older adults during a hyperinsulinaemia–hyperaminoacidaemia clamp, but not under fasting conditions (Smith et al., 2011b, Lalia et al., 2017, Smith et al., 2011a). In addition, a review by Jeromson et al., 2015 inidacted that LCn-3 PUFAs can reduce muscle protein breakdown. These effects appear to involve modulation of mTOR-related signalling pathways and improved insulin sensitivity within skeletal muscle (Gingras et

al., 2007; Huang et al., 2011; Kamolrat and Gray, 2013). In the context of ageing, where anabolic resistance limits responsiveness to nutritional and mechanical stimuli, LCn-3 PUFAs may therefore help partially restore sensitivity to anabolic inputs.
The second potential mechanism involves changes in cell turnover, specifically the balance between satellite cell proliferation and fusion, and myonuclear loss however, this mechanism is not yet fully understood with data lacking (Gray & Mittendorfer, 2018). Another potential mechanism involves external changes such as, increasing blood flow (Gray & Mittendorfer, 2018). For example, fish oil has been shown to enhance blood flow, brachial artery dilation, and vascular conductance in healthy middle-aged adults during exercise (Walser, Giordano & Stebbins, 2006).

Furthermore, another mechanism through which LCn-3 PUFAs may influence sarcopenia is via reducing chronic low-grade inflammation (Dalle et al., 2017). As detailed previously, ageing is associated with a persistent inflammatory state, commonly referred to as inflammaging, which has been implicated in anabolic resistance, increased muscle protein breakdown, and impaired muscle repair (Fulop et al., 2018; Dalle et al., 2017). EPA and DHA influence inflammatory processes by altering prostaglandin synthesis and reducing the production of pro-inflammatory cytokines, including tumour necrosis factor-α and interleukin-6 (Funk, 2001; Horia & Watkins, 2007; Thota et al., 2018). Through these actions, LCn-3 PUFAs may reduce catabolic signalling and contribute to a more favourable inflammatory environment for the maintenance of skeletal muscle mass and function in older adults.

Chronic inflammation is also known to interact with anabolic signalling pathways central to muscle protein metabolism. Sustained inflammatory signalling has been suggested to impair activation of the mammalian target of rapamycin pathway, a key regulator of muscle protein synthesis, thereby accelerating muscle loss with advancing age (Walrand et al., 2011; Weichhart, 2018; Liu & Sabatini, 2020). By reducing inflammaging, LCn-3 PUFAs may improve anabolic responsiveness and improve the effectiveness of nutritional and exercise-based interventions aimed at preserving muscle mass (Dalle et al., 2017).

Mitochondrial dysfunction represents another key mechanism underlying sarcopenia, contributing to reduced energy availability, increased fatigue, and impaired muscle quality (Ibebunjo et al., 2013; Kumar et al., 2019). Evidence suggests that LCn-3 PUFA

supplementation can reduce oxidative stress by limiting reactive oxygen species formation and preserving mitochondrial function, thereby supporting mitochondrial efficiency (Ibebunjo et al., 2013; Lalia et al., 2017). In addition, supplementation with LCn-3 PUFAs has been shown to increase gene expression related to mitochondrial function in healthy older adults (Yoshino et al., 2016). Given the energetic demands of muscle contraction and muscle protein synthesis, preservation of mitochondrial function may be particularly important for maintaining muscle strength and mass with ageing.

Furthermore, emerging evidence suggests that LCn3 PUFAs, particularly EPA and DHA, can play a critical role in improving neuromuscular function (Hayman et al., 2024) (Figure 1.10). The negative impact of ageing on the central nervous system may be delayed by DHA, thereby improving neuromuscular function (Boga and Basak, 2023; Turczyn et al., 2022). Additionally, DHA has been shown to enhance nerve conduction velocity in older adults by improving the contractile activity of skeletal muscle (Pinzon et al., 2023). DHA may also elevate cerebral choline and acetylcholine levels (Horrocks and Farooqui, 2004), potentially accelerating synaptic transmission at the neuromuscular junction and thereby enhancing muscle strength (Jeromson et al., 2015). Moreover, LCn3 PUFAs may increase M-wave amplitude, which could indicate improved neuromuscular transmission. In addition to that, LCn3 PUFAs may also reduce electromechanical delay (Rodacki et al., 2012). As stated previously, one of the mechanisms by which muscle strength may be improved is through the enhancement of neuromuscular function. However, the mechanisms by which LCn-3 PUFAs may enhance muscle strength via neuromuscular function remain unknown (Hayman et al., 2024). Figure 1.11 illustrates both the known and unknown effects of LCn-3 PUFA supplementation on neuromuscular function (Hayman et al., 2024). Thus, further research to investigate the neuromuscular mechanisms underlying strength improvements is needed.

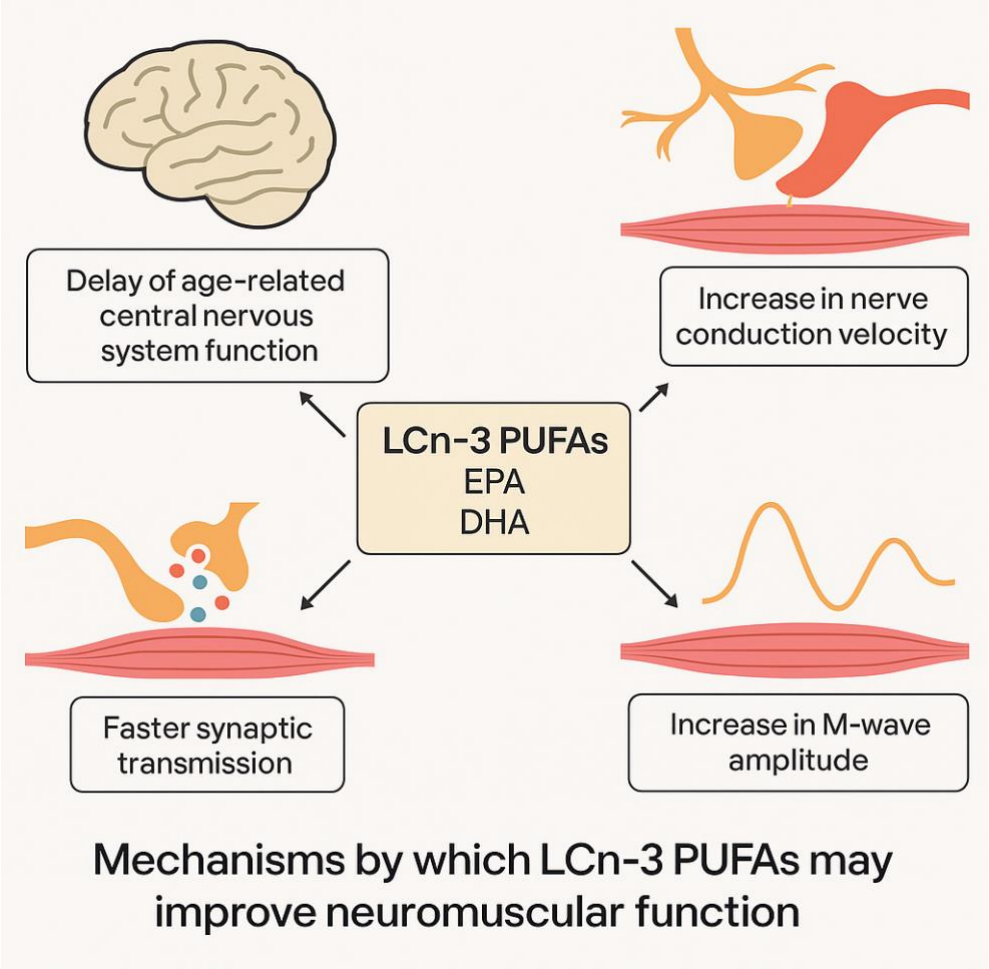

Figure 1.10 Possible mechanisms responsible for the beneficial effects of LCn-3 PUFAs neuromuscular function. LCn-3 PUFA, long-chain n-3 polyunsaturated fatty acid. This conceptual figure was created by the author based on published study (Hayman et al., 2024), with assistance from a generative artificial intelligence tool (ChatGPT, OpenAI) for initial figure structuring. All content was reviewed, verified, and finalised by the author.

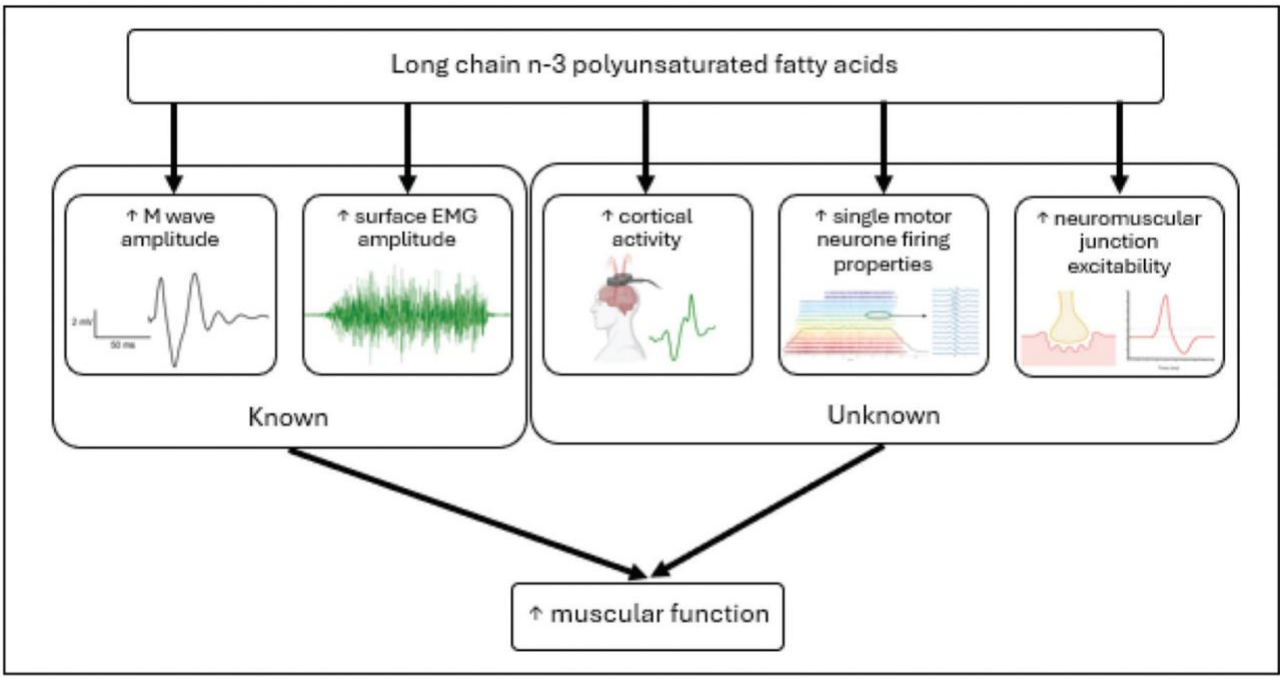

Figure 1.11 the known and unknown impact of LCn-3 PUFA supplementation on the neuromuscular system and muscular function. LCn-3 PUFA, long-chain n-3 polyunsaturated fatty acid. (Hayman et al., 2024).

Although sarcopenia is clinically defined and diagnosed using established criteria, the experimental chapters of the present thesis focused on healthy older adults rather than individuals with diagnosed sarcopenia. This approach was taken to better understand age-related changes in muscle strength and function before the onset of clinically defined sarcopenia. Therefore, the emphasis of the present thesis was on identifying factors and strategies that may help prevent the development of sarcopenia, rather than on the treatment of established disease.

Aims and Hypothesis

1) To investigate the associations of n-3 fatty acid intake with handgrip strength and muscle mass indices in older adults and whether these associations differed by physical activity status through a cross-sectional study from UK Biobank. We hypothesised that n-3 fatty acid intake would be associated with handgrip strength and muscle mass indices in older adults in physical active older adults than non-physical active.

2) To determine whether krill oil supplementation enhances the effects of a pragmatic home resistance exercise programme on adaptations in muscle strength and size, physical function and motor unit function in healthy older adults through doubled-blind RCT. We hypothesized that krill oil supplementation would amplify the beneficial effects of resistance exercise on muscle strength, size, physical function and motor unit function.

3) To explore the enablers and barriers toward home-based resistance exercise for older adults through a qualitative study.

CHAPTER 2: The associations of n-3 fatty acid intake with handgrip strength and muscle mass indices in older adults: a cross-sectional study from UK Biobank

2.1 Introduction

There is strong evidence that low muscle strength and mass are associated with a higher risk of mortality and morbidity (Celis-Morales et al., 2018). Muscle mass and strength are not, however, constant across the life course and progressively decline from around the fourth decade (Dodds et al., 2014). This process has been termed sarcopenia, which has been defined as a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death (Cruz-Jentoft et al., 2010).

Thus far, there is no effective pharmacological treatment for sarcopenia (Cruz-Jentoft and Sayer, 2019) and so lifestyle changes, such as diet and exercise, are often suggested. There is a wealth of literature that resistance exercise, regardless of age, can increase muscle strength and mass (Fyfe et al., 2022; Manas et al., 2021). On top of this, a growing body of literature indicates that supplementation with n-3 fatty acids may be beneficial. There are three main n-3 fatty acids: ALA, EPA, and DHA (Harris, 2010). ALA cannot be synthesized by the human body and can be found in plant oils like flaxseed, soybean, and canola oils, while EPA and DHA are primarily found in fish and seafood (Harris, 2010).

There is evidence that EPA and DHA supplementation, via fish and krill oil, can increase muscle strength and mass in healthy older adults (Alkhedhairi et al., 2022; Smith et al., 2015; Timraz et al., 2023). Furthermore, it has been shown that fish oil supplementation may enhance some of the beneficial effects of exercise on muscle strength in older women, but not men (Da Boit et al., 2017). There has been little work showing the efficacy of ALA rich supplements in increasing muscle strength or mass (Cornish and Chilibeck, 2009). Previous observational studies have investigated the association between n-3 fatty acids and muscle health in older adults, however, findings remain inconsistent and depend largely on how n-3 fatty acid exposure has been assessed. Bae et al. (2022) examined the associations between EPA and DHA intake and handgrip strength in older adults and reported no association in men after adjustment for age, BMI, socioeconomic factors, smoking status, energy intake, and

physical activity. In contrast, older women who consumed EPA and DHA at or above the adequate intake had significantly lower odds of low grip strength compared with those consuming below the recommended intake. Other observational studies have reported positive associations between fatty or oily fish intake and handgrip strength in older adults (Robinson et al., 2008; Gedmantaite et al., 2020). However, these studies did not directly measure n-3 fatty acid intake, instead using oily fish consumption as a proxy. This limits interpretation, as oily fish provides several nutrients in addition to n-3 fatty acids, including high-quality protein, vitamin D, magnesium, and other compounds, all of which may influence muscle strength and function (Rondanelli et al., 2020). Furthermore, these studies did not examine whether associations differed according to levels of physical activity, which may modify the relationship between diet and muscle health.

Evidence regarding muscle mass is similarly mixed. Systematic reviews and meta-analyses of n-3 fatty acid supplementation trials in older adults have generally reported little or no effect on muscle mass, even when supplementation is combined with exercise interventions (Esteves et al., 2023). On the other hand, other reviews have suggested a potential beneficial effect of n-3 fatty acids on muscle mass, although these conclusions are often based on a small number of studies and should be interpreted with caution due to differences in study design and participant characteristics (Timraz et al., 2023). It is important to acknowledge that much of the existing evidence is derived from supplementation studies rather than habitual dietary intake, limiting its relevance to population-based dietary behaviours.

Taken together, although observational and interventional studies suggest that omega-3 fatty acids may be associated with muscle strength, particularly in women, there remains a lack of large-scale observational studies using direct estimates of habitual n-3 fatty acid intake, rather than proxy measures such as oily fish consumption. Furthermore, much of the existing evidence is derived from supplementation trials, which typically involve relatively small sample sizes, and those that include exercise interventions focus almost exclusively on resistance exercise. Whilst these data are important, the relationship between n-3 fatty acid intake, rather than supplementation, and general physical activity, rather than structured resistance exercise, remains largely unknown. This information may be more relevant for

informing practical, population-level public health strategies aimed at preventing or delaying sarcopenia.

Therefore, the aim of the current study was to investigate the associations between n-3 fatty acid intake and indices of handgrip strength and muscle mass in older adult participants from the UK Biobank study. A secondary aim was to examine whether these associations differed according to physical activity status.

2.2 Methods

2.2.1 Study design

The current study is a cross-sectional study, and data were collected by the UK Biobank. Further details about the methods employed in the UK Biobank are in appendix 1. The strengthening the reporting of observational studies in epidemiology (STROBE) statement was followed (Von Elm et al., 2008). In the current analysis 53,170 participants were included (25,324 men and 27,846 women). The criteria for selecting participants were as follows: participants aged 60 years or older with complete data for outcome, predictor and covariate variables. The primary outcomes were grip strength index and muscle mass index, the predictor variable was n-3 fatty acid intake, and the covariates were sociodemographic factors (age, ethnicity/race, Townsend deprivation index), physical activity, multimorbidity count, total energy intake, body fat percentage and the month of assessment.

2.2.2 Outcome assessment

Height was assessed by a Seca 202 stadiometer (Seca GmbH, Hamburg, Germany) to the nearest metre. Grip strength was measured by using a Jamar J00105 hydraulic hand dynamometer (Lafayette Instrument USA) once in each hand. The current analysis used the mean of the values from the right hand and left hand, expressed as a grip strength index relative to height in kg/m2.

Grip strength is a widely used and clinically relevant measure of muscle strength in older adults and is commonly employed in epidemiological studies, clinical assessments, and intervention trials (Cruz-Jentoft et al., 2019). Furthermore, the EWGSOP2 has recommended the use of grip strength as the primary outcome measure for identifying probable sarcopenia in clinical and research settings. Measuring grip strength is simple and inexpensive, making it suitable for research studies and routine clinical practice (Cruz-Jentoft et al., 2019). Grip strength is a strong predictor of adverse health outcomes, including longer hospital stays, increased functional limitations, poorer health-related quality of life, and increased mortality (Ibrahim et al., 2016; Leong et al., 2015). Grip strength correlates moderately with muscle strength in other body compartments and therefore can be used as a proxy measure of overall muscle strength. When standardised testing procedures are applied, handgrip dynamometry demonstrates excellent test–retest reliability in older

populations, with intraclass correlation coefficients typically exceeding 0.90 (Bohannon, 2015). The Jamar dynamometer has been extensively validated and is widely used for measuring grip strength in both clinical and research contexts (Cruz-Jentoft et al., 2019). Grip strength has also been shown to be associated with lower-limb muscle strength, physical function, disability, and adverse health outcomes, including morbidity and mortality (Dodds et al., 2014). However, it is important to note that grip strength primarily reflects upper-limb muscle strength and may not fully represent lower-limb or whole-body strength adaptations (Bohannon, 2015). This limitation was addressed in the present study by including additional assessments of muscle strength such as knee extensor muscle strength and neuromuscular function. Other limitation is that in some cases, grip strength assessment may not be feasible, such as in individuals with advanced arthritis or stroke-related hand impairment.

Muscle mass was measured using the Tanita BC418MA body composition analyser (Tanita Europe BV, Amsterdam, the Netherlands) using bioimpedance and employing the equations of Janssen et al. (Janssen et al., 2000), and the muscle mass index, relative to height, calculated as kg/m2. Bioelectrical impedance analysis (BIA) is a widely used, non-invasive method for assessing body composition and skeletal muscle mass in older adults and has been shown to be reliable when standardised measurement conditions are applied (Kyle et al., 2004). Previous studies have reported high test-retest reliability for whole-body and regional body composition measurements, with intraclass correlation coefficients typically exceeding 0.99 and coefficients of variation below 2% under controlled conditions (Merrigan et al., 2022; Looney et al., 2024).

An important strength of BIA is its feasibility in older adult and community-based settings. The method is portable, rapid, non-invasive, does not involve exposure to radiation, and is less costly than DXA, computed tomography, or magnetic resonance imaging (Kyle et al., 2004). As a result, BIA is commonly used in large-scale studies and has been recognised by major consensus groups, including EWGSOP2 and AWGS, as an acceptable method for field-based assessment of muscle mass (Gonzalez & Heymsfield, 2017). However, several limitations of BIA should be acknowledged. First, BIA measurements are highly dependent on hydration status, and deviations from standardised conditions can influence measurement reliability and accuracy (Looney et al., 2024). BIA estimates may also be affected by recent food and

fluid intake, physical activity, and body position. This highlights the importance of strict standardisation of pre-assessment conditions. Second, BIA may overestimate or underestimate muscle mass in certain populations, depending on the prediction equations used and individual body composition characteristics (Merrigan et al., 2022). Third, agreement between different BIA devices can vary, and longitudinal assessments should therefore be conducted using the same device and standardised protocol (Kyle et al., 2004). Finally, although BIA demonstrates acceptable validity in cross-sectional comparisons with DXA and imaging-based techniques, its sensitivity for detecting small, intervention-induced changes in muscle mass is less well established. Therefore, whilst BIA is appropriate for assessing muscle mass in older adults and for monitoring changes within individuals over time, DXA remains the preferred reference method in research settings when precise measurement of muscle mass is required (Kyle et al., 2004; Gonzalez & Heymsfield, 2017).

2.2.3 Predictor variable assessment

To measure n-3 fatty acid intake a Web-based 24 -h-recall questionnaire (The Oxford WebQ) was used (Perez-Cornago et al., 2021). The mean value of n-3 fatty acid intake was calculated for participants who completed more than one online dietary questionnaire (see the appendix 1) and expressed as grams per day. Furthermore, The Oxford WebQ has been validated against an interviewer-administered 24-hour dietary recall questionnaire (Galante et al., 2016). The mean correlation coefficient for 21 nutrients obtained from the Oxford WebQ compared with the interviewer-administered recall was 0.60, with most nutrient correlations ranging between 0.50 and 0.90 (Galante et al., 2016).

An important strength of the Oxford WebQ is its feasibility in large-scale studies through automatic data capture, reduced administrative burden, and the ability to be administered repeatedly via the internet at reduced cost. The acceptability of repeated administration in UK Biobank was substantial, with 53% of invited participants completing the questionnaire at least once, and 66% completing it on more than one occasion (Galante et al., 2016).

However, several limitations should be acknowledged. First, the Oxford WebQ assesses dietary intake over a single 24-hour period, which may not represent an individual's habitual dietary pattern, particularly for foods consumed occasionally such

as fatty fish (Greenwood et al., 2019). Repeated administration is necessary to estimate habitual intake. Second, dietary assessment methods including the Oxford WebQ are prone to measurement error, particularly for nutrients such as n-3 fatty acids where intake is concentrated in a limited number of food sources and where day-to-day variability is considerable (Greenwood et al., 2019). The correlation coefficients between dietary estimates of n-3 fatty acids and biomarkers have ranged from 0.40 to 0.75 (Lukens et al., 2022). Third, the Oxford WebQ is dependent on participant memory and accurate reporting, and errors may occur due to social desirability bias or other factors (Greenwood et al., 2019). Despite these limitations, the Oxford WebQ provides a practical and well-validated tool for assessing dietary n-3 fatty acid intake in large-scale studies, particularly when multiple administrations are obtained.

2.2.4 Covariate assessment

Physical activity was self-reported using the short form of the International Physical Activity Questionnaire (IPAQ) and expressed as metabolic equivalents (MET-min/week). In the current analysis, physical activity was categorized as ‘active’ if participants met or exceeded the moderate/vigorous activity recommendation of 600 MET-min/week (IPAQ Research Committee, 2005), and as ‘inactive’ if they did not meet the recommendation.

Participants self-reported their race/ethnicity as white, South Asian, black, Chinese, other, or mixed ethnic background. Deprivation was assessed using the Townsend deprivation index based on the participant's postcode of residence (Townsend and Beattie, 1988). The Townsend index is based on four census variables: unemployment, non-car ownership, non-house ownership, and household overcrowding. Multimorbidity such as hypertension, diabetes, angina, stroke, heart attack, cancer, asthma and chronic obstructive pulmonary disease were self-reported by the participants during the touchscreen questionnaire and then confirmed by UK Biobank staff during the verbal interview. These conditions were collectively used to form a multimorbidity count, considering if participants had one, two, three, four and five or more of 43 chronic illnesses (see the appendix 2). The total energy intake was measured using the Web-based 24-h-recall questionnaire. The mean value of total energy intake was calculated for participants who completed more than one online dietary questionnaire and expressed as kcal per day. Body fat percentage was

measured using bioimpedance with the Tanita BC418MA body composition analyser (Tanita Europe BV, Amsterdam, the Netherlands).

Covariates were selected a priori based on previous literature and their known associations with both n-3 fatty acid intake and muscle strength and muscle mass in older adults. Age was included because increasing age is associated with declines in muscle mass and muscle strength (Cruz-Jentoft et al., 2019). Sex was included due to known differences between men and women in muscle strength, muscle mass, and fatty acid metabolism, as well as evidence suggesting sex-specific responses to n-3 fatty acids (Caslake et al., 2008). Ethnicity and socioeconomic status, assessed using the Townsend deprivation index, were included because social and environmental factors may influence dietary intake and health outcomes. Indeed, socioeconomic deprivation has been associated with poorer diet quality, including lower fish and n-3 fatty acid intake, and with poorer physical function and muscle strength in older adults (Darmon & Drewnowski, 2008).

Physical activity was included due to its well-established role in maintaining muscle strength and muscle mass. In addition, individuals who are more physically active are more likely to have healthier dietary patterns, including higher fish consumption (Cartee et al., 2016). Total energy intake was included to account for overall dietary intake, as individuals with higher energy intake generally consume greater absolute amounts of nutrients, including n-3 fatty acids (Willett et al., 1997). Multimorbidity count was included to account for the influence of chronic disease burden, as the presence of chronic conditions is associated with reductions in muscle strength and muscle mass and may also influence dietary behaviours (Ryan et al., 2015).

Body fat percentage was included due to its association with muscle outcomes. While higher adiposity is generally associated with poorer muscle quality, previous evidence suggests that higher body fat may be protective in the context of clinically defined weakness, particularly when handgrip strength is used as the outcome (Batsis et al., 2023). Therefore, adjusting for body fat percentage allowed the association between n-3 fatty acid intake and muscle outcomes to be examined independent of adiposity. Month of assessment was included to account for potential seasonal variation in dietary intake, including fish consumption, and physical activity levels (van Staveren et al., 1986).

2.2.5 Statistical methods

The outcomes variables were grip strength index (kg/m2) and muscle mass index (kg/m2), with n-3 fatty acid intake as the predictor variable, all used as continuous variables. Multivariable linear regression analyses were performed to explore the associations between n-3 fatty acid intake and grip strength index and muscle mass index in men and women separately. A series of models with an increasing number of covariates were used: Model 1 was unadjusted; Model 2 adjusted for age, ethnicity, deprivation index, and month of assessment; Model 3 further adjusted for total energy intake; Model 4 additionally adjusted for multimorbidity count; and Model 5 further adjusted for body fat percentage. These models were used to examine how adjustment for different covariates influenced the associations. To assess the role of physical activity in the relationship of n-3 fatty acid intake with grip strength and muscle mass, the analysis was also stratified by physical activity status (active/inactive). STATA MP14 (Stata Corp LLC, College Station, Texas) was used to perform the statistical analyses with the significance level set at $\alpha = 0.05$.

2.3 Results

Out of 502,369 participants recruited to the UK Biobank, 53,170 participants (25,324 men and 27,846 women) aged 60 years or older with complete data were included. Participants were excluded for the following reasons: 284,898 were younger than 60 years old, and 164,301 had missing or incomplete data for one or more study variables, including 1566 for grip strength index, 5216 for muscle mass index, 131,770 for n-3 fatty acid intake, 1201 for ethnicity, 203 for deprivation index, 47,410 for physical activity, 4 for multimorbidity count, 151,218 for total energy intake, and 824 for body fat percentage.

Table 2.1 illustrates the cohort characteristics of the included participants. Briefly, the mean age of the cohort was 63.8 years, with 47.6% being women. The mean BMI was 26.5, and the mean body fat percentage was 30.7%. Based on the Lipschitz criteria, 39.7% of the population was classified as overweight. The prevalence of multimorbidity was 71.6%. Differences between men and women are also shown in Table 1. Men had higher grip strength and muscle mass indices, but lower body fat percentages compared to women. However, men exhibited higher BMI and a greater prevalence of overweight. No significant differences in inactivity or multimorbidity were observed between sexes.

2.3.1 Grip strength index

Associations of n-3 fatty acid intake with grip strength index are presented in Table 2.2. In model 1 (unadjusted), n-3 fatty acid intake was positively associated with grip strength index in women with a 0.04 kg/m2 (95% CI 0.01 to 0.06 kg/m2) higher grip strength index seen in those who were active and a 0.04 kg/m2 (95% CI 0.00 to 0.07 kg/m2) higher grip strength index in those who were inactive for each additional gram of n-3 fatty consumed per day. No association was seen in men who were active (p=0.913) or inactive (p=0.680).

In model 2, after adjusting for age, ethnicity, deprivation index, and month of assessment, n-3 fatty acid intake was positively associated with grip strength index in women with a 0.04 kg/m2 (95% CI 0.01 to 0.07 kg/m2) higher grip strength index seen in those who were active and a 0.04 kg/m2 (95% CI 0.01 to 0.07 kg/m2) higher grip strength index in those who were inactive for each additional gram of n-3 fatty

consumed per day. No association was seen in men who were active (p=0.913) or inactive (p=0.730).

Table 2.1 Cohort characteristics

	All (n=53,994)	**Men (n=25,773)**	**Women (n=28,221)**
Age (years)	63.8 (2.7)	64.0 (2.7)	63.6 (2.7)
Weight (kg)	75.5 (13.6)	82.4 (11.8)	69.1 (11.8)
Height (m)	1.684 (0.090)	1.752 (0.064)	1.622 (0.059)
N-3 fatty acid intake g/day	2.09 (0.8)	2.1 (0.8)	2.0 (0.8)
Grip strength index (kg/m²)	10.1 (2.9)	12.2 (2.4)	8.3 (2.0)
Muscle mass index (kg/m²)	7.6 (1.4)	8.9 (0.78)	6.4 (0.68)
Total energy intake (kcal/day)	2190.0 (452.6)	2397.4 (433.3)	2000.6 (381.4)
BMI (kg/ m²)	26.5 (4.0)	26.8 (3.5)	26.2 (4.3)
Deprivation index, n (%)			
Lower	21,220 (39.30)	10,531 (40.86)	10,689 (37.88)
Middle	19,174 (35.51)	9,081 (35.23)	10,093 (35.76)
Higher	13,600 (25.19)	6,161 (23.90)	7,439 (26.36)
Ethnicity, n (%)			
White	53,041 (98.23)	25,339 (98.32)	27,702 (98.16)
Mixed	325 (0.60)	120 (0.47)	205 (0.73)
South Asian	400 (0.74)	231 (0.90)	169 (0.60)
Black	159 (0.29)	56 (0.22)	103 (0.36)
Chinese	69 (0.13)	27 (0.10)	42 (0.15)
BMI Categories, n (%)			
Under weight (< 18.5 kg/m2)	256 (0.47)	44 (0.17)	212 (0.75)
Normal weight (18.5-24.9 kg/m2)	20,280 (37.56)	8,082 (31.36)	12,198 (43.22)
Overweight (25.0 to 29.9 kg/m2)	24,375 (45.14)	13,402 (52.00)	10,973 (38.88)
Obese (≥30.0 kg/m2)	9,083 (16.82)	4,245 (16.47)	4,838 (17.14)
Central Obesity, n (%)			
No	38,529 (71.37)	19,468 (75.55)	19,061 (67.55)
Yes	15,457 (28.63)	6,302 (24.45)	9,155 (32.45)
Physical Active, n (%)			
Inactive	22,732 (42.10)	10,914 (42.35)	11,818 (41.88)
Active	31,262 (57.90)	14,859 (57.65)	16,403 (58.12)
Comorbidities, n (%)			
No	15,250 (28.24)	7,199 (27.93)	8,051 (28.53)
Yes	38,744 (71.76)	18,534 (72.07)	20,170 (71.47)

Data presented as mean and (SD) for continuous variable and as frequency of Data presented as mean and (SD) for continuous variable and as frequency of observations and % for categorical variables. BMI body mass index; SD standard deviation; n number.

Following further adjustment for total energy intake in model 3, the positive association remained in women, regardless of whether they were physically active or inactive with a 0.04 kg/m2 (95% CI 0.01 to 0.07 kg/m2) higher grip strength index seen in those who were active and a 0.04 kg/m2 (95% CI 0.01 to 0.08 kg/m2) higher grip strength index in those who were inactive for each additional gram of n-3 fatty consumed per day. No association was seen in men who were active (p=0.336) or inactive (p=0.204).

Following further adjustment for multimorbidity count, in model 4, the positive association remained in women, regardless of whether they were physically active or inactive with a 0.03 kg/m2 (95% CI 0.00 to 0.06 kg/m2) higher grip strength index seen in those who were active and a 0.04 kg/m2 (95% CI 0.00 to 0.08 kg/m2) higher grip strength index in those who were inactive for each additional gram of n-3 fatty consumed per day. No association was seen in men who were active (p=0.375) or inactive (p=0.272).

After further adjustment for body fat percentage in model 5, the positive association between n-3 fatty acid intake and grip strength index persisted in women, regardless of physical activity status. For each additional gram of n-3 fatty acids consumed per day, grip strength index increased by 0.03 kg/m2 (95% CI: 0.00 to 0.06 kg/m2) in active women and by 0.04 kg/m2 (95% CI: 0.00 to 0.07 kg/m2) in inactive women. No significant association was observed in men, whether they were active (p=0.405) or inactive (p=0.323).

2.3.2 Muscle mass index

Associations of n-3 fatty acid intake with muscle mass index are presented in Table 2.2. In model 1 (unadjusted), n-3 fatty acid intake was positively associated with muscle mass index in both men and women regardless of whether they were active or inactive. In active participants there was a 0.03 kg/m2 (95% CI 0.02 to 0.04) higher muscle mass index in men, and a 0.03 kg/m2 (95% CI 0.02 to 0.03) higher muscle mass index in women, for each additional gram of n-3 fatty consumed per day. Similarly, in inactive participants, there was a 0.05 kg/m2 (95% CI 0.03 to 0.06 kg/m2) higher muscle mass index in men, and a 0.03 kg/m2 (95% CI 0.02 to 0.04) higher muscle mass index in women, for each additional gram of n-3 fatty consumed per day. In model 2, after adjusting for age, ethnicity, deprivation index, and month of assessment, n-3 fatty acid intake was positively associated with muscle mass index in both men and women regardless of whether they were active or inactive. In active

participants there was a 0.03 kg/m2 (95% CI 0.02 to 0.04) higher muscle mass index in men, and a 0.03 kg/m2 (95% CI 0.02 to 0.03) higher muscle mass index in women, for each additional gram of n-3 fatty consumed per day. Similarly, in inactive participants, there was a 0.05 kg/m2 (95% CI 0.03 to 0.06 kg/m2) higher muscle mass index in men, and a 0.03 kg/m2 (95% CI 0.02 to 0.04) higher muscle mass index in women, for each additional gram of n-3 fatty consumed per day.

Following further adjustment for total energy intake, in model 3, n-3 fatty acid intake was negatively associated with muscle mass index in inactive women with a - 0.01 kg/m2 (95% CI - 0.02 to 0.00 kg/m2) lower muscle mass index for each additional gram of n-3 fatty consumed per day. No associations were seen in active women (p=0.725) or in men regardless of whether they were active (p=0.863) or inactive (p=0.504).

Following further adjustment for multimorbidity count, in model 4, no associations were seen in men who were active (p=0.970) or inactive (p=0.338) or women who were active (p=0.843) or inactive (p=0.058). After further adjustment for body fat percentage in model 5, no significant associations were observed in either active (p=0.858) or inactive (p=0.250) men, or in active (p=0.909) or inactive (p=0.187) women.

Table 2.2 the association of N-3 fatty acid intake with handgrip strength and muscle mass indices in older adults

	Active				Inactive			
	Men (n= 14,627)		Women (n=16,196)		Men (n= 10,697)		Women (n=11,650)	
	Beta (95% CI)	P-value	Beta (95% CI)	P-value	Beta (95% CI)	P-value	Beta (95% CI)	P-value
Model 1								
Handgrip strength Index (kg/m^2)	0.001 (-0.03, 0.03)	0.913	0.04 (0.01 ,0.06)	0.003	0.008 (-0.03, 0.05)	0.680	0.04 (0.00 ,0.07)	0.012
Muscle mass index (kg/m^2)	0.03 (0.02, 0.04)	<0.0001	0.03 (0.02, 0.03)	<0.0001	0.05 (0.03, 0.06)	<0.0001	0.03 (0.02, 0.04)	<0.0001
Model 2								
Handgrip strength Index (kg/m^2)	-0.001 (-0.03 ,0.03)	0.913	0.04 (0.01 ,0.07)	0.002	0.007 (-0.03 ,0.04)	0.730	0.04 (0.01 ,0.07)	0.011
Muscle mass index (kg/m^2)	0.03 (0.02, 0.04)	<0.0001	0.03 (0.02, 0.03)	<0.0001	0.05 (0.03, 0.06)	<0.0001	0.03 (0.02, 0.04)	<0.0001
Model 3								
Handgrip strength Index (kg/m^2)	0.01 (-0.01, 0.05)	0.336	0.04 (0.01, 0.07)	0.006	0.02 (-0.01, 0.07)	0.204	0.04 (0.01, 0.08)	0.012
Muscle mass index (kg/m^2)	-0.001 (-0.01, 0.01)	0.863	-0.001 (-0.01, 0.007)	0.725	0.005 (-0.009, 0.02)	0.504	-0.01 (-0.02, -0.0006)	0.039
Model 4								

Handgrip strength Index (kg/m^2)	0.01 (-0.02, 0.05)	0.375	0.03 (0.008, 0.06)	0.011	0.02 (-0.02, 0.07)	0.272	0.04 (0.006, 0.08)	0.020
Muscle mass index (kg/m^2)	-0.0002 (-0.01, 0.01)	0.970	-0.0009 (-0.01, 0.008)	0.843	0.007 (-0.007, 0.02)	0.338	-0.01 (-0.02, 0.0003)	0.058
Model 5								
Handgrip strength Index (kg/m^2)	0.01 (-0.02, 0.05)	0.405	0.03 (0.005, 0.06)	0.019	0.02 (-0.02, 0.06)	0.323	0.04 (0.006, 0.07)	0.022
Muscle mass index (kg/m^2)	-0.001 (-0.01, 0.01)	0.858	0.0005 (-0.009, 0.01)	0.909	0.008 (-0.006, 0.02)	0.250	-0.008 (-0.02, 0.004)	0.187

Table 2.2 Results are presented as regression coefficients (β) with 95% confidence intervals (CI) from multivariable linear regression models. Model 1 was unadjusted. Model 2 was adjusted for age, ethnicity, Townsend deprivation index, and month of assessment. Model 3 was additionally adjusted for total energy intake. Model 4 was additionally adjusted for multimorbidity count. Model 5 was additionally adjusted for body fat percentage. Statistical significance was set at $p < 0.05$

2.4 Discussion

The present study investigated the associations of n-3 fatty acid intake with handgrip strength index and muscle mass index in older adults with a secondary aim to determine whether these associations differed by physical activity status. This study found that n-3 fatty acid intake was positively associated with grip strength index in women, but not in men, regardless of their physical activity status, across all five models. Although n-3 fatty acid was positively and significantly associated with muscle mass index, regardless of their activity status in model 1 and 2, this association was no longer seen in model 3 in men, regardless of their activity status, and active women. However, there was a negative association between n-3 fatty acid intake and muscle mass index in inactive women. In contrast, in model 4 and 5 no associations were observed regardless of activity status. These findings suggest a sex-specific effect of n-3 fatty acid intake on grip strength, with no effect on muscle mass, although as the magnitude of these associations was very weak their usefulness in designing interventions to treat or prevent the development of sarcopenia is likely limited.

The current study found a positive association between n-3 fatty acid intake and handgrip strength in older women only. This finding is in agreement with the results of Bae et al., (2022), who investigated the associations of EPA and DHA intake with lower handgrip strength in older Koreans. After adjustment for confounding factors such as age, household income, BMI, marital status, education level, smoking status, energy intake, and physical activity status they found no association between EPA and DHA intake and grip strength in older men. On the other hand, the odds of lower grip strength in older women who consumed EPA and DHA at or above the adequate intake (150 mg/d for women aged 65 to 74 years and 140 mg/d for women aged 75 years) were 32% lower, compared to older women consuming EPA and DHA below the adequate intake. In partial agreement, Robinson et al., (2008) found a positive relationship between fatty fish intake and grip strength in older adults, which was slightly stronger in women compared to men. Grip strength was 0.48 kg higher in women and 0.43 kg in men for every additional portion of oily fish consumed a week. On the other hand, Gedmantaite et al., (2020) found a positive association, of a similar magnitude, between the intake of oily fish and grip strength in both older men and women. Caution must be exercised when interpreting these latter studies as oily fish contains not only n-3 fatty acids but also proteins, carnitine, magnesium, and vitamin D, all of which may influence muscle health (Rondanelli et al., 2020).

Previous work that has investigated the combined effect of resistance exercise and n-3 fatty acid intake, in the form of fish oil supplementation, found that it enhanced adaptations to resistance exercise in muscle strength (maximal isometric torque) in older women but not in men (Da Boit et al., 2017). This is in agreement with the current data where we found that there was a higher grip strength index in women, but not men, with higher n-3 fatty acid intake in active, and inactive, participants. Taken together, our data support previous work which has indicated that there may be sex-differences in the effects of n-3 fatty acids on muscle strength. However, it is worth noting that none of the randomised controlled trials have reported sex-differences in the effects of n-3 fatty acid supplementation on muscle strength, although thus far none have been sufficient powered to do this (Alkhedhairi et al., 2022; Smith et al., 2015). Several biological mechanisms may explain the observed sex-specific association between n-3 fatty acid intake and muscle strength. Women appear to incorporate EPA and DHA into plasma and muscle phospholipids more efficiently than men, potentially enhancing membrane fluidity and intracellular signalling involved in muscle contraction and neuromuscular function (Caslake et al., 2008; Giltay et al., 2004). Sex hormones may also play a role, as oestrogen has been shown to influence lipid metabolism, inflammatory pathways, and muscle repair processes, potentially augmenting the anabolic or anti-inflammatory effects of n-3 fatty acids in women (Giltay et al., 2004; McGlory et al., 2019). Furthermore, n-3 fatty acids may preferentially influence muscle strength through improvements in neuromuscular function rather than muscle size, which may explain the observed improvements in grip strength in the absence of corresponding increases in muscle mass (Phillips et al., 2024). Further studies are, however, necessary to explore this matter.

Another important finding is that n-3 fatty acid intake was not associated with muscle mass index in older adults, regardless of their physical activity status. The lack of such an association in older adults is consistent with a systematic review and meta-analysis by Esteves et al., (2023) who investigate the effect of n-3 fatty acid supplementation on muscle mass, function and strength in healthy older adults and young. They found no effect of n-3 fatty acid supplementation, with some studies including concurrent exercise interventions, on muscle mass in young and older adults. On the other hand, Timraz et al., (2023) in their systematic review found n-3 fatty acid supplementation, with no concurrent exercise intervention, may have a positive effect on muscle mass.

However, the previous systematic review included only four studies, so it should be interpreted with caution due to the small number of included studies, although this assertion is also supported by acute studies showing that fish oil supplementation increases muscle protein synthesis responses to amino acids and insulin (Smith et al., 2011a; Smith et al., 2011b), but not exercise (Da Boit et al., 2017; McGlory et al., 2016). The reasons for a lack of association in the current study, particularly in inactive participants, are not clear. They could be due to the validity of the bioelectrical impedance analysis (BIA) to quantify fat free/muscle mass, as this is not the gold standard method (Esteves et al., 2023). Additionally, several studies examining the fish and krill oil supplementation on muscle mass or muscle mass index using BIA in healthy or unhealthy older adults' populations found no significant effect (Alkhedhairi et al., 2022; Krzymińska-Siemaszko et al., 2015; Ogasawara et al., 2018; Daďová et al., 2020; Akita et al., 2019) where effects are seen with direct measurement of muscle size by ultrasound (Alkhedhairi et al., 2022) and MRI (Smith et al., 2015).

It is worth considering the clinical relevance of our results. Although the current study found a positive association between n-3 fatty acids and grip strength index in women, the effect size was very small. Indeed, for every gram/day higher n-3 fatty acid intake there was a 0.03 kg/m2 higher grip strength index in active women and 0.04 kg/m2 higher grip strength in inactive women. This equates to an increase of ~0.5 % in grip strength index for a 40 % higher n-3 fatty acid intake. These findings suggest that within the normal dietary intake range the associations between n-3 fatty acid intake and grip strength are not clinically relevant, with no associations with muscle mass. It may be that increases specifically in EPA/DHA intake, with the current measure or n-3 fatty acid intake also including ALA, in the range seen in supplementation studies is needed to stimulate increases in muscle strength and mass in older adults.

A key strength of the present study was the large sample size. Moreover, important confounders were used to adjust the analysis. However, this study has clear limitations. First, UK Biobank participants may represent the general United Kingdom population, but there is a possibility of indicating a ‘healthy volunteer’ selection bias since participants have a lower disease frequency and are less likely to be obese (Fry et al., 2017). Second, muscle mass index was measured by BIA, the validity of which is debatable. Third, the current study used standing height as a covariate, where knee height (which is not available in the UK Biobank) might be optimal since it may remain

relatively stable with age and not decrease due to anatomical changes such as spinal compression (Hickson and Frost, 2003). Finally, causality cannot be established to confirm the association in this study due to the cross-sectional design.

2.5 Conclusion

This study has demonstrated that although n-3 fatty acid was significantly associated with grip strength index in older women, regardless of their activity status, this association was weak in terms of magnitude and is unlikely to be clinically relevant. Additionally, n-3 fatty acid was not associated with muscle mass index in older adults. Therefore, manipulation of n-3 fatty acid intake within the normal dietary range is unlikely to be an effective strategy to prevent and/or treat sarcopenia and n-3 fatty acid supplements may be required. Further large scale randomised controlled trials are required to confirm this assertion.

CHAPTER 3: The effects of krill oil supplementation on adaptations in muscle strength, size, physical function and motor unit function to a pragmatic home-based resistance exercise intervention in older adults

3.1 Introduction

It has been predicted that worldwide the percentage of older people globally, aged 65 and over, will increase from 10% in 2024 to approximately 16% in 2050, highlighting a global shift in ageing demographics (Desa, 2019). Indeed, in the UK, from 2019 to 2030, it has been predicted that the number of older adults aged over 65 years will increase by 21.8% (Age UK, 2019). Whilst this should be celebrated ageing has many consequences, such as a decline in muscle mass and neuromuscular function, which can lead to reduced strength and physical performance. These changes often begin around the age of 40 and may result in sarcopenia (Aagaard et al., 2010, Dodds et al., 2014, Cruz-Jentoft et al., 2019). Sarcopenia has been defined by EWGSOP2 as “a progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality” (Cruz-Jentoft et al., 2019). However, it is important to acknowledge that there is no scientific consensus on the definition or measurement of sarcopenia (McLean & Kiel, 2015), making it challenging to establish its prevalence.

Recent estimates suggest that globally, between 10% and 27% of individuals over the age of 60 have sarcopenia based on the EWGSOP classification (Petermann-Rocha et al., 2022). This decline in muscle strength and mass can lead to increased dependency, difficulty performing activities of daily living (Hairi et al., 2010), and a decrease in quality of life (Oh et al., 2014), as well as higher rates of morbidity and mortality (Celis-Morales et al., 2018). Additionally, the excess health and social care costs associated with muscle weakness were estimated at approximately £2.5 billion in the UK in 2018 (Pinedo-Villanueva et al. 2019). Preventing or delaying the adverse outcomes of sarcopenia is vital for older people and wider society.

Currently, there are no pharmacological treatments available for the prevention or management of sarcopenia (Cruz-Jentoft et al., 2019), however, a substantial body of evidence indicating that resistance exercise, regardless of age, can increase muscle

mass, strength, function and neuromuscular function in older adults, thereby attenuating the adverse outcomes of sarcopenia (Manas et al., 2021, Fyfe, Hamilton & Daly, 2022, Grgic et al., 2020, Gamage et al., 2025). As such, resistance exercise can be an effective strategy to both prevent and treat sarcopenia for older adults (Dent et al., 2018). For this reason, the World Health Organization recommends that older adults engage in moderate to high intensity muscle-strengthening activities, such as resistance exercises, at least twice a week to improve physical function (World Health Organization, 2020).

Nevertheless, many older adults do not meet these guidelines. In Scotland, for instance, only 12% of women and 14% of men aged 65 and over met the UK's recommendation to perform muscle-strengthening exercises twice a week (Strain et al., 2016). Several barriers contribute to this low participation rate, including limited access to gyms, lack of equipment, and a general dislike of the gym environment (Burton et al., 2017, Dismore et al., 2020). Therefore, strategies to improve participation and adherence to resistance exercise among older adults are essential. One pragmatic and feasible solution is home-based resistance exercise using minimal equipment, such as resistance bands. This approach has been shown to safely improve muscle strength, physical function, power, balance (Thiebaud, Funk & Abe, 2014, Manas et al., 2021).

In addition to resistance exercise, there is a growing body of literature indicating that supplementation with LCn-3 PUFA can increase muscle strength and size in healthy older adults (Alkhedhairi et al. 2022, Smith et al. 2015, Ma et al. 2021). A recent meta-analysis found that LCn-3 PUFA supplementation, primarily in the form of fish oil, combined with supervised, gym-based resistance training, improved muscle strength and physical function (Cornish et al., 2022). While most studies have used fish oil as the primary supplement, krill oil presents a promising alternative source of LCn-3 PUFAs. Notably, when krill oil supplements are compared to fish oil supplements, they produce similar increases in plasma EPA and DHA levels, but at a lower dose of EPA and DHA (Ulven et al., 2011). Furthermore, when krill oil and fish oil are compared at equivalent EPA and DHA doses, krill oil leads to a greater increase in the omega-3 index (Ramprasath et al., 2013). On top of this, krill oil contains bioactive compounds that may enhance muscle health, such as astaxanthin and choline (Moretti et al., 2020,

Liu et al., 2018). Furthermore, krill oil specifically DHA may influence neuromuscular function, as it is highly concentrated in the brain and supports the regulation of the central nervous system, potentially slowing age-related decline in neuromuscular performance (Hayman et al., 2024). DHA may also improve nerve conduction velocity and synaptic transmission (Hayman et al., 2024). This is important as the mechanisms through which LCn-3 PUFA influence muscle remain unknown although the work of Alkhedhairi et al. 2022 indicated that this may be neuromuscular in origin due to an increase in the M-wave following 6 months of krill oil supplementation in older adults.

The combined effects of resistance exercise and LCn-3 PUFAs supplementation have been investigated as a potential intervention to counteract sarcopenia. However, the evidence remains inconsistent. A meta-analysis by Cornish et al. (2022) found that LCn-3 PUFAs supplementation combined with resistance exercise improved lower-body muscle strength and physical function, but not muscle mass or gait speed in older adults. In contrast, a more recent meta-analysis by Dam et al. (2025) reported that the benefits were mainly limited to physical function, specifically chair rise performance, with no effects on muscle strength or mass. These differences may be explained by variations in study inclusion criteria, such as differences in participant age ranges, supplement composition, and exercise protocols. Importantly, most previous studies have focused mainly on muscle mass, strength and functional outcomes. However, there is evidence suggesting that age-related declines in muscle strength may involve neuromuscular dysfunction, rather than muscle atrophy alone (Jones et al., 2022; Hepple & Rice, 2016; Anagnostou & Hepple, 2020; McNeil et al., 2005). On top of this, none of the studies included in these meta-analyses assessed motor unit function using advanced techniques such as iEMG. This limits our understanding of the neuromuscular mechanisms underpinning strength improvements. This is important, particularly given emerging evidence indicating that LCn-3 PUFA supplementation may improve neuromuscular function (Gray & Mittendorfer, 2018; Hayman et al., 2024).

Furthermore, none of the studies included in either meta-analysis used krill oil supplementation in conjunction with resistance exercise. This is important because krill oil differs from fish oil in that EPA and DHA are mainly phospholipid-bound and it

also contains other bioactive compounds such as astaxanthin and choline, which may enhance bioavailability and potentially influence neuromuscular outcomes (Ulven et al., 2011; Ramprasath et al., 2013; Moretti et al., 2020). Indeed, Alkhedhairi et al. (2022) showed that krill oil supplementation can increase muscle size, strength and may also improve neuromuscular excitability in older adults, supporting its relevance in this context. In addition, previous intervention studies commonly used around 4 g/day of fish or krill oil when reporting beneficial effects on muscle and neuromuscular outcomes in older adults. For example, Smith et al. (2011a; 2011b) used a 4 g/day fish oil protocol and reported improvements in muscle anabolic responses in older adults. Likewise, Da Boit et al. (2017) used a 4 g/day fish oil protocol during resistance training and reported improvements in muscle strength, but not muscle mass, in women but not men. Similarly, Alkhedhairi et al. (2022) used 4 g/day krill oil and reported improvements in muscle strength and size, alongside improved neuromuscular excitability indicated by an increase in M-wave amplitude.

Intervention durations of approximately 12 to 16 weeks have commonly been used in resistance training studies in older adults and are generally considered sufficient to elicit meaningful improvements in muscle strength and physical function (Lu et al., 2021). This is supported by resistance training studies in older adults with sarcopenia, such as elastic band–based training performed three times per week for 16 weeks, which improved muscle strength and physical function (Seo et al., 2014). In contrast, shorter intervention durations may be insufficient to detect meaningful changes in muscle strength and neuromuscular function in older adults (Liu & Latham, 2009). On top of that, LCn-3 PUFAs supplementation studies indicate that erythrocyte EPA and DHA (omega-3 index) generally require sustained supplementation, with protocols of 12 weeks or longer often needed to raise omega-3 index to recommended levels (Dempsey, Rockwell & Wentz, 2023). Thus, intervention durations beyond 12 weeks appear appropriate when the aim is to capture both training adaptations and changes in omega-3 index.

With respect to exercise design, most previous trials used supervised, facility-based resistance exercise programmes, which may limit feasibility and real-world applicability for older adults. However, many older adults do not participate in gym-based

resistance exercise (Strain et al., 2016), partly due to barriers such as access, cost and dislike of the gym environment, as discussed earlier in this thesis (Burton et al., 2017). Therefore, home-based resistance exercise has been proposed as a pragmatic and feasible option for older adults, and it can be effective in improving muscle strength and physical function (Manas et al., 2021; Zhang et al., 2022). Finally, NMJ transmission instability was included as the primary outcome, as it provides a mechanistic insight into neuromuscular function and can be quantified using near-fibre iEMG techniques (Hourigan et al., 2015; Piasecki et al., 2016). Secondary outcomes included muscle strength, muscle size, physical function and motor unit characteristics to provide a broader assessment of muscular and neuromuscular adaptations.

Taken together, the current evidence highlights clear gaps in the literature and supports the need for a well-designed RCT to determine whether krill oil supplementation can enhance muscle strength and neuromuscular adaptations to a pragmatic home-based resistance exercise programme in older adults.

Chapter 2 examined the association between habitual dietary n-3 fatty acid intake and indices of muscle strength and mass in older adults. Due to the cross-sectional design, these findings cannot establish causality. The observed associations between n-3 fatty acid intake and muscle strength index were small, evident only in women, and may not be clinically meaningful. This may indicate that habitual dietary n-3 fatty acid intake has little influence on muscle strength in older adults. However, it is also possible that typical dietary intakes of n-3 fatty acids are insufficient to elicit measurable effects on muscle strength and neuromuscular outcomes. Therefore, the findings of Chapter 2 do not provide direct evidence for or against a causal role of n-3 fatty acids intake in older adults. Instead, they highlight the limitations of observational dietary data for addressing this question. In this context, intervention studies using controlled supplementation are required to determine whether higher and more standardised n-3 fatty acid exposure can influence muscle and neuromuscular adaptations.

On top of this, Chapter 2 relied on self-reported dietary intake, which is subject to measurement error (Beydoun et al., 2007). This measurement error may weaken estimated associations, making it difficult to detect true relationships (Beydoun et al., 2007). Therefore, a RCT with supplementation in Chapter 3 was needed to overcome

these limitations. With respect to sex differences, although a statistically significant association was observed only in women in Chapter 2, the effect size was very small, and no association was observed for muscle mass in either sex. Given the above limitations it was not considered sufficiently robust to justify restricting the RCT to women only. Therefore, both men and women were included in Chapter 3 to allow assessment of the intervention in a broader older adult population, without assuming the absence of benefit in men based on weak observational evidence.

The RCT presented in Chapter 3 was designed to address these gaps by examining whether krill oil supplementation can augment adaptations to a pragmatic resistance exercise programme in older adults. This study also aimed to investigate neuromuscular mechanisms, including NMJ transmission instability, which have been largely overlooked in previous work. Therefore, the aim of this Chapter was to determine whether krill oil supplementation can enhance the effects of a pragmatic resistance exercise programme on adaptations in muscle strength and size, physical function, and motor unit function in healthy older adults, using a double-blind randomised controlled trial to establish causality. It was hypothesised that krill oil supplementation would augment the effects of resistance exercise on the primary outcome, NMJ transmission instability, as well as on secondary outcomes including muscle strength and size, physical function, and motor unit characteristics such as motor unit firing rate and firing rate variability over the 16-week intervention period.

3.2 Methods

3.2.1 Study design

This study was a double-blind, randomised controlled trial. Following baseline assessments, participants were randomly assigned to either the krill oil group or the control group for the 16-week study period, during which all participants engaged in the same resistance exercise intervention. Random allocation was performed by an independent researcher (who was not involved in participant recruitment or assessment) through a 1:1 ratio using sealedenvelope.com. The study was registered on ClinicalTrials.gov (NCT05869513).

3.2.2 Participants

Forty-six older adult participants were enrolled for this study between May 2023 and May 2024 in Glasgow, UK. Recruitment was conducted through advertisements on social media platforms such as Nextdoor, Facebook, and Yammer, as well as via posters, flyers in local shops, and presentations delivered through the University of the Third Age. Inclusion criteria required participants to be aged 60 years or older and not currently engaging in regular resistance exercise (defined as less than 1 hour per week). Exclusion criteria included the presence of health conditions such as active cancer or cancer in remission for less than five years, seizure disorders, stroke, Parkinson's disease, dementia, diabetes, severe cardiovascular disease, uncontrolled hypertension (>150/90 mmHg at baseline), COPD, kidney disease, ambulatory impairments that would limit the ability to complete muscle function assessments, a history of femoral neck fracture or major hip/knee surgery, and the use of medications known to affect muscle (e.g., corticosteroids). Participants were also excluded if they had implanted electronic devices (e.g., pacemaker, defibrillator, insulin pump), were on anticoagulant therapy, had seafood allergies, consumed more than one portion of oily fish per week, were already taking fish oil, krill oil, or other n-3 PUFA supplements, or had a BMI greater than 35 kg/m2.

Ethical approval for the study was granted by the College of Medical, Veterinary & Life Sciences Research Ethics Committee at the University of Glasgow (Reference: 200220084). The study adhered to the principles of the Declaration of Helsinki, and all participants provided written informed consent prior to participation.

3.2.3 Supplementation

Participants were asked to take supplements for 16 weeks whilst keeping their normal dietary intake and physical activity habits. To monitor fish consumption throughout the study period, all participants were provided with a fish consumption log (see appendix 3). The krill oil group received a daily dose of 4 grams of krill oil (SuperbaBoost™). Each 1 g capsule of the supplement contained 322 mg of LCn-3 PUFAs (193 mg EPA and 96 mg DHA) and 79 mg of choline. The control group received a daily dose of 4 grams of mixed vegetable oil, including refined palm kernel oil, refined maize oil, a blend of cold-pressed extra virgin olive oil, and medium-chain triglycerides (in a ratio of 4:4:3:2). The mixed vegetable oil was formulated to provide a fatty acid composition similar to that found in the typical European diet. Participants took four capsules per day (two with breakfast and two with lunch). Both the krill oil and mixed vegetable oil capsules were identical in shape and taste. Aker Biomarine Antarctic AS (Lysaker, Norway) provided both types of capsules but had no role in any part of the study except for supplying the capsules. The krill oil dosage of 4 g/day was selected based on previous intervention studies that showed beneficial effects on muscle and neuromuscular outcomes in older adults using this dose. Smith et al. (2011a; 2011b) used 4 g/day fish oil and reported improvements in muscle protein synthesis and anabolic responses in older adults. Additionally, Da Boit et al. (2017) used 4 g/day fish oil during resistance training and reported improvements in muscle strength. Similarly, Alkhedhairi et al. (2022) used 4 g/day krill oil and reported improvements in muscle strength and size, alongside improved neuromuscular excitability as indicated by increased M-wave amplitude.

3.2.4 Resistance Exercise Intervention

Participants were instructed to perform home-based resistance exercises using body weight and/or elastic resistance bands over a 16-week period. Each participant was provided with six resistance bands of varying resistance levels. The exercise programme consisted of 3 (minimum) to 6 (maximum) sets per week (participants were required to complete at least 3 sets but were encouraged to perform up to 6 sets), with each set comprising six exercises, with three targeting the upper limbs and three targeting the lower limbs (see appendix 4). Each set included 8 to 20 repetitions of the six exercises. All the exercises were performed at vigorous intensity level, measured using the OMNI perceived exertion scale (Buskard et al. 2019, Robertson et al. 2003).

Participants were asked to perform these exercises to the point where they scored 4 to 5 (somewhat easy) in the first week, and 8 to 9 (hard) in the following weeks on the OMNI scale. Different difficulty options were given either by using different tension levels of resistance bands or by modifying body weight exercises, and participants adjusted the difficulty level to reach an exertion score of 8 to 9 in 8–20 repetitions. The intervention was progressive meaning that intensity, and difficulty level, increased during the 16 weeks of the study. If the participant was able to perform more than 20 repetitions at an exertion score of 8 to 9 on the Borg scale, they were advised to move to the next difficulty level. Participants were advised that these exercises could be performed throughout the week at the participant's preference, such as in discrete sessions or split throughout the week. The resistance exercise protocol was designed based on evidence-based guidelines for sarcopenia prevention and treatment in older adults. Specifically, Hurst et al. (2022) recommended that an optimal resistance exercise programme for older adults with sarcopenia should consist of two exercise sessions per week involving a combination of upper and lower body exercises performed with a vigorous intensity effort for 1 to 3 sets of 6 to 12 repetitions. This recommendation is consistent with the American College of Sports Medicine guidelines, which recommend that older adults perform resistance exercises for major muscle groups 2 to 3 days per week using moderate to high intensity loads corresponding to 8 to 12 repetitions (Chodzko-Zajko et al., 2009). Therefore, the exercise prescription used in the current study is consistent with these evidence-based recommendations for resistance exercise in older adults at risk of sarcopenia. Initially all participants were shown the exercises and asked to perform them with the researcher (AA), who holds a master's degree in physical therapy, to ensure they performed the exercises correctly. Additionally, participants were provided with an exercise manual (see appendix 5) that illustrated all the exercises in both visual and written forms, as well as YouTube video links sent to their email. Finally, participants were given an exercise log (see appendix 6) to track their adherence and progress.

3.2.5 Outcomes

Change in motor unit function specifically NMJ transmission instability was assessed as the primary outcome. The secondary outcomes were the change in muscle strength including grip strength and knee extensor muscle strength, muscle size, chair raise test, gait parameters such as gait speed, cadence, step length and stride length, force steadiness, firing rate, firing rate variability and fatty acid composition. The lead

researcher AA who was blinded to group assignment during the study period made all the measurements at baseline, 8 weeks and 16 weeks.

3.2.5.1 Grip strength

Grip strength was measured using a Jamar hand dynamometer, with three trials conducted on each hand. Participants were seated with their elbow flexed at 90° and were instructed to support their arm and squeeze the dynamometer as hard as possible. The average value from both hands was used in the analysis. Grip strength is a widely used and clinically relevant measure of muscle strength in older adults and is commonly employed in epidemiological studies, clinical assessments, and intervention trials (Cruz-Jentoft et al., 2019). Furthermore, the EWGSOP2 has recommended the use of grip strength as the primary outcome measure for identifying probable sarcopenia in clinical and research settings. Measuring grip strength is simple and inexpensive, making it suitable for research studies and routine clinical practice (Cruz-Jentoft et al., 2019).

Grip strength is a strong predictor of adverse health outcomes, including longer hospital stays, increased functional limitations, poorer health-related quality of life, and increased mortality (Ibrahim et al., 2016; Leong et al., 2015). Grip strength correlates moderately with muscle strength in other body compartments and therefore can be used as a proxy measure of overall muscle strength. When standardised testing procedures are applied, handgrip dynamometry demonstrates excellent test–retest reliability in older populations, with intraclass correlation coefficients typically exceeding 0.90 (Bohannon, 2015). The Jamar dynamometer has been extensively validated and is widely used for measuring grip strength in both clinical and research contexts (Cruz-Jentoft et al., 2019). Grip strength has also been shown to be associated with lower-limb muscle strength, physical function, disability, and adverse health outcomes, including morbidity and mortality (Dodds et al., 2014). However, it is important to note that grip strength primarily reflects upper-limb muscle strength and may not fully represent lower-limb or whole-body strength adaptations (Bohannon, 2015). This limitation was addressed in the present study by including additional assessments of muscle strength such as knee extensor muscle strength and neuromuscular function. Other limitation is that in some cases, grip strength assessment may not be feasible, such as in individuals with advanced arthritis or stroke-related hand impairment.

3.2.5.2 Knee extensor muscle strength

The knee-extensor muscles strength of the right leg was measured during isometric MVC through a load cell (Biometrics Ltd, Newport, UK). Participants were positioned in a dynamometer secured with belts and their knee fixed at a 90° angle. They were asked to perform a minimum of three contractions for 5 seconds as hard as possible with a minimum of 1 minute rest between each attempt. If the third attempt exceeded the second by more than 10%, indicating a potential learning effect, additional attempts were performed until two consecutive values were within 10% of each other. The highest recorded value was used for analysis. Furthermore, knee extensor muscle strength is widely used and well validated in older adults and in populations with, or at risk of sarcopenia (Cruz-Jentoft et al., 2019). In the literature, the isometric knee extension test is commonly used as a complementary assessment to handgrip strength, as it provides information on both the neural and muscular capacity of the knee extensor muscles, which are essential for physical function (Rodríguez-Rosell et al., 2018).

Isometric knee extension strength has demonstrated excellent intra- and inter-session reliability in adult populations, with intraclass correlation coefficients typically exceeding 0.90 (Ruschel et al., 2015; Courel-Ibáñez et al., 2020). Importantly, recent work in older adults has shown high to very high repeatability of the Isometric knee extension test, alongside significant associations with functional outcomes including gait speed, TUG, sit-to-stand performance and grip strength (Courel-Ibáñez et al., 2020). These findings support the relevance of isometric knee extensor strength as an indicator of lower-limb function in older adults (Cruz-Jentoft et al., 2019).

Nevertheless, isometric knee extensor strength test assessed at a fixed knee angle reflects muscle strength at a specific joint position and may not fully represent force production across the full range of motion or during dynamic tasks (Ferreira et al., 2023).

3.2.5.3 Muscle size

An ultrasound imaging device (Echoblaster 128 Ext; Telemed Ltd, Vilnius, Lithuania) was used to measure muscle thickness of the right vastus lateralis (VL) muscle. Participants were asked to lie in a supine position, and images were collected at the

midpoint of the thigh after identifying and marking the anatomical location with a pen (defined as 50% of the distance between the greater trochanter and the lateral condyle of the femur). Ultrasound-derived muscle thickness is a widely used, non-invasive method for assessing skeletal muscle size in older adults and has been shown to be repeatable and valid when standardised procedures are applied (Ismail, 2020). Previous work has demonstrated high repeatability of vastus lateralis muscle thickness measurements using ultrasound, with coefficients of variation typically below 5% (Takai et al., 2013). Furthermore, ultrasound imaging has been shown to correlate strongly with gold-standard imaging techniques, including MRI and CT (Ismail, 2020). Specifically, muscle thickness measured using ultrasound has been shown to correlate strongly with vastus lateralis cross-sectional area (r=0.82) and muscle volume (r=0.76) assessed by MRI (Ismail, 2020), with similar findings reported in middle-aged and older adults (Takai et al., 2013).

Further validation studies have shown that ultrasound-derived muscle thickness at the mid-thigh is a strong predictor of knee extensor muscle volume, explaining approximately 42 to 75% of the variance in MRI-derived muscle volume across a wide age range (Miyatani et al., 2002; Miyatani et al., 2004). Ultrasound-derived muscle thickness has also been shown to be associated with whole-body and limb-specific lean mass measured using DEXA, supporting its use as a proxy measure of skeletal muscle mass in older adults (Takai et al., 2013). Taken together, these findings indicate that ultrasound-derived muscle thickness provides a valid estimate of both local muscle size and broader indices of lean tissue mass (Ismail, 2020).

An important strength of ultrasound assessment is its feasibility in older adult populations, as it is portable, relatively low cost, and does not involve exposure to ionising radiation compared to MRI or DEXA (Nijholt et al., 2017). However, ultrasound-derived muscle thickness represents a linear measure obtained at a single anatomical site and may not fully reflect three-dimensional muscle architecture or regional changes across the entire muscle (Miyatani et al., 2004). On top of this, measurements are dependent on operator skill and probe placement; however, this limitation can be minimised through the use of standardised protocols and consistent anatomical landmarking (Ismail, 2020). Furthermore, although ultrasound measures of muscle thickness demonstrate strong cross-sectional validity, their sensitivity for detecting small, intervention-induced changes in muscle mass is less well established,

and ultrasound is therefore not considered the gold standard for assessing muscle size (Esteves et al., 2023).

3.2.5.4 Chair rise test

Physical function was assessed using the chair rise test. Participants were instructed to rise to a full standing position and return to a seated position as many times as possible within 30 s, with their arms crossed over the chest to minimise assistance from the upper limbs. Chair height was standardised, and participants were encouraged to perform the task as quickly and safely as possible throughout the test. The chair rise test is a widely used and validated measure of lower-limb muscle function and physical performance in older adults and is recommended as part of physical performance assessment batteries for sarcopenia (Cruz-Jentoft et al., 2019). Performance on the chair rise test has been shown to be associated with lower-limb muscle strength, mobility, balance, and independence in activities of daily living (Jones et al., 1999; Lord et al., 2002). The test demonstrates good to excellent test–retest reliability in older adult populations, with intraclass correlation coefficients typically reported above 0.80 when standardised testing protocols are applied (Jones et al., 1999; Bohannon, 2011).

An important strength of the chair rise test is its feasibility in older adult populations, as it requires minimal equipment, is time-efficient, and reflects functional tasks commonly performed in daily life. However, performance on the chair rise test may be influenced by factors such as balance, joint pain, or cardiovascular limitations, in addition to muscle strength, and therefore should be interpreted as a composite measure of physical function rather than a direct measure of muscle strength alone (Bohannon, 2011; Lord et al., 2002). Chair rise performance was therefore interpreted together with direct assessments of muscle strength and neuromuscular function in this study.

3.2.5.5 Gait parameters

The gait parameters measured were gait speed, cadence, step length, and stride length, using an electrical gait analysis mat (GAITRite system; CIR Systems Inc., Clifton, NJ, USA). The GAITRite mat is 4.6 meters long and 61 cm wide, embedded with numerous sensors and connected to a computer for data collection. Participants were asked to walk across the mat at their own pace and return to the starting point at

the beginning of the mat. The GAITRite system has been widely validated and demonstrates excellent reliability for the assessment of spatiotemporal gait parameters in older adults. Previous studies have reported high test–retest reliability for gait speed, cadence, step length, and stride length, with intraclass correlation coefficients typically exceeding 0.90 when standardised testing protocols are applied (Bilney et al., 2003; McDonough et al., 2001). Gait speed derived from GAITRite assessment is a well-established indicator of physical function and health status in older adults and has been shown to be associated with mobility, disability, falls risk, and mortality (Studenski et al., 2011; Cruz-Jentoft et al., 2019).

An important strength of instrumented gait assessment using the GAITRite system is that it provides objective and reproducible measures of multiple spatiotemporal gait parameters under standardised conditions (Bilney et al., 2003; McDonough et al., 2001). The system is non-invasive, requires minimal participant burden, and is well tolerated by older adults (Bilney et al., 2003). However, gait assessment conducted over relatively short walkways may be influenced by acceleration and deceleration phases, which can affect spatiotemporal gait parameters (Lindemann et al., 2008). In addition, gait assessment at self-selected walking speed reflects habitual walking patterns but may not fully reflect maximal walking capacity (Bohannon, 1997; Studenski et al., 2011). These limitations were addressed in the present study by applying consistent testing procedures and interpreting gait outcomes alongside complementary measures of muscle strength and physical function.

3.2.5.6 Blood sample

Fatty acid composition was measured through blood samples, butterfly needles inserted in an antecubital vein and collected at baseline, week 8 and week 16. Blood samples were stored at −80 °C and shipped for analysis by an external company (Omegaquant) for fatty acid composition analysis. The percentage of total identified fatty acids was reported as the fatty acid composition. The sum of 20:5n-3 (EPA) and 22:6n-3 (DHA) was adjusted using a regression equation (r = 0.97) to estimate the omega-3 index in red blood cells (RBCs). Furthermore, the Omega-3 Index represents the RBC content of the two LCn-3 PUFAs, EPA and DHA. It is a well-established and widely used technique and provides a valid and reliable analytical measure of LCn-3 PUFA status (Harris, 2010).

3.2.5.7 Force steadiness

Once MVC was determined, isometric voluntary contractions lasting 20 seconds were performed at both 10% and 25% MVC, with 30 seconds of rest between contractions. This was explained to participants using a monitor screen displaying target lines set at 10% and 25% MVC, and they were asked to maintain the force along these target lines. At each contraction intensity, participants were given a single familiarisation trial before performing four voluntary contractions at 10% MVC and four at 25% MVC. Participants performed these contractions alternately between 10% and 25% MVC. Spike2 software (v9.06, Cambridge Electronic Design, Cambridge, UK) was used to display the force signals in real time on the monitor screen. These isometric voluntary contractions at 10% and 25% MVC were the same contractions used for the iEMG analysis (details below), where the force output was used to assess force steadiness, and motor unit function was evaluated using iEMG. Force steadiness was represented as the coefficient of variation of force [CoV; (SD/mean) × 100]. The average of force variability (CoV) at each contraction level was used for analysis. Previous work has shown that the CoV demonstrates predictive validity for functional outcomes (Pethick et al., 2023). The selection of 10% and 25% MVC contraction intensities was based on evidence showing that lower contraction intensities demonstrate superior reliability compared to higher intensities (Bieler et al., 2014).

However, it is important to acknowledge that there are clear limitations. The validity of CoV is context-dependent, with weak associations between force steadiness and physical function observed in some populations such as knee osteoarthritis patients (r^2=0.03) (Seynnes et al., 2022). The measurement was limited to submaximal contractions as CoV may be inappropriate for sustained maximal contractions where torque progressively declines (Pethick et al., 2023).

3.2.5.8 Motor unit function

Motor unit function specifically motor unit firing rate, firing rate variability and NMJ transmission instability was assessed via iEMG. iEMG is a well-established and technically complex method for isolating individual motor unit function, providing valuable insights into neuromuscular function (Piasecki, Stashuk, 2023). To identify the motor point of the VL muscle, low-intensity percutaneous electrical stimulation was applied using a constant current stimulator (Digitimer DS7A, Welwyn Garden City,

UK). Stimulation began at 50 mV and was gradually increased unless the participant requested to stop. The motor point was defined as the site where the smallest electrical current produced the largest visible muscle twitch (Botter et al., 2011). If the motor point could not be identified the mid-point area of VL muscles was identified instead. Once the motor point was located it was marked with a pen. A disposable concentric needle (74025-45/25 Neuroline; Ambu, Baltorpbakken, Denmark) was used for recording. The grounding electrode placed over right patella (Ambu Neuroline Ground, Baltorpbakken, Ballerup, Denmark). Instructions were then given on how to perform isometric leg extension to familiarise the participants with the test. An alcohol wipe was used to clean the identified motor point and the surrounding area in preparation for needle insertion. Before inserting the needle, participants were asked to relax their right leg to facilitate the needle insertion into the motor point in VL muscle belly. Signal activity was inspected by the researcher. Once the needle was inserted, participants were asked to perform eight contractions alternating between 10% and 25% MVC (four at 10% MVC and four at 25% MVC). This was explained by asking participants to follow a target line set at 10% and 25% MVC on a screen in front of them which displayed force and EMG signals through Spike2 (version 9, CED) software to provide real-time visual feedback. Each isometric leg extension contraction lasted for 20 seconds, with 30 seconds rest intervals between contractions. To ensure recordings at various depths of the VL muscle, two repositioning techniques were used between contractions: first, rotating the bevel 180°, and second, slightly retracting the needle by 10 to 25 mm (Jones et al., 2021). Once all contractions were completed, the lead researcher withdrew and disposed of the needle. iEMG signals were amplified using a D440 (Digitimer, Welwyn Garden City, UK) and recorded using a CED Micro 1401 (Cambridge Electronic Design, Cambridge, United Kingdom) at 50 kHz, bandpass filtered between 10 Hz and 10 kHz.

Furthermore, iEMG is a relatively inexpensive and minimally invasive procedure that offers several advantages for assessing motor unit structure and function (Atherton & Wilkinson, 2023). The technique enables recording of individual motor unit potentials from muscles at varying depths without signal quality degradation, overcoming limitations of surface EMG particularly in populations with greater subcutaneous tissue such as elderly, diabetic, or obese individuals (Atherton & Wilkinson, 2023). The rigid structure of the concentric needle allows repositioning between or during contractions at various muscle depths, which is important given that motor unit potential

characteristics and fibre-type composition differ from deep to superficial regions of some muscle groups (Atherton & Wilkinson, 2023).

However, it is important to acknowledge that there are several limitations. Signal quality and subsequent decomposition success are heavily dependent on suitable initial needle positioning to ensure high signal-to-noise ratio, minimal needle movement to maintain signal quality and motor unit potential shapes, and appropriate contraction intensity and duration (Atherton & Wilkinson, 2023). Excessive noise interference, commonly originating from 50 or 60 Hz power supplies, may require additional grounding of force transducers, amplifiers, and testing equipment (Atherton & Wilkinson, 2023). Needle movement can alter the shape of successive motor unit potentials, rendering them difficult to identify. Finally, signal decomposition, while efficient, requires visual inspection and editing of all individual motor unit potentials and their corresponding trains to ensure accurate interpretation of neuromuscular function (Atherton & Wilkinson, 2023).

3.2.6 iEMG analysis

Decomposition-based quantitative electromyography (DQEMG) software was used to extract motor unit potential trains (MUPTs) (Parsaei et al., 2009). The lead researcher performed visual inspection of individual MUP templates to confirm accurate cursor placement at the onset, endpoint, positive peak, and negative peak of the waveform. Additionally, cursors placement was repositioned and adjusted as needed during this review process. Furthermore, a near-fibre MUP (NFM) represented as a calculation of individual MUP templates (Piasecki, Garnés-Camarena & Stashuk, 2021). Visual inspection was not only for individual MUP templates but also for Individual NFMs, during this inspection any contamination from other NFMs the lead researcher had excluded them from the analysis. MUP parameters were used to estimate firing rate and firing rate variability, whereas NMJ transmission instability was estimated from NF jiggle, which is derived from NFM parameters (Piasecki, Garnés-Camarena & Stashuk, 2021).

3.2.7 Sample size

The sample size chosen for the current study was based upon the primary objective of the mechanistic outcome of NMJ transmission instability. There is no agreed minimally clinically important difference in NMJ transmission instability, but we

considered a difference of 20% to be physiologically relevant and so with an SD of 23%, alpha 0.05 and power 80%, we required 22 participants per group and to allow for drop out we recruited 25 participants per group.

3.2.8 Statistical analysis

An independent samples t-test was used to compare exercise adherence and fish consumption between groups. To determine the interaction and time effects on the outcome variables, a mixed ANOVA was conducted using SPSS Statistics. A post-hoc t-test with Bonferroni correction was performed if a significant interaction effect was observed, to identify differences between the intervention and control groups. A paired-samples t-test was applied to assess changes over 16 weeks, comparing pre- and post-intervention data. Ninety-five percent confidence intervals (CIs) were used to present the magnitude of the effect over the 16 weeks. Results were reported as mean and SD for all time points. Due to the complexity of iEMG data, R statistical software was used for the analysis. Statistical significance was set at $p<0.05$.

3.3 Results

3.3.1 Participant characteristics

Sixty participants were enrolled between May 2023 and May 2024, with 14 participants withdrawn prior to follow up, leaving 46 participants (22 male and 24 female) included in the final analysis (Figure 3.1). Participant characteristics, the average number of sets of each exercise completed per week and weekly fish consumption are displayed in Table 3.1. Mean age, weight, and height were similar between the two groups at baseline and there were no differences in the number of sets of exercises (p=0.087) or fish consumption (p=0.663) over the intervention period.

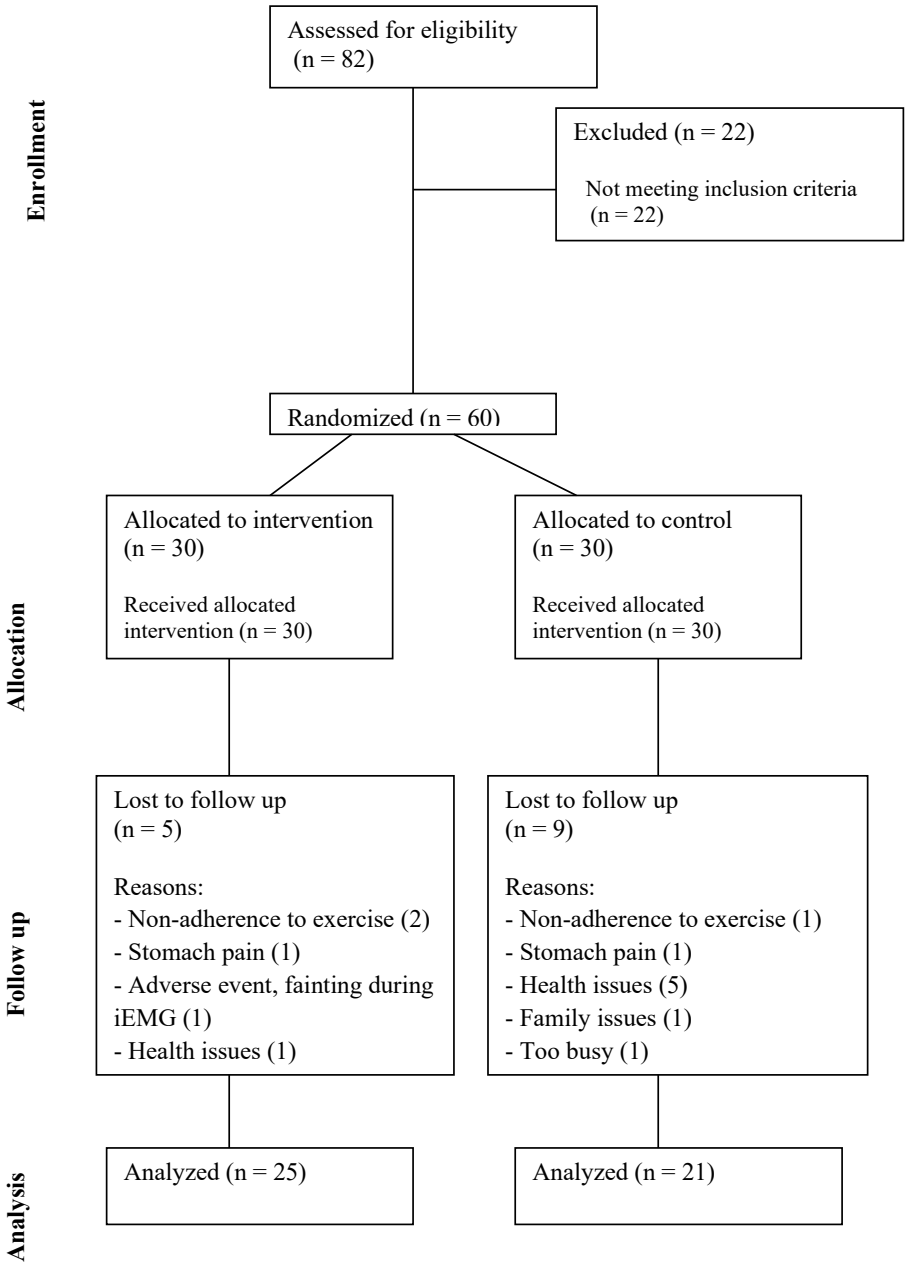

Figure 3.1 the CONSORT diagram showing the flow of participants through each stage of a randomized trial.

Table 3.1 Participant characteristics, Exercise sets and fish consumption in control and krill oil group

	Control	Krill Oil
Female, n (%)	10 (48)	14 (56)
Age (years)	68.0 (5.5)	67.4 (5.7)
Weight (kg)	74.3 (14.2)	74.2 (15.3)
Height (cm)	167.4 (8.9)	167.9 (8.0)
Exercise sets per week	4.2 (1.3)	4.6 (1.6)
Fish consumption (portion per week)	0.9 (0.5)	0.9 (0.5)

Data are presented as mean ± SD unless otherwise stated. Between-group comparisons at baseline were performed using independent samples t-tests for continuous variables and chi-square tests for categorical variables. No statistically significant baseline differences were observed unless indicated. SD: standard deviation.

3.3.2 Muscle function and size

Data for grip strength, knee extensor strength, 30 second chair stand test score, force steadiness and VL thickness data are presented in table 3.2. Effects of time (p=0.014), but not interaction (p=0.076) effects, were found for grip strength in the ANOVA. Post-hoc tests showed that, over the 16-week intervention period, grip strength increased by 2.7 kg (95%CI: 1.3, 4.4, p<0.001) in the krill group with no change in the control group, 0.3 kg (95%CI: -1.0, 1.3, p=0.618). For knee extensor maximal torque the ANOVA revealed a time∗treatment interaction effect (p=0.041), but not an effect of time (p=0.661). Post-hoc tests showed that, over the 16-week intervention period, knee extensor maximal torque increased by 7.8 Nm (95%CI: 0.1, 14.3, p=0.04) in the krill group with no change in the control group, −3.8 Nm (95%CI: -11.9, 3.7, p=0.337). Although there was no interaction (p=0.638) effect a time effect (p<0.001) was seen for 30 second chair stand test score. Post-hoc tests showed that, over the 16-week intervention period, 30 second chair stand test score increased by 2.1 repetitions (95%CI: 1.2, 2.9, p<0.001) in the krill group and by 1.6 repetitions (95%CI: 0.7, 2.5, p<0.001) in the control group. Analysis of VL thickness data revealed no effects of time (p=0.151) or interaction effects (p=0.737).

Analysis revealed no interaction (p=0.190) effect; however, a time effect (p<0.001) was found for force variability at 10% MVC. Post-hoc tests showed that, over the 16-week intervention period, force variability at 10% MVC decreased by 0.6 % (95%CI: 1.2, -0.1, p=0.019) in the krill and by 1.6 % (95%CI: -2.5, -0.4, p=0.014) in the control

group. Likewise, for force variability at 25% MVC no interaction (p=0.680) effect was observed, but a time effect (p<0.001) was seen. Post-hoc tests showed that, over the 16 week intervention period, force variability at 25% MVC decreased by 1.3 % (95%CI: -1.8, -0.6, p<0.001) in the krill group and by 1.2 % (95%CI: -2.0, -0.5, p=0.003) in the control group.

3.3.3 Gait parameters

Data for gait parameters are showed in Table 3.3. The analysis revealed time (p=0.009), but no interaction effects (p=0.723) for gait speed. Post-hoc tests showed that, over the 16-week intervention period, gait speed increased by 5.3 cm/sec (95%CI: -0.04, 11.81, p=0.051) in the control group with no change in the krill group, 3.8 cm/sec (95%CI: -0.85, 8.57, p=0.104). Similarly, effects of time (p=0.014), but not interaction (p=0.092) effects, were found for cadence. Post-hoc tests showed that, over the 16-week intervention period, cadence increased by 3.3 steps/min (95%CI: 0.76, 5.91, p=0.014) in the control group with no change in the krill group, 1.3 steps/min (95%CI: (-0.88, 3.51, p=0.230).

Analysis also revealed that for step length there was no interaction (p=0.737) effect, however, a time effect (p=0.018) was found. Post-hoc tests showed that, over the 16-week intervention period, step length did not change, 1.4 cm (95%CI: (-0.19, 3.16, p=0.080), in the krill group or in the control group, 1.2 cm (95%CI: -0.80, 3.23, p=0.223). For stride length effects of time (p=0.018), but not interaction effects (p=0.737), were found in the ANOVA. Post-hoc tests showed that, over the 16-week intervention period, stride length did not change in the krill, 2.8 cm (95%CI: -0.63, 6.23, p=0.105), or control groups, 2.0 cm (95%CI: -1.96, 6.01, p=0.301).

3.3.4 Blood results

Table 3.4 shows the fatty acid data. The analysis revealed time (p<0.001) and interaction effects (p<0.001) for EPA. Post-hoc tests showed that, over the 16-week intervention period, EPA increased by 2.0% (95%CI: 1.2, 2.5, p<0.001) in the krill group with no change in the control group, 0.3 % (95%CI: -0.0, 0.7, p=0.132). Similarly, effects of time (p<0.001) and interaction effects (p<0.001), were found for DPA. Post-hoc tests showed that, over the 16-week intervention period, DPA increased by 1.1% (95%CI: 0.5, 1.3, p<0.001) in the krill group and by 0.5% (95%CI: 0.3, 0.7, p<0.001) in the control group. Analysis also revealed there were time (p<0.001) and interaction

(p<0.001) effects for DHA. Post-hoc tests showed that, over the 16-week intervention period, DHA increased by 2.1% (95%CI: 1.0, 2.6, p<0.001) in the krill group with no change in the control group, 0.2 % (95%CI: -0.1, 0.7, p=0.212). For omega-3 index effects of time (p<0.001) and interaction effects (p<0.001) were found in the ANOVA. Post-hoc tests showed that, over the 16-week intervention period, omega-3 index increased by 4.2 % (95%CI: (2.3, 5.0, p<0.001) in the krill group with no change in the control group, 0.4 % (95%CI: -0.1, 1.4, p=0.139).

3.3.5 Intramuscular electromyography (iEMG)

Data from the iEMG during contractions performed at 10% maximal voluntary force are presented in table 3.5 and figure 3.2. Analysis of firing rate data at 10% MVC revealed no effects of time (p=0.747) or interaction effects (p=0.511). Similarly, analysis revealed no time (p=0.168), or interaction effects (p=0.732) for NMJ transmission instability. Although firing rate variability at 10% MVC showed no effect of time (p=0.647) an interaction effect (p=0.018) was found. Post-hoc tests showed that, over the 16-week intervention period, firing rate variability decreased by 0.01 % (95%CI: (-0.02, -0.00, p=0.010) in the krill group with no change in the control group, 0.002 % (95%CI: 0.005, 0.009, p=0.890).

Data from the iEMG during contractions performed at 25% maximal voluntary force are presented in table 3.5 and figure 3.3. Analysis of firing rate at 25% MVC revealed no effects of time (p=0.910) or interaction effects (p=0.682). The analysis also revealed no time (p=0.060) or interaction effects (p=0.836) for NMJ transmission instability at 25% MVC. For firing rate variability at 25% MVC no effects of time (p=0.805) or interaction (p=0.197) were found in the analysis.

Table 3.2 Muscle thickness, grip strength, maximal torque, chair rise test and forces steadiness in control and krill oil groups at baseline, 8 weeks and 16 weeks.

	Control				Krill				time p value	time*treatment p value
	Baseline	**8 weeks**	**16 weeks**	**Change from baseline to 16 weeks (95% CI)**	**Baseline**	**8 weeks**	**16 weeks**	**Change from baseline to 16 weeks (95% CI)**		
VL thickness (mm)	20.3 (0.9)	20.4 (0.9)	21.1 (1.1)	0.8 (-0.3, 2.2)	20.6 (0.9)	20.3 (0.9)	20.9 (1.0)	0.3 (-0.7, 1.2)	0.151	0.737
Grip strength (kg)	30.1 (2.2)	30.4 (2.4)	30.4 (2.3)	0.3 (-1.0, 1.3)	26.9 (2.0)	29.0 (2.1)	29.7 (2.1)	2.7 (1.3 ,4.4)	0.014	0.076
Maximal torque (Nm)	113.7 (8.0)	111.1 (8.2)	109.9 (8.4)	-3.8 (-11.9, 3.7)	107.3 (7.3)	113.7 (7.5)	114.5 (7.7)	7.8 (0.1, 14.3)	0.661	0.041
Chair rise test (number)	13.8 (0.5)	14.5 (0.6)	15.4 (0.6)	1.6 (0.7, 2.5)	13.6 (0.5)	14.8 (0.6)	15.7 (0.5)	2.1 (1.2, 2.9)	<0.001	0.638
Force variability (CoV) at 10%	5.1 (0.4)	3.7 (0.3)	3.5 (0.4)	-1.6 (-2.5, -0.4)	4.2 (0.4)	3.3 (0.2)	3.6 (0.3)	-0.6 (-1.2, -0.1)	<0.001	0.190
Force variability (CoV) at 25%	3.7 (0.4)	2.8 (0.3)	2.5 (0.2)	-1.2 (-2.0, -0.5)	3.4 (0.4)	2.1 (0.3)	2.1 (0.2)	-1.3 (-1.8, -0.6)	<0.001	0.680

Data are presented as mean and SD. Outcomes were analysed using a mixed-design ANOVA with group (control vs krill oil) as the between-subject factor and time (baseline, 8 weeks, 16 weeks) as the within-subject factor. Where significant interaction effects were observed, post-hoc t-tests with Bonferroni

Table 3.3 Gait speed, cadence, step length and stride length in control and krill oil groups at baseline, 8 weeks and 16 weeks

	Control				Krill				time p value	time*treatment p value
	Baseline	**8 weeks**	**16 weeks**	**Change from baseline to 16 weeks (95% CI)**	**Baseline**	**8 weeks**	**16 weeks**	**Change from baseline to 16 weeks (95% CI)**		
Gait speed (cm/sec)	129.3 (4.6)	134.7 (4.4)	135.2 (4.3)	5.8 (-0.04, 11.81)	131.9 (4.3)	135.1 (4.1)	135.4 (4.0)	3.8 (-0.85, 8.57)	0.009	0.723
Cadence (steps/min)	111.4 (2.3)	114.5 (2.1)	114.8 (2.1)	3.3 (0.76, 5.91)	112.6 (2.2)	112.4 (2.0)	113.7 (2.0)	1.3 (-0.88, 3.51)	0.014	0.092
Step length (cm)	69.6 (2.0)	70.7 (2.1)	70.8 (2.1)	1.2 (-0.80, 3.23)	70.1 (1.9)	72.1 (1.9)	71.6 (2.0)	1.4 (-0.19, 3.16)	0.018	0.737
Stride length (cm)	140.0 (4.1)	142.0 (4.2)	142.0 (4.2)	2.0 (-1.96, 6.01)	141.0 (3.8)	144.7 (3.9)	143.8 (4.0)	2.8 (-0.63, 6.23)	0.031	0.746

correction were performed. Paired-samples t-tests were used to assess within-group changes over 16 weeks. Statistical significance was set at $p < 0.05$. SD standard deviation; VL Vastus Lateralis, mm millimetres, kg kilograms, Nm, Newton-meters, CoV coefficient of variation.

Data are presented as mean and SD. Outcomes were analysed using a mixed-design ANOVA with group (control vs krill oil) as the between-subject factor and time (baseline, 8 weeks, 16 weeks) as the within-subject factor. Where significant interaction effects were observed, post-hoc t-tests with Bonferroni correction were performed. Paired-samples t-tests were used to assess within-group changes over 16 weeks. Statistical significance was set at $p < 0.05$. SD standard deviation.

Table 3.4 Fatty acid composition in control and krill oil groups at baseline, 8 weeks and 16 weeks

	Control				Krill				time p value	time*treatment p value
	Baseline	**8 weeks**	**16 weeks**	**Change from baseline to 16 weeks (95% CI)**	**Baseline**	**8 weeks**	**16 weeks**	**Change from baseline to 16 weeks (95% CI)**		
Eicosapentaenoic Acid (%)	0.9 (0.1)	1.0 (0.1)	1.2 (0.2)	0.3 (-0.0, 0.7)	1.1 (0.1)	2.6 (0.1)	3.1 (0.2)	2.0 (1.2, 2.5)	<0.001	<0.001
Docosapentaenoic Acid - n3 (%)	2.8 (0.07)	2.9 (0.09)	3.3 (0.1)	0.5 (0.3, 0.7)	2.9 (0.07)	3.5 (0.09)	4.0 (0.1)	1.1 (0.5, 1.3)	<0.001	<0.001
Docosahexaenoic Acid (%)	5.5 (0.2)	5.8 (0.2)	5.7 (0.2)	0.2 (-0.1, 0.7)	5.4 (0.2)	6.9 (0.2)	7.5 (0.2)	2.1 (1.0, 2.6)	<0.001	<0.001
Omega-3 Index (%)	6.5 (0.3)	6.9 (0.3)	6.9 (0.4)	0.4 (-0.1, 1.4)	6.5 (0.3)	9.6 (0.3)	10.7 (0.4)	4.2 (2.3, 5.0)	<0.001	<0.001

Data are presented as mean and SD. Outcomes were analysed using a mixed-design ANOVA with group (control vs krill oil) as the between-subject factor and time (baseline, 8 weeks, 16 weeks) as the within-subject factor. Where significant interaction effects were observed, post-hoc t-tests with Bonferroni correction were performed. Paired-samples t-tests were used to assess within-group changes over 16 weeks. Statistical significance was set at $p < 0.05$. SD standard deviation.

Table 3.5 iEMG data during contractions performed at 10% and 25% maximal voluntary force in control and krill oil groups at baseline, 8 weeks and 16 weeks.

	Control				Krill				time p value	time*treatment p value
	Baseline	**8 weeks**	**16 weeks**	**Change from baseline to 16 weeks (95% CI)**	**Baseline**	**8 weeks**	**16 weeks**	**Change from baseline to 16 weeks (95% CI)**		
FR (Hz) at 10%	7.9(1.5)	8.0 (1.6)	7.8 (1.7)	-0.07 (-0.5, 0.4)	8.0 (1.4)	8.2 (1.5)	8.1 (1.7)	0.1 (-0.3, 0.6)	0. 747	0.511
FR (Hz) at 25%	8.2 (1.8)	8.4 (1.8)	8.2 (1.6)	-0.03 (-0.5, 0.5)	8.4 (1.7)	8.3 (1.8)	8.2 (1.6)	-0.1 (- 0.7, 0.3)	0. 910	0.682
NF Jiggle (%) at 10%	9.8 (6.8)	9.7 (6.0)	8.2 (7.0)	-1.57 (-3.7, 0.6)	10.3 (6.3)	9.2 (5.5)	8.2 (6.8)	-2.1 (-4.2,0.0)	0.168	0.732
NF Jiggle (%) at 25%	15.3 (8.8)	14.7 (7.6)	12.8 (6.4)	-2.5 (-5.0, 0.0)	14.9 (8.5)	14.1 (7.4)	12.0 (6.8)	-2.9 (-5.5, -0.2)	0.060	0.836
FRVAR (CoV) at 10%	0.09 (0.02)	0.09 (0.02)	0.09 (0.02)	0.002 (0.005, 0.009)	0.10 (0.02)	0.09 (0.02)	0.09 (0.02)	-0.01 (-0.02, -0.00)	0.647	0.018
FRVAR (CoV) at 25%	0.09 (0.02)	0.10 (0.03)	0.10 (0.01)	0.001 (-0.00, 0.00)	0.10 (0.02)	0.10 (0.03)	0.09 (0.01)	-0.007 (-0.01, 0.00)	0.805	0.197

Data are presented as mean and SD. Outcomes were analysed using a mixed-design ANOVA with group (control vs krill oil) as the between-subject factor and time (baseline, 8 weeks, 16 weeks) as the within-subject factor. Where significant interaction effects were observed, post-hoc t-tests with Bonferroni correction were performed. Paired-samples t-tests were used to assess within-group changes over 16 weeks. Statistical significance was set at $p < 0.05$. SD standard deviation. SD standard deviation, FR firing rate, Hz hertz, NF Jiggle near-fibre Jiggle, FRVAR firing rate variability, CoV, coefficient of variation.

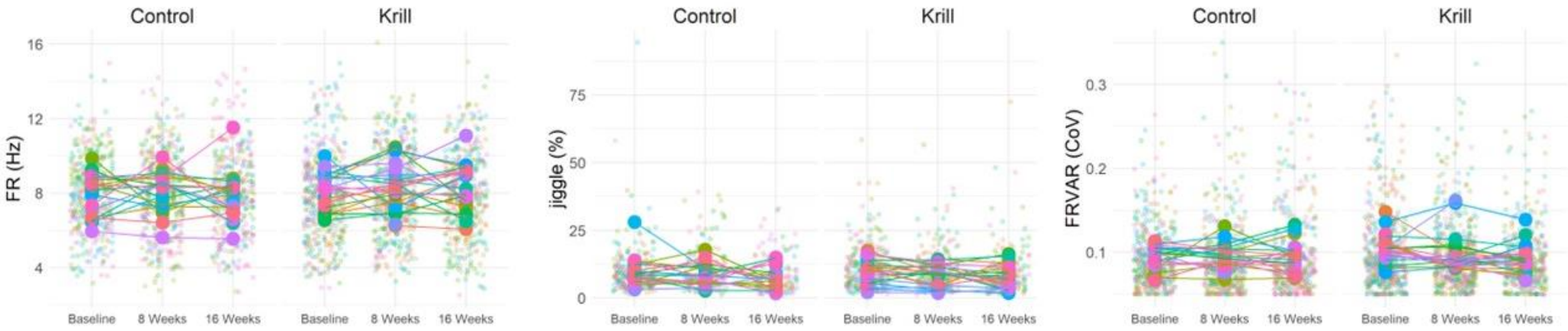

Figure 3.2 Mean values of iEMG data during contractions performed at 10% maximal voluntary force at baseline, 8 weeks and 16 weeks.

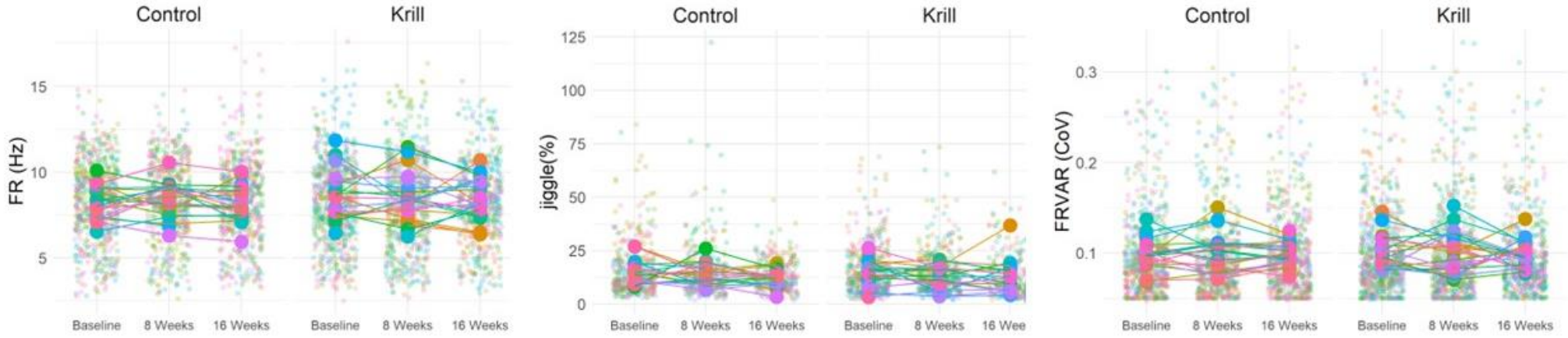

Figure 3.3 Mean values of iEMG data during contractions performed at 25% maximal voluntary force at baseline, 8 weeks and 16 weeks.

3.4 Discussion

The purpose of this double blind randomised controlled trial was to determine whether krill oil supplementation enhances the effects of a pragmatic, home-based resistance exercise programme on adaptations in muscle strength and size, physical function and motor unit function in healthy older adults. Over a 16-week intervention period, participants received either 4 g/day of krill oil or a matched vegetable oil placebo, alongside a structured resistance training regimen. Krill oil supplementation significantly improved knee extensor strength and motor unit firing rate variability compared to the control group; however, no additional benefits were observed for muscle size, physical function, or other neuromuscular outcomes.

The current study found no effect of krill oil, in addition to resistance exercise training, on grip strength. This finding aligns with previous research by Rolland et al. (2019), who reported that supplementation with LCn-3 PUFAs, as part of a multidomain intervention including physical activity, had no significant impact on grip strength compared to placebo in older adults. In contrast, Lee, Jo, and Khamoui (2019) observed a significant increase in grip strength in both the resistance training plus fish oil group and the resistance training-only group, while grip strength declined significantly in the control group. However, both of these studies warrant cautious interpretation. Rolland et al. (2019) did not include a targeted resistance training component, and Lee Jo, and Khamoui (2019) reported within-group changes without presenting between-group comparisons to establish statistical significance. In the current study, although not statistically significant it is worth pointing out that the current study did show a change in grip strength of 2.7 kg (SD = 0.76 kg) in the krill group over 16 weeks, with a 0.3 kg (SD = 0.58 kg) change in the control group ($p=0.07$). This is possibly indicative of an effect, but with the relatively small sample size the current study did not have the statistical power to detect such a difference. The difference in grip strength observed in the current study is equivalent to the decline seen over a ~5-year age span from 60 to 65 years (Dodds et al., 2014), thus, one could argue that these results are clinically important, although the minimal clinically important difference (MCID) is indicated to be around 5-6.5kg (Bohannon, 2019). It is important to clarify that the study was powered (80% power, $\alpha=0.05$) for the primary outcome of NMJ transmission instability, requiring 22 per group (25 recruited to account for dropout) thus, the sample size was appropriate for neuromuscular outcomes. Whilst the study was underpowered to detect small effects in outcomes

such as muscle strength measures, this does not indicate inadequate power for the primary neuromuscular outcomes for which the study was designed.

Consistent with the existing literature, the current study found that krill oil supplementation, in combination with resistance exercise training, increased lower body strength, measured via knee extensor maximal isometric torque in older adults (Cornish et al., 2022). However, this finding is contrary to previous systematic reviews and meta-analyses which found that LCn-3 PUFA supplementation, on top of resistance exercise training, had no effect on lower limb neuromuscular function in older adults (Dam et al., 2025). The discrepancy between the two meta-analyses may be due to differences in inclusion criteria. For example, Dam et al., (2025) included older adults aged ≥65 years, whereas Cornish et al. (2022) included participants aged ≥55 years. Additionally, in the meta-analysis of Dam et al., (2025) studies using n-3 PUFAs or an n-3-6-9 blend were included. The two meta-analyses, therefore, included different sets of studies. Furthermore, the Dam et al., (2025) study, measured broader neuromuscular function, with most assessing leg strength using maximal dynamic leg press strength, whereas in Cornish et al. (2022) the majority of the included studies used isometric knee-extensor strength to assess lower-body strength. The current study design is more closely aligned, and in agreement, with the work of Cornish et al. Considering the magnitude of effect, whilst there is no widely agreed MCID for knee extensor strength, Ruhdorfer, Wirth, and Eckstein (2015) suggested that a 4% reduction in isometric muscle strength can be considered a clinically relevant difference. The effect of krill oil in the current study was 7.8% and thus these results may represent a clinically meaningful improvement. Furthermore, this improvement is equivalent to reversing approximately 3-4 years of age-related strength decline, as leg strength typically decreases by approximately 2-3% per year in older adults (Goodpaster et al., 2006).

Furthermore, in contrast to earlier findings, which suggested that LCn-3 PUFA supplementation, on top of resistance exercise training, had a significant and large effect on the chair rise test (Cornish et al., 2022, Dam et al., 2025), the current study did not observe a similar effect. However, both meta-analyses showed high heterogeneity with Cornish et al., (2022) reporting (I^2 = 78%; p=0.0003) and Dam et al., (2025) (I^2 = 92%; p < 0.001). Thus, these results should be interpreted with caution, indeed, both meta-analyses reported no effect of resistance exercise combined with

LCn-3 PUFA supplementation on the chair rise test when studies with a potentially high risk of bias, lack of a placebo supplement, use of supplements not in form of EPA and DHA from fish oil and reporting largest effect size (SMD = 3.16) were excluded (Cornish et al., 2022; Dam et al., 2025). Consistent with the previous findings (Schättin et al., 2019, Cornish et al., 2022, Dam et al., 2025), the present study also found that home-resistances exercise plus krill oil had no significant effect on gait parameters such as gait speed, cadence, step length and stride length when compared to the control group.

In regard to muscle size, measured via VL thickness, the current study found no significant difference between the krill and the control groups. Similarly, both meta-analyses by Cornish et al. (2022) and Dam et al. (2025) found that LCn-3 PUFA supplementation, on top of resistance exercise training, had no effect on muscle size in older adults. Taken alongside the increases in lower limb strength these data indicate that the benefits of LCn-3 PUFA supplementation may be neuromuscular in origin, rather than via effects on muscle size. There is previous data to support this, in the absence of exercise with the study of Alkhedhairi et al., (2022) showing an increase in the M wave amplitude which may indicate improving neuromuscular transmission and, on top of this, when combined with resistance exercise the study of Rodacki et al., (2012) showing effects of fish oil on activation levels and electromechanical delay. The current study explored this with measures of force steadiness (a functional outcome influenced by neuromuscular control) and application of iEMG finding that krill oil supplementation had no effect on force steadiness, firing rate or NMJ transmission instability at both 10% and 25% MVC but did observe an improvement in firing rate variability at 10%, but not 25%, MVC.

A possible explanation for this improvement in firing rate variability at 10% MVC builds on the observations that ageing is associated with greater variability in the common synaptic input to motor neurons (Castronovo et al., 2018) and that alterations in the strength of common synaptic input can lead to increases in firing rate variability (Castronovo et al., 2015). Previous data has shown that, LCn-3 PUFA, specifically DHA, likely enhance the effects of common synaptic input in the brain due to improvements in neuronal excitability, synaptic transmission, and neurotransmitter signalling (Metherel et al., 2024; Logan, 2003; DiNicolantonio & O'Keefe, 2020). Indeed, DHA may also help preserve central nervous system function during ageing,

thereby mitigating age-related declines in neuromuscular function (Boga & Basak, 2023; Turczyn et al., 2022) since it is the most abundant LCn-3 PUFA found in the brain (Petermann et al., 2022). These effects may collectively enhance the strength of common synaptic input, which in turn could reduce firing rate variability. Another possible explanation is that the reduction in firing rate variability may result from decreased synaptic noise (Kornatz, Christou & Enoka, 2005). Indeed, LCn-3 PUFAs have been shown to decrease random fluctuations in the transmembrane potential of neurons in perfusion studies, thereby stabilizing electrical activity (DiNicolantonio & O'Keefe, 2020) which in turn may improve the firing rate variability. Future studies are needed to confirm this speculation. It is possible that these changes in firing rate variability may contribute to the enhancement in knee extensor strength with krill oil as previous work has demonstrated a strong inverse exponential relationship (r^2=0.72 ± 0.07) between firing rate variability and muscle force (Moritz et al., 2005), indicating that more consistent motor unit firing can support greater force output.

Furthermore, the improvements observed in the current study could be attributed to the specific properties of krill oil. For example, krill oil contains EPA and DHA predominantly in phospholipid form, whereas fish oil contains these fatty acids in triglyceride form (Ulven et al., 2011). when krill oil supplements are compared to fish oil supplements, they produce similar increases in plasma EPA and DHA levels, but at a lower dose of EPA and DHA (Ulven et al., 2011). Furthermore, when krill oil and fish oil are compared at equivalent EPA and DHA doses, krill oil leads to a greater increase in the omega-3 index (Ramprasath et al., 2013). On top of this, krill oil contains bioactive compounds that may enhance muscle health, such as astaxanthin and choline (Moretti et al., 2020, Liu et al., 2018). These krill-specific bioavailability and compositional differences may have contributed to the observed improvements in firing rate variability and knee extensor strength in the current study, although this remains speculative without direct head-to-head comparisons.

As far as we know, this is the first study to measure motor unit function such as firing rate, firing rate variability, and NMJ transmission instability, using LCn-3 PUFAs supplementation such as krill oil in older adults. Therefore, it is difficult to compare these results with fish oil supplementation, since no published studies have measured these specific neuromuscular outcomes. This limits our ability to determine whether the observed improvements in firing rate variability at 10% MVC are specific to krill oil

or would be similarly observed with fish oil supplementation. Furthermore, direct comparison of knee extensor strength with previous studies is also challenging. Most studies included in the meta-analyses by Cornish et al. (2022) and Dam et al. (2025) presented their lower limb strength results as percentages rather than absolute values, and similarly, most of the included RCTs themselves reported lower body strength as percentages as well. This makes direct comparison to the absolute torque values (Nm) reported in the current study difficult. Additionally, the heterogeneity in strength assessment methods such as isometric versus dynamic contractions, different joint angles, and different equipment across studies adds to this difficulty. These findings highlight the importance of future studies that directly compare krill oil and fish oil supplementation using standardised neuromuscular assessment protocols, including both strength outcomes reported in absolute values and motor unit function measurements, to determine whether the observed benefits are specific to the krill oil or generalisable to LCn-3 PUFAs supplementation more broadly.

However, it is important to mention that the interpretation of the firing rate variability findings should be approached with caution. Of the three motor unit function outcomes measured at both 10% and 25% MVC (firing rate, firing rate variability, and NMJ transmission instability at each intensity), only one outcome showed a significant improvement: firing rate variability at 10% MVC. This raises the question of whether this finding represents a true physiological effect or could be attributed to statistical chance, particularly given the multiple comparisons conducted. With six separate statistical tests performed on motor unit outcomes, the probability of observing at least one statistically significant result by chance alone increases (Type I error). Future studies are needed to confirm and strengthen confidence in our results. Thus, this result should be interpreted as preliminary evidence requiring confirmation rather than definitive proof of krill oil's effects on motor unit function.

Novelty contribution

Although previous studies have shown conflicting results regarding LCn-3 PUFA supplementation and resistance exercise, the current study makes several important contributions that advance the field. First, most of existing studies showing conflicting functional outcomes have not examined the underlying mechanisms. The current study provides the first direct mechanistic evidence through iEMG assessment of

motor unit function. This mechanistic insight may explain why some studies show benefits while others do not. By identifying this mechanism, the current study moves beyond simply adding another data point to the conflicting functional outcome literature. Second, the current study confirms and extends recent meta-analytic evidence. Our findings are consistent with Cornish et al. (2022) and Phillips et al. (2024), demonstrating that LCn-3 PUFAs provide clinically meaningful improvements in lower limb strength (7.8% increase in knee extensor strength) that are neuromuscular in origin rather than due to muscle hypertrophy. This replication strengthens the evidence base whilst providing the mechanistic explanation that was previously lacking.

Third, the current study examines three novel elements. First, krill oil specifically (not fish oil), which has better absorption and additional bioactive compounds (Ulven et al., 2011; Ramprasath et al., 2013; Moretti et al., 2020). Second, home-based rather than gym-based exercise, which addresses real-world participation barriers (Burton et al., 2017; Dismore et al., 2020). Third, motor unit function characteristics including firing rate, firing rate variability, and NMJ transmission instability, which have not been previously examined in this context. The finding that only firing rate variability at 10% MVC improved (1 of 6 neuromuscular outcomes measured) raises the possibility of chance. However, this is unlikely for several reasons. First, the improvement was intervention-specific, occurring in the krill oil group only, not the control group. Second, it occurred alongside clinically meaningful strength gains exclusively in the krill oil group, providing evidence across multiple outcome levels. Finally, the established relationship between reduced firing rate variability and greater force capacity (Moritz et al., 2005) supports a mechanistic link rather than chance.

Taken together, the current study reconciles conflicting strength and functional outcomes in the literature by providing mechanistic evidence. The current findings confirm that LCn-3 PUFAs improve lower limb strength, as reported by Cornish et al. (2022), but not physical function or muscle mass. However, Dam et al. (2025) reported improvement only in physical function, particularly in chair rise test. The current study is the first to assess motor unit function using iEMG in this context. The current study identified firing rate variability as the specific neuromuscular pathway through which krill oil enhances muscle strength. Thus, the current study advances understanding from describing what happens (strength improves, as per Cornish et al.) to explaining

how it happens (via improved motor unit firing rate variability). This mechanistic insight, combined with findings being in agreement with Phillips et al. (2024) that benefits are neuromuscular rather than hypertrophic in origin.

Limitations

This study has a number of limitations. Firstly, the generalizability of these findings to people with sarcopenia is limited, as the current participants were considered healthy older adults. Secondly, we did not control participants' dietary intake for the exercise intervention period. Finally, there is a potential for reporting bias, as participants performed the exercises at home and self-reported their activity using exercise logs.

3.5 Conclusion

Taken together, the current study, alongside previous evidence, indicates that LCn-3 PUFA supplementation can result in small but clinically meaningful improvements in lower limb muscle strength responses to resistance exercise training and that these benefits may relate to concomitant improvements in neuromuscular function (Phillips et al., 2024). We speculate that the improvement in firing rate variability may result from the effects of LCn-3 PUFAs on enhancing the strength of common synaptic input and reducing synaptic noise.

CHAPTER 4: Enablers and barriers toward home-based resistance exercise for older adults: qualitative study.

4.1 Introduction

It has been predicted that in the UK the number of people who are over 65 years old will increase by 21.8% from 2019 to 2030 (Age-UK,2019). In 2019, 1 in 11 people in the world were over 65 years old, and it is expected that by 2050, this ratio will increase to 1 in 6. Ageing has many consequences, one of which is the progressive decrease in muscle mass and muscle strength and that occurs from approximately 40 years of age and can result in sarcopenia (Dodds et al., 2014, Cruz-Jentoft et al., 2019). Recent data estimates that between 10% and 27% of those over the age of 60 years of age globally have sarcopenia (Petermann-Rocha et al. 2022). Sarcopenia is associated with many adverse outcomes such as cardiac and respiratory diseases, an increase in mortality, falls and fractures and mobility issues which in turn may lead to the decreased quality of life and loss of independence (Cruz-Jentoft et al., 2019). Sarcopenia also has wide economic costs (Mijnarends et al., 2018) Indeed, older adults with sarcopenia are five times more likely to have high costs of hospitalization than older adults without sarcopenia. (Antunes et al., 2017). Additionally, it has been estimated that the excess health and social care cost related to muscle weakness was around £2.5 billion in 2018 in the UK. (Pinedo-Villanueva et al. 2019). It is clear, therefore, that preventing or delaying sarcopenia is vital for older people and wider society.

So far, no pharmacological treatment has been shown to be effective for management of sarcopenia (Cruz-Jentoft et al., 2019). There is, however, a large body of research demonstrating that resistance exercise, regardless of age, can increase muscle mass and muscle strength in older people and attenuate the manifold consequences of sarcopenia (Grgic et al. 2020, Fyfe et al. 2022, Manas et al. 2021). Resistance exercise is, therefore, recommended for older adults to both prevent and treat sarcopenia (Dent et al., 2018). Indeed, the World Health Organization recommends older adults perform moderate to high intensity muscle strengthening activities such as resistance exercises twice a week to improve their physical function (World Health Organization, 2020). Despite of this, very few older adults meet these recommendations. For example, in Scotland only 14% of men and 12% women who are over 65 years old

meet the UK guidelines for performing muscle strengthening exercise twice a week (Strain et al., 2016).

A previous systematic review suggests that the barriers for older adults to participate in resistance exercise included lack of equipment, available exercise program, access to exercise facilities, family and work obligations (Burton et al., 2017). In addition to the lack of understanding and awareness of the importance of resistance exercise, physical and psychological challenges such as the inability to perform resistance exercise due to the decline in physical strength associated with ageing, are also reported barriers by older adults toward resistance exercise (Hurst et al., 2023). Furthermore, a dislike of the gym environment and a fear of self-injury in the gym are other barriers for older adults preventing participation in resistance exercises (Dismore et al., 2020). Therefore, a pragmatic and feasible solution is needed to improve participation and adherence to resistance exercise. Home-based resistance exercises with minimal equipment may be a practical solution to overcome these barriers. Indeed, home-based resistance exercises can improve the physical ability and strength of older adults (Thiebaud, Funk & Abe, 2014). Moreover, home-based resistance exercises can enhance muscle strength, power, balance and can be performed safely (Manas et al. 2021).

Previous studies have explored motivators and barriers toward home-based resistance exercise in older adults, however, these studies have been limited in scope. Indeed, most studies have focused primarily on lower body exercises, with upper body exercises excluded (Fyfe et al., 2022, Tyldesley-Marshall et al., 2021, Arkkukangas et al., 2017, Jansons et al., 2023). Furthermore, all of these studies have examined home-based resistance exercise using only lower body weight exercises without equipment such as resistance bands, no previous study has comprehensively investigated the enablers and barriers specifically toward resistance band exercises combined with body weight exercises targeting both upper and lower body muscle groups. This represents an important research gap, as resistance bands offer several practical advantages for older adults, including low cost, portability, ease of storage, and adjustable resistance levels. It is worth noting that Jansons et al., (2023) specifically recommended that future research should investigate home-based interventions using minimal equipment such as resistance bands and should include upper body exercises, as older adults reported that having access to simple equipment

and being able to exercise multiple muscle groups were important motivators for adherence to home exercise. Even previous studies examining resistance band exercises have also shown limitations in their applicability to home-based resistance exercise. For example, Rathleff et al. (2017) investigated elastic band exercises in frail geriatric inpatients, however, this study focused on feasibility and adherence during short-term hospitalisation. Thus, the enablers and barriers toward home-based exercise were not explored. On top of this, the intervention in this study used elastic bands only, with body weight exercises being excluded. It is important to acknowledge that the hospital context differs substantially from home-based settings, as older adults performing exercises at home face unique challenges such as lack of supervision, environmental factors, and motivational barriers. Similarly, Davis et al. (2022) examined elastic band resistance exercises in older adults, however, their study was conducted in a laboratory setting as a single-session intervention. Furthermore, this study focused specifically on balance training and fall prevention rather than comprehensive resistance exercise program. It is worth noting that their intervention also used elastic bands only without body weight exercises and examined immediate perceptions in a supervised setting rather than exploring the enablers and barriers toward sustained home-based exercise participation.

Therefore, the current study addresses this gap by exploring, for the first time, the enablers and barriers toward a home-based resistance exercise intervention that combines both resistance bands and bodyweight exercises targeting both upper and lower body muscle groups in older adults. Although no statistically significant differences were found between the krill oil group and the control group in measures of physical function and muscle control in Chapter 3, a significant time effect was observed for several muscle strength and physical function outcomes indicating the potential effectiveness of this intervention to counteract or prevent sarcopenia in older adults.

However, it could be argued that the home-based resistance exercise intervention alone did not result in improvements in muscle strength. There are several factors that help to address this argument. Although the control group in Chapter 3 did not show improvements in muscle strength, improvements (time effect) were observed in physical function, including chair rise performance ($p<0.001$), gait speed ($p=0.051$), cadence ($p=0.014$), and force steadiness at 10% ($p=0.014$) and 25% ($p=0.003$) MVC.

This does indicate some, although small, effectiveness of the intervention. It is also worth noting that the study did not have a true no-exercise control group and so chapter 3 cannot, and indeed was not designed to, quantify the effects of the exercise intervention alone.

The functional improvements observed are unlikely to be explained by changes in muscle strength. It is more likely that these improvements are due to the characteristics of the training programme, including a greater number of lower-limb exercises, combined with an emphasis on high-speed movements during exercise (Cadore & Izquierdo., 2018). From this perspective, enhanced activation of fast-twitch muscle fibres and improvements in neuromuscular coordination may have contributed to the improvements in physical function (Lopes et al., 2016). It is important to acknowledge that even in the absence of strength gains, these improvements in physical function may be clinically meaningful, as they may help older adults maintain independence, improve quality of life, and reduce the risk of injury and falls. This is particularly relevant given that reduced physical function is a defining feature of severe sarcopenia according to the EWGSOP2 criteria. Therefore, the current exercise intervention may contribute to preventing progression to severe sarcopenia. Furthermore, the finding that home-based resistance exercise improved physical function without corresponding increases in muscle strength in healthy older adults has been found in other previous resistance exercise studies, including both supervised (Niyazi et al., 2024) and unsupervised interventions (Liang et al., 2024). These studies have shown improvements in physical function, balance, and falls risk, even in the absence of significant strength gains. This reinforces the functional relevance of such exercise programmes.

It is also important to acknowledge that the sample size in Chapter 3 was not designed to detect statistically significant differences in muscle strength outcomes. The study was powered to examine neuromuscular outcomes, particularly NMJ transmission instability, which represents a key novel contribution of this work and has not previously been assessed in this context. It is therefore possible that the absence of significant strength changes may reflect limited statistical power rather than a true lack of adaptation. Thus, a larger sample size may have detected significant changes in muscle strength, including in the control group.

The current Chapter aims to explore the enablers and barriers toward home-based resistance exercise for older adults.

4.2 Method

4.2.1 Study design

This qualitative study was part of the Krill Oil Resistance Exercise Ageing (KOREA) study, introduced in chapter 3 and was carried out in Glasgow, UK, from May 2023 to May 2024. (RCT study NCT05869513, ClinicalTrials. gov). Briefly, the KOREA study investigated whether krill oil supplementation enhances the effects of a pragmatic resistance exercise programme for 16 weeks on muscle strength, size, physical function and motor unit function in older adults. Ethical approval of the study was received from the College of Medical, Veterinary & Life Sciences Research Ethics Committee at University of Glasgow (200220084).

4.2.2 Participants

A subgroup of 10 participants (5 male and 5 female) from the 46 participants of the KOREA study were included in the current study. Participants in KOREA study were recruited through advertisements on social media platforms such as Nextdoor, Facebook, and Yammer, as well as via posters, flyers in local shops, and presentations at the University of the Third Age. The inclusion criteria to participate were aged 60 years and over and not participating in regular resistance exercise training. Participants were excluded if they had health issues such as diabetes, severe cardiovascular disease, seizure disorders and cancer. For more details see (Chapter 3). A participant information sheet, along with a brief explanation of the study by the researcher, was provided to potential participants and consent was obtained. A subgroup of 10 participants was invited to participate in the current qualitative interviews after completing the KOREA study. The invitations were extended to the first five males and females who completed the study and agreed to be interviewed.

4.2.3 Home-based resistance exercise intervention

Participants were asked to perform home-based resistance exercises using body weight and/or elastic resistance band exercises for 16 weeks. Participants were given 6 resistance bands of different resistance. Participants were also asked to perform 3 to 6 sets of 6 exercises per week, 3 for the upper limb and 3 for the lower limb (see appendix 4) with each set of the 6 exercises consisting of 8 to 20 repetitions. All the exercises were performed at vigorous intensity level, measured using the OMNI

perceived exertion scale (Buskard et al. 2019, Robertson et al. 2003). Participants were asked to perform these exercises to the point where they scored 4 to 5 (somewhat easy) in the first week, and 8 to 9 (hard) in the following weeks on the OMNI scale. Different difficulty options were given, and participants increased or decreased the difficulty level to reach an exertion score of 8 to 9 in 8-20 repetitions. The intervention was progressive meaning that intensity, and difficulty level, increased during the 16 weeks of the study. If the participant was able to perform more than 20 repetitions at an exertion score of 8 to 9 on the Borg scale, they were advised to move to the next difficulty level. Participants were advised that these exercises could be performed throughout the week at the participant's preference, such as in discrete sessions or split throughout the week. Initially all participants were shown the exercises and asked to perform them with the researcher (AA), who holds a master's degree in physiotherapy, to ensure they performed the exercises correctly. Additionally, participants were provided with an exercise manual (see appendix 5) that illustrated all the exercises in both visual and written forms, as well as YouTube video links sent to their email. Finally, participants were given an exercise log (see appendix 6) to track their adherence and progress.

4.2.4 Data collection

Data was collected through semi-structured interviews, which were conducted at the University of Glasgow face-to-face by the lead researcher (AA) between October and November 2023, following completion of the 16-week intervention period. In order to identify the enablers and barriers toward home-based resistance exercise, a semi-structured interview guide was developed based on the research aims and a review of relevant literature on enablers and barriers toward exercise participation in older adults (Burton et al., 2017; Hurst et al., 2023). The interview guide included 13 open-ended questions (see Appendix 7) designed to explore participants' motivations for participation and challenges encountered. The questions were designed to allow participants to share their experiences in their own words. Further questions were asked based on the participants' answers to explore emerging themes, clarify points, or obtain additional details (Braun & Clarke, 2021).

Each interview was digitally audio-recorded with participant consent and lasted approximately 25 minutes. Interviews were transcribed verbatim by 1st Class Secretarial Services, with all identifying information removed to ensure confidentiality.

4.2.5 Data analysis

Reflexive thematic analysis was used to analyse the data. This method is widely used in sport and exercise research (Braun, Clarke & Weate, 2016) and it provides a method to identify, analyse, and interpret patterns across the dataset. It relies on the researcher's subjectivity, which plays a key role in the analysis process (Braun, Clarke, 2021). Meaning is generated through the researcher's interpretation of the data, and the saturation point is determined by their judgment (Braun, Clarke, 2021). The current study used an inductive approach, where themes were developed and emerged directly from the data during the analysis process. Furthermore, in this approach, the researcher plays an active role in interpreting the data, and concepts such as “bias” are understood as part of the interpretive process rather than as threats to validity (Braun, Clarke, 2021). Therefore, the value of the findings lies in their transferability, that is, the extent to which readers may judge the findings to be relevant to other contexts, rather than in universal generalisability (Braun, Clarke, 2021). This does not mean that the study is without limitations; in particular, the findings cannot necessarily be generalised to other populations.

A key limitation of reflexive thematic analysis from quantitative perspective is that the findings are shaped by the researcher’s interpretation of the data, meaning that the generated themes do not represent objective truths but rather one possible interpretation (Braun & Clarke, 2021). As a result, different researchers may have identified alternative themes from the same dataset. However, within the reflexive thematic analysis approach, this subjectivity is acknowledged and considered an inherent and acceptable aspect of the method, provided it is clearly recognised and transparently reported (Braun & Clarke, 2021).

The six phases of reflexive thematic analysis were followed (Braun, Clarke, 2021). Analysis began with familiarisation with the dataset, where AA read and re-read each transcript multiple times during and after the transcription process. Following this was coding, where AA identified segments of the data that appeared interesting and generated initial codes using NVivo software. The coding approach was inductive, meaning codes were developed from the data rather than being driven by existing theoretical frameworks. However, as coding progressed, some codes were informed by the research question and existing literature on exercise adherence in older adults.

Initial themes were then generated by grouping codes that shared patterns of meaning. AA created individual visual maps to explore relationships between codes and experiment with different ways of organizing the data.

Themes were then developed and reviewed by examining them in relation to the coded extracts and the dataset as a whole. AA returned to the transcripts to check whether the themes were well-supported across the dataset. Some initial themes were merged when they represented similar ideas, while others were split when they included too broad a range of meanings. The previous phases were performed by AA. However, three authors, AA, SG, and GR refined, defined, and named the themes. Each theme was defined to articulate its scope and boundaries, and names were developed that captured what each theme was about. NVivo software was used to code the data and identify the themes.

4.2.6 Philosophical position and rationale for reflexive thematic analysis

This study was underpinned by a constructionist interpretivist epistemological position, which views knowledge and meaning as socially constructed and contextually situated rather than as objective truths waiting to be discovered (Braun & Clarke, 2021). From this perspective, participants' accounts of their experiences with home-based resistance exercise are understood not as direct reflections of a singular reality, but as sense-making shaped by their social, cultural, and personal contexts. The researcher's role is therefore not to uncover pre-existing truths, but to interpret and construct meaning from the data through an active, reflexive engagement with participants' accounts. This philosophical stance informed all aspects of the research design, from interview question development to the analytic process.

A qualitative approach was selected over a mixed-methods design as it was deemed most appropriate for addressing the research aim of exploring the enablers and barriers toward home-based resistance exercise in depth and from participants' perspectives. While quantitative approaches could identify what proportion of participants experienced specific motivator or barriers, a qualitative design allows for rich, contextualised understanding of how and why certain factors act as enablers or barriers, and the meanings participants attach to their experiences (Braun & Clarke, 2013). The depth of understanding provided by qualitative methods was particularly

important given the lack of previous comprehensive qualitative research on simplistic, minimal-equipment home-based resistance exercise interventions for older adults.

Reflexive thematic analysis was chosen as the analytic method for several reasons. First, reflexive thematic analysis is well-suited to constructionist epistemologies, as it acknowledges the active role of the researcher in theme development and recognises that themes are constructed through the researcher's engagement with the data rather than simply emerging from it (Braun & Clarke, 2021). Second, reflexive thematic analysis's flexibility makes it appropriate for exploratory research where the aim is to identify, analyse, and interpret patterns of meaning across a dataset (Braun et al., 2016). Third, reflexive thematic analysis was chosen over coding reliability approaches to thematic analysis as these align with post-positivist epistemologies that emphasise objectivity and replicability, values incompatible with our interpretivist stance that views researcher subjectivity as central to, rather than a threat to, quality analysis.

4.3 Results

Ten participants (5 male and 5 female) were invited to take part, and all completed a semi-structured interview. All participants were white British and aged between 61 and 81 years (mean age 67.8 years). Figure 4.1 displays our themes of enablers and barriers toward home-based resistance exercise. Five themes were identified from the reflexive thematic analysis: 1) Flexibility and simplicity of home-based resistance exercise (enabler), 2) Navigating commitment (enabler), 3) The perceived benefits of home-based exercise (enabler), 4) Learning home-based resistance exercise (barrier) and 5) Indolence and procrastination (barrier).

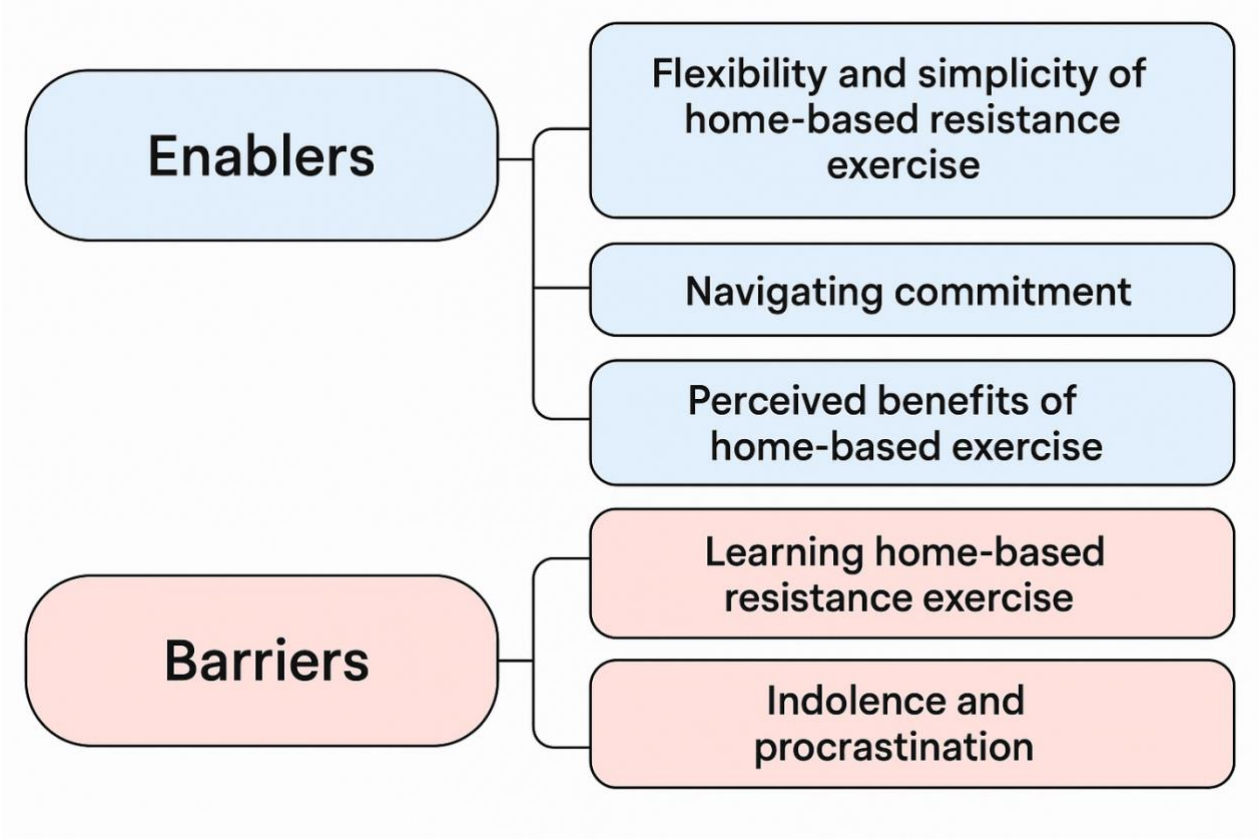

Figure 4.1 Enablers and barriers toward home-based resistance exercise.

4.3.1 Enablers toward home-based resistance exercise

Theme 1: Flexibility and simplicity of home-based resistance exercise

Participants regularly evoked the notion of the simplicity and flexibility of home-based resistance exercises as a key enabler to participate in such exercise. For example, many participants positively reported the clarity and explanatory nature of the instructions for performing the exercises as having contributed to making the exercises simple and easy to follow.

"It [home-based resistance exercise] was quite simple […] it was all very well explained […] and I found that quite straightforward" (male aged 62)

"I thought anybody, a youngster could do that and an old person can do that" (male aged 76)

Furthermore, simplicity and flexibility were also frequently characterized in terms of feasibility of home-based resistance exercises. Participants commonly described the exercises as not requiring special equipment or taking long to perform. Additionally, participants reported the notion that they were in control of when to exercise, with no need for further preparation. This, therefore, makes the exercises easier and more convenient to perform at home without any pressure.

"The resistance bands are great because you do them at home […] it's convenient to do. You don't need any special equipment. You don't need to get changed. You don't need to go anywhere to do it. You know, you've got the resistance bands at home. You pick them up, you do the exercise, and it's easy. Simple" (male aged 70)

"I think that it is easier doing it in the house [..] Just because you don't need to go out the house and it is easy enough just to do it if you have got five or ten minutes to do another […] it doesn't take too long. You don't need to put in time, make time, you can just do it every day" (female aged 63)

Furthermore, participants reported what they liked or found interesting about the resistance bands. Some participants mentioned that resistance bands were easy to access due to the flexibility of using them anywhere, as they are simple equipment.

Others expressed that the bands allowed for a variety of exercises to be performed, which was a positive.

"Having stuff lying around your house and you see it and you think, oh, I will do a couple of minutes of […] resistance bands […] I think exercise bands, from my small experience, I would think that is the way to go because you can use them all over the place, legs...I think, yes" (male aged 76)

In addition, some participants expressed that they like the resistance bands as they could easily control the resistance level as they progressed.

"I found with the resistance bands, you're in control of it […] I quite liked the idea you could then go up a band if you felt it was getting a bit too easy" (female aged 73)

Most participants expressed a positive feeling and enjoyment of performing resistance band exercises.

"I've discovered resistance bands, you know, and I've discovered that I enjoy using them" (male aged 70)

"I quite enjoyed it. Actually, I really didn't think I would enjoy it" (male aged 62)

"I enjoyed doing them [the resistance band exercises]" (female aged 62)

As a result of the simplicity and flexibility of home-based resistance exercises participants commonly emphasized the ease of performing home-based resistance exercises and how effortlessly these activities could be integrated into their regular routines and daily lifestyles. Indeed, some participants managed to perform exercises while traveling, and others did so during work breaks.

"You might be at home all day and think in the morning, oh, I will do some of that, and walk away from it. Then later in the day, afternoon, go back and do some more […] It is easy to do" (male aged 76)

"I took it [resistance bands] to Croatia with me and we're going away again before Christmas and that will be coming with me there" (male aged 66)

With home-based resistance exercise being characterised as simple and flexible, it is unsurprising that some participants reported that they would continue performing home-based resistance exercise after the study finish.

"I will continue to do it off my own bat because it is something I can do quite easily. I don't have to get dressed up in a tracksuit and go to a gym or do anything" (male aged 76)

Theme 2: Navigating commitment

It was clear from the data that participants shared a common motivator in the form of keeping to a commitment to perform home-based resistance exercises. Two key types of commitment were identified. The first commitment for some participants was the exercise log which participants linked with a sense of achievement, as it provided a sense of purpose, focus, and a record of their progress. Conversely, one participant found that not using the exercise log was associated with not adhering to this commitment.

"I think the fact I had to fill out a chart, that helped because I was filling it out and I was conscious if I had not done as many as I should." (male aged 62)

"I found that meant you were ticking off the exercise which was good, it gives you a focus and it gives you a purpose for it, which I liked […] I'm going to try and make up my own sheet, because I think you need that, you need to have a record of what you're doing, otherwise I think you just think, oh, I've done enough, and put it away." (female aged 73)

"Log, no, I forgot about that. I didn't start it, that was the trouble. If I'd started it, I probably would have kept to it" (male aged 64)

The second commitment expressed by some participants was the sense of responsibility toward the study and the concern to not negatively affect the study or the researcher.

"If I didn't have the discipline of trying to work for your study, I would probably have given up the exercises after the first week or two. It's only been the idea that there is someone else relying on me has motivated me to say, hey, this is not for you. This is for a study." (male aged 64)

"I knew that if I'm doing this for you, that's an extra motivation" (female aged 81)

Often participants reported a number of motivational strategies that assisted them to adhere to their commitments to complete the home-based resistance exercises. Establishing a daily routine of exercising where many participants consider the exercises as part of their daily activity. A specific time during the day was often designated by the participants to perform the exercises, which usually linked with other routine activities. For example, in early morning after breakfast, during tea break at work, while watching tv, at the end of the day with other activities like cleaning their teeth and putting in eye drops or even at holiday.

"It was more a case of, oh, god, I haven't done anything today, I should do something. What I do very often, […] Some channels have adverts, so what I tried to do was do the exercises when the adverts were on […] I could be sitting at home, even during the day or during the morning. I am going to have a cup of coffee I think, it is about time for a cup of coffee." Before I do that, I will do five minutes resistance" (male aged 76)

"I've fitted it in around my work and I feel the benefits of it […] sometimes at work during the day if I was on my tea break, I would maybe stand in the staff room and could do the press ups against the wall or just my calf raises" (female aged 61)

The exercise log was used by many of them as a reminder to perform these exercises. However, occasionally participants reported the resistance band left in sight and a personal diary as a reminder of their commitment to adhere to home-based resistance exercises.

"The chart [exercise log] just sat beside my computer. My computer in my spare room. I do a bit of online gaming, so it just sat there and that was the reminder to do." (male aged 62)

"Having stuff [resistance bands] lying around your house and you see it and you think, oh, I will do a couple of minutes of […] resistance bands." (male aged 76).

Theme 3: The perceived benefits of home-based exercise

Nearly all participants regularly evoked the idea that they can obtain benefit from home-based resistance exercises. The benefits included that it could build muscle strength and help with energy levels. Therefore, this building of muscle strength was seen by several participants as highlighting the value of home-based resistance exercises compared to other forms of physical activity.

"I just think it's [home resistance exercises] good that the fact that you can improve your muscle strength as you get older" (female aged 62)

"I felt it [home resistance exercises] gave me energy and made me feel better when I was going out to work" (female aged 61)

"I find that [home resistance exercises] more important now than dieting or doing aerobic exercise, I quite like the idea of feeling that you're trying to build some muscle which I think is important" (female aged 73)

Building on this another very common pattern in the data which was the necessity of home-based resistance exercises for older adults due to their benefits.

"It's still beneficial to do it [home resistance exercises]. Beneficial mentally, beneficial physically and it helps the aging process as well" (male aged 66)

"I've read about the benefits of strength exercising when you're older really. I think they've proved that it does help you" (female aged 62)

"I think any exercise as you get older is really beneficial" (female aged 73)

Thus, most participants emphasised the importance the physical benefits of home-based resistance exercise such as improving strength and balance as essential for maintaining independence in daily living as we age. The reverse was also stated by some participants who expressed fears about losing those physical benefits and being physically unable to perform such activities.

"I am thinking my life, I can do things better and longer if I keep to these simple exercises, resistance bands." (male aged 76)

"I like to keep strong, you know. You know just to do everyday things." (male aged 70)

"What happened in my family with my uncle who's only eight years older than me, and a big strong man and needing to be lifted up out of a chair to stand up, it's like, I need to pay attention, I don't want to be like that. […] I don't want to be falling down, I don't want to not be able to walk." (female aged 81)

Individuals seeing their own results for grip strength, muscle thickness and the sit to stand test, was noted as a motivation for many participants to continue to perform home-based resistance exercise.

"I think you having told me the results it's given me motivation to continue doing it" (male aged 70)

"If you said that my strength had improved in some of the things then I think it would be worth keeping going and doing these things regularly." (male aged 66)

Some participants also noticed a physical improvement in their daily living activities, which motivated them to keep performing the home-based resistance exercises.

"I noticed I was walking better – ah, my walking speed improved, I go up from Guy's is quite hilly and what was a 20-25 minute walk became a 15 minute walk [..] I think it's [home resistance exercises] imperative, because I've seen the difference" (female aged 81)

"I think I would continue [home resistance exercises], maybe not as many […] Because I feel the definition in my arms […] So, I can feel, definitely a difference in my arms." (female 61)

Conversely, noticing weakness in muscle strength or having a preconceived notion about losing muscle strength or mass with age motivated many participants to perform home-based resistance exercises. This idea was expressed and described in many different ways such as *"strength"*, *"to be strong"*, *"keep toned"* and *"keep fit".*

"The reason I wanted to participate in this was that I noticed that I was losing strength, I wasn't as strong as I used to be, I've noticed that over the last two years" (female aged 61)

"I'm going to keep doing the exercises. Because there's a lot of evidence that you lose muscle mass as you get older" (male aged 62)

"The main motivation for doing them [home resistance exercises] is to keep fit, and keep, you know keep toned" (male aged 70)

Some participants were motivated by gaining some physical benefits and protection against health issues that might occur due to a sedentary lifestyle or obesity, sometimes described as the desire to be in good shape or to lose weight.

"If I was to work in an office, I think I would be more concentrating, thinking about I have to go out there and do something[exercises]." (male aged 76)

"If I tend to put a few inches on, you know, round my waist and then that encourages me to do it again […] I like to try and keep in good shape, you know. I like my clothes to fit." (male aged 70)

In order to obtain these benefits from home resistance exercises some participants stated that it needs to be done properly and regularly.

"How well I'm doing the exercises, that would affect how much it will help" (male aged 64)

"Our muscles all deteriorate if we don't look after them […] I have realised […] that I really have to...just a few minutes a day doing something, but you have got to do it on a regular basis." (male aged 76).

As a consequence of the benefits that home-based resistance exercises can provide, some participants express their commitment to continue to perform it.

"It's [home resistance exercises] making me feel stronger that I would continue to do it." (female aged 61)

"The resistance band is still worth having because you need to do that little thing every day, it's beneficial in itself." (male aged 66)

Other participants expressed their enjoyment of the home-based resistance exercises.

"I think to have a few exercises that you can go and do that you know that you are going to benefit from would be a great thing" (male aged 76)

"I enjoyed doing it for the benefit that it brought me" (male aged 66)

4.3.2 Barriers toward home-based resistance exercise

Theme 4: Learning home-based resistance

In almost all participants, this was the first time they had used resistance bands, and one participant took a step forward by reading about the resistance bands to learn more.

"The resistance band, I'd never done that before" (male aged 66)

"I've always done resistance exercises but not with bands" (male aged 70)

"I've read a lot about it, and I even know, like, if you go to a physiotherapist and you've got an injury, they'll give you bands to…so, it must help you improve." (female aged 62)

Some participants highlighted their unfamiliarity with resistance bands and that it took some time to get used to, reporting some challenges and difficulties performing the exercises at first. However, this barrier was overcome by taking time to get used to the resistance bands and acquiring the skills to use them properly.

"I'm new to this [resistance bands], I have to give myself time to get used to it" (female aged 81)

"The calf one, I found that difficult at first" (male aged 62)

After 4 months of using the resistance bands, participants had varying perspectives about exercising with the resistance bands. The majority of the participants found it challenging due to the bands having different resistance levels, with variation between the different exercises. One participant realised that the resistance bands were not suitable for him due to his shoulder pain, with body weight exercises being a better choice.

"I didn't think they [resistance band exercises] were easy. I thought they were…they were quite hard. I was breathless at the end of some of them" (female aged 62)

"Because the resistance band had its problem, with my shoulder primarily […] I felt I would be doing the exercises more correctly by using the body weight system rather than the resistance band" (male aged 64)

Some participants found the resistance bands easy for certain exercises. Participants reported the reasons as the strength of their leg muscles made the leg press against the bands too easy. However, some of them demonstrated persistence to address this challenge by folding the band over *"doubled"* in order to add additional resistance. Others decided to ignore this issue which led them to reflect and express regret that they did not put in extra effort.

"That [leg press] was too easy to do because the weight and power in your legs it was easy to push it forward […] I can double up your hardest band […] to make it hard for me" (male aged 76)

"Some of the exercises were quite easy, even although I did go up a band […] you can feel the resistance a wee bit […] I've ticked the boxes and then that's it finished for today, but I didn't feel maybe I had pushed myself" (female aged 73)

Theme 5: Indolence and procrastination

Many participants expressed the barriers of indolence and procrastination, both implicitly and explicitly. This was expressed less frequently explicitly in ways such as "*my personal laziness" and "I'll do it later"* but more frequently was expressed implicitly in ways such as *"my mental attitude"*, *"boredom"* and *"cognitive thing"*, however, almost all of them expressed that this barrier can be addressed.

"Just my personal laziness. That's something we all have to overcome […] it's a barrier, but it's I can overcome it […] sometimes you think […] I'll do my exercises, I'll leave it for a, I'll do it later." (male aged 70)

"My mental attitude […] if I'm going to be stubborn and not do it, it's like…I've been talking recently with a couple of people and they're describing things and it's like, but you've just told me what you don't like about your life but you're not doing anything about your life." (female aged 81)

Some participants reported factors contributing to indolence and procrastination. For example, home-based resistance exercises may interfere with daily activity and be seen as a burden.

"I have flats to look after, my wife wants me to do some work in the house. It's late and I'm tired and I'm fed up and want to go to bed and as I say, human nature says, I'll do it tomorrow." (male aged 64)

"I could imagine for some people there might be a barrier because it [home resistance exercises] imposes on their day." (male aged 66)

Another contributing factor to indolence and procrastination was a fear of commitment while others reported the exercise routine may become boring, though this was mentioned less frequently.

"The worst thing you can do, in my experience, is fear it [commitment to exercises]. You or feel as though you don't want to do it [home resistance exercises]." (male aged 66)

"I think maybe eventually the routine of it [home resistance exercises], I think you really have to find a way of changing it about a bit […] so that you don't get bored with thinking, you know, another year's time I'm probably thinking, well, I've done these." (female aged 73)

Sometimes this indolence and procrastination led some participants to try to fit home-based resistance exercises into a limited amount of time, usually at the end of the day. This may result in feeling the exercises were physically exhausting. Eventually this may lead to the participants not performing the exercises.

"If you had a busy week and you were out two or three days and then you were trying to cram in, that was the only thing, is trying to make sure that you try to space it out over the week, even when you were out.[…] because sometimes at night you're too tired to do them" (female aged 73)

"If I came back from Edinburgh, last bus, 11 o'clock […] get home by about 1:20 in the morning, then have something to eat, and then think, it's 2:30, I'm going to bed [not doing the exercises]" (male aged 64)

4.4 Discussion

The present study explored the enablers and barriers towards home-based resistance exercises in older adults. From our interviews, we identified five key themes: 1) Flexibility and simplicity of home-based resistance exercise (enabler), 2) Navigating commitment (enabler), 3) The perceived benefits of home-based exercise (enabler), 4) Learning home-based resistance exercise (barrier) and 5) Indolence and procrastination (barrier).

In accordance with the present results, previous studies have demonstrated that the flexibility of home-based resistance exercise (lower limb body weight exercises) was an enabler to participate in such exercise (Jansons et al., 2023). In the current study the flexibility and simplicity of home-based resistance exercise, such as being easy to follow, not taking long to perform and their ease of integration into daily routines, was reported by participants as a positive, and this is consistent with previous studies. For example, Arkkukangas et al. (2017), in their qualitative study, explored the experiences of older adults participating in the Otago exercise program, which is combination of strength, endurance and balance exercises, at home. Participants reported that they found the exercises easy to follow and perform, easy to integrate into daily routines, and that they could be done at any time throughout the day.

Similarly, Jansons et al., (2023) reported that older adults performing lower limb body weight exercises at home reported that the exercise was flexible due to their ability to be integrated into routine activities and completed at any time of the day, and they did not require a significant amount of time. Many participants in the current study viewed the home-based resistance exercises as easy to follow and perform, and reported they were feasible as they did not require special equipment or take long to perform. Indeed, our findings are also supported by previous work from Simek et al., (2015) who suggested that older adults prefer home exercise programs that are structured with simple and easy exercises, fit into their daily routine, and are time efficient. Participants in the works of Simek also valued autonomy, such as the ability to choose when, how long, and which exercises to perform, criteria which the current resistance exercise program fulfils.

Our finding was in agreement with earlier studies which found that older adults using resistance bands consider them as simple easy to use equipment (Rathleff et al.,

2017). Additionally, in the current study, most participants expressed a positive feeling and enjoyment toward exercising using resistance bands, a finding previously reported by Rathleff et al., (2017) and Davis et al., (2022). For older adults to view physical activity as engaging, it needs to be enjoyable (Davis et al., 2022) and this may also contribute to participants indicating they would continue home-based resistance exercises.

Several participants reported that they liked that they could easily control the resistance level of the resistance bands as they progressed. This gradual increase in the difficulty of the physical activity interventions may improve older adults' motivation to exercise (Phillips, Schneider & Mercer, 2004, Davis et al., 2022) and progressing at their own pace can in turn improve their engagement in physical activity (Boulton, Horne & Todd, 2018) and allow older adults to exercising within their capabilities (Phillips, Schneider & Mercer, 2004). Our findings, supported by a previous study on home-based lower limb exercises for older adults suggested that future studies of home-based exercises should provide exercise equipment such as resistance bands to promote physical improvements, motivation, and adherence to home-based exercises (Jansons et al., 2023).

Some participants in the current study reported they would continue performing home-based resistance exercises after the study ended. This is likely linked to the self-efficacy theory, where people who feel confident in performing behaviours are more likely to engage in and persist with them (Bandura, 1977). In this context, in the current study the home-based exercises were, as mentioned previously, viewed by the participants as easy and simple, which likely increased their self-efficacy, although we did not measure this in the current study. We contend that this sense of confidence made the exercises feel achievable, motivating participants to continue. Indeed, it has previously been shown that higher self-efficacy in older adults is a significant predictor of engagement in physical activity (Perkins et al., 2008).

Other motivators were identified in this study, such as navigating commitment. This finding was also reported by Walker, Valentiner & Langberg, (2018) who found that committing was a motivation to initiate physical activity in patients with type 2 diabetes. Participants in the current study identified the exercise log as helping to provide them with such a commitment. Likewise, Arkkukangas et al., (2017) found an exercise diary encouraged older adults to perform the prescribed exercises. Also, the participants in

the current study employed other motivational strategies to help them adhere to the exercises like the exercise log, personal diary and leaving the resistance bands in sight. All of which were strategies such as reminders, nudges and cues that can promote the formation of habit (Hagger et al., 2020). Furthermore, it has been suggested that there are two dimensions of commitment to exercise behaviour “want to” and “have to” (Wilson et al., 2004). Our participants were motivated by “have to” commitment, which was driven by an obligation and sense of duty to submit the exercise log to the researcher and completing the study requirement of exercises. They were also motivated by the “want to” commitment which was driven by the satisfaction and enjoyment of discovering the resistance bands and the benefit of home-based resistance exercises, as mentioned previously. This 'want-to' commitment can significantly predict continued exercise behaviour (Wilson et al., 2004). Successfully changing behaviour requires shifting commitment into a new routine of daily activities (Walker, Valentiner, & Langberg, 2018) - a shift our participants have already made by adhering to home-based resistance exercises and establishing a daily exercise routine.

The current findings of the self-reported benefits of home-based resistance exercise are consistent with previous studies where older adults reported that home-based exercises were associated with benefits such as building muscle strength and improving energy (Fyfe et al., 2022, Tyldesley-Marshall et al., 2021, Arkkukangas et al., 2017, Jansons et al., 2023). Many of our participants not only viewed the home-based resistance exercises as necessary for older adults, due to their benefits but also noted that they need to be done properly and regularly. This finding is contrary to a previous study in which frail older adults lacked an understanding of the benefits of resistance exercises (Hurst et al., 2023), possibly due to the fact that only one participant had previously engaged in regular exercise, whereas in the current study, many participants had performed exercise prior the study. This knowledge of the benefits of home-based resistance exercises led some participants in the current study to express their commitment to continue to perform home-based resistance exercises to achieve the benefits. Moreover, the current research was consistent with previous studies where it was found that participants were motivated by the physical benefits of home-based resistance exercise such as improvements in strength, balance, walking (Burton et al., 2017, Jansons et al., 2023) and being independent with increasing age (De Groot, Fagerström, 2011). This is likely to be related to the health beliefs model

where one is likely to engage in a particular health behaviour if they obtain benefits from it (Janz, Becker, 1984).

In the current study, participants were also motivated to continue performing home-based resistance exercise after seeing their results, whether positive or negative. Previous studies support the importance of designing exercise programs that allow participants to see and monitor their progress which in turn, motivates them to continue exercising. (Cooper et al., 2022, Valenzuela et al., 2018). This is an important issue for future research, as well as for healthcare providers who may want to consider providing portable devices for measuring strength or physical function when designing or prescribing home-based resistance exercise programs.

Learning home-based resistance exercise was a barrier that most participants reported overcoming. Additionally, most found resistance band exercises challenging, while some did not. This aligns with a study by Davis et al. (2022), which found that resistance band balance exercises were appropriately challenging for most older adults, though some did not share this view. In the present study, some participants felt they did not exert extra effort to make the exercises more challenging. Similarly, Davis et al. (2022) noted that some participants, upon reflection, felt the sets and repetitions could have been increased.

In the current study one of the reported barriers toward participation in home-based resistance exercise was indolence and procrastination, which is in line with previous studies. Cowan, Nash & Anderson-Erisman, (2012) found indolence was the 9th most prevalent barrier toward exercises in spinal cord injury participants, although it was the most impactful barrier toward exercise, with participants who report this as a barrier being 19 times less likely to engage in exercise. On top of this, procrastination has previously been reported to be associated with poor engagement in wellness behaviours, including exercise (Sirois, Melia-Gordon & Pychyl, 2003), although it can be overcome by improving self-efficacy (Sirois, 2004). As reported earlier, the flexibility and simplicity of the current home-based resistance exercise may help participants to improve their self-efficacy and overcome these barriers. On top of that, our participants report that the barriers of indolence and procrastination can be overcome, for example, by taking immediate action of exercising as soon as the thought comes to your mind. Our findings highlight the importance of ensuring home-based resistance exercise

programs are flexible and simple which in turn can help participants develop self-efficacy to overcome barriers like indolence and procrastination. Additionally, our home-based resistance exercise intervention seems to be an effective solution to counteract other common barriers for older adults to engage in resistance exercises such as time constraints, the complexity of the exercises, restricted access to facilities and cost (Burton et al., 2017).

Novelty contribution

The present study provides qualitative insight into participation in home-based resistance exercise among older adults by exploring key enablers and barriers. To the authors knowledge, this is the first qualitative study to specifically examine a home-based resistance exercise programme that combines resistance band with body weight exercises targeting both the upper and lower body in older adults. Previous qualitative research in home-based resistance exercise has predominantly focused on lower limb exercises alone. Therefore, the present findings extend existing literature by examining a broader and more adaptable home-based resistance exercise approach.

Overall, the findings indicate that home-based resistance exercise combining resistance bands and body weight exercises is perceived as feasible, acceptable, and enjoyable by older adults. Participants valued the flexibility and simplicity of the programme, including the ability to perform exercises at home, integrate sessions into daily routines, and exercise with minimal equipment and time commitment. These features appeared to reduce perceived barriers to participation and supported continued engagement with the programme. The inclusion of resistance bands alongside body weight exercises was viewed particularly positively, as it allowed participants to regulate exercise intensity and progression according to individual capability. This adaptability appeared to enhance confidence and enjoyment, which may, in turn, support adherence. Participants also described developing a sense of commitment to the programme.

Finally, the study highlights the motivational importance of feedback and perceived progress in home-based resistance exercise. Participants described increased

motivation associated with monitoring change over time, suggesting that simple and portable assessment tools may enhance engagement. This finding has practical implications for the design of home-based interventions and adds to the literature by linking feedback mechanisms with motivation and adherence in older adult populations. Taken together, these findings suggest that a home-based resistance exercise programme incorporating both resistance band and body weight exercises is feasible and enjoyable for older adults and may support adherence. However, further research is required to assess long term adherence for this home-based resistance exercise programme.

4.5 Conclusion

In the current study, older adults found the flexibility and simplicity of home-based resistance exercise in addition to its perceived benefits such as receiving feedback on their results and a sense of commitment as key enablers to participate in such exercises. Learning home-based resistance exercise as well as indolence and procrastination were barriers to participating in home-based resistance exercises. However, these barriers were successfully addressed by the participants. Future studies and healthcare providers, such as physiotherapists and other exercise specialists, should focus on combining body weight exercises with resistance bands and providing portable devices, like grip strength measuring devices, when they design or prescribe home-based resistance exercise, to enhance engagement in these exercises.

CHAPTER 5: General discussion

This general discussion aims to integrate the findings of the three studies presented in Chapters 2, 3, 4 to provide a comprehensive overview of the thesis. The aim of Chapter 2 was to investigate the associations of n-3 fatty acid intake with handgrip strength and muscle mass indices in older adults and whether these associations differed by physical activity status. Chapter 3 aimed to determine whether krill oil supplementation enhances the effects of a pragmatic home resistance exercise programme on adaptations in muscle strength and size, physical function and motor unit function in healthy older adults, Furthermore, the aim of Chapter 4 was to explore the enablers and barriers toward this home-based resistance exercise intervention.

Summarising the main findings of this thesis, although n-3 fatty acid intake was positively associated with handgrip strength index in older women, regardless of physical activity status, but not in men, the magnitude of this association was very small and unlikely to be clinically relevant. Additionally, n-3 fatty acid intake was not associated with muscle mass index. These findings indicate that supplementation strategies may be required to improve muscle strength and size. Following this, chapter 3 demonstrated that krill oil supplementation can result in small but clinically meaningful improvements in lower limb muscle strength responses to resistance exercise training, which itself had broad benefits, and that these effects may relate to concomitant improvements in neuromuscular function. We speculate that the improvement in motor unit function particularly, firing rate variability may result from the effects of LCn-3 PUFAs on enhancing the strength of common synaptic input and reducing synaptic noise which in turn may improve the muscle strength. Finally, this thesis found that older adults were motivated to participate in the home-based resistance exercise because the perceived benefits of this exercise such as receiving feedback on their results, their sense of commitment and the flexibility and simplicity of such exercise. Learning home-based resistance exercise as well as indolence and procrastination were both barriers that participants were able to overcome.

The data from chapter 2 showed n-3 fatty acid intake positively associated with handgrip strength index in older women, regardless of their physical activity status, but not men and not associated with muscle mass index in older adults. The findings are in agreement with other findings in the literature, such as Bae et al. (2022), who investigated the associations of EPA and DHA intake with lower handgrip strength in

older Koreans. They found no association between EPA and DHA intake and grip strength in older men. However, older women who met or exceeded the adequate intake (150 mg/d for women aged 65 to 74 years and 140 mg/d for women aged 75 years) had 32% lower odds of reduced grip strength compared to older women consuming EPA and DHA below the adequate intake. Several biological mechanisms may explain these sex-specific differences. First, women appear to incorporate EPA and DHA into plasma and muscle phospholipids more efficiently than men. This may enhance membrane fluidity and signalling involved in muscle contraction and neuromuscular function (Caslake et al., 2008; Giltay et al., 2004). Second, estrogen affects n-3 fatty acid metabolism. Indeed, women have higher DHA concentrations due to estrogenic effects on fatty acid metabolism and enzyme activity (Giltay et al., 2004). Third, women have a higher prevalence of sarcopenia compared to men (Janssen et al., 2019). This is due to lower baseline muscle mass and strength throughout their lifespan, which in turn may lead to functional impairment and physical disability (Janssen et al., 2019). Thus, creating greater potential for improvement from supplementation. However, the evidence remains limited due to methodological issues. Indeed, most RCTs, including the study in Chapter 3, have not been adequately powered to examine sex-specific differences (Alkhedhairi et al., 2022; Smith et al., 2015). Furthermore, many trials have not reported sex-stratified analyses. Therefore, large-scale RCTs with adequate power and pre-specified sex-stratified analyses are needed before sex-specific clinical recommendations can be made.

The lack of the association between n-3 fatty acid intake and muscle mass index in older adults is consistent with a systematic review and meta-analysis by Esteves et al. (Esteves et al., 2023) who investigate the effect of n-3 fatty acid supplementation on muscle mass, function and strength in healthy older adults and young. They found no effect of n-3 fatty acid supplementation, with some studies including concurrent exercise interventions, on muscle mass in young and older adults. Although the study in chapter 2 found a positive association between n-3 fatty acids and grip strength index in older women, the effect size was very small. Thus, these findings suggest that within the normal dietary intake range the associations between n-3 fatty acid intake and grip strength are not clinically relevant, with no associations with muscle mass. It may be that increases specifically in EPA/DHA intake, with the current measure or n-3 fatty acid intake, in the range seen in supplementation studies is needed to stimulate increases in muscle strength and mass in older adults.

Although physical activity status did not appear to influence the association in chapter 2, it is important to highlight that among various types of physical activity, resistance exercise is the most effective intervention for enhancing muscle strength and size in older adults (Giallauria et al., 2015), particularly progressive resistance training (Liu & Latham, 2009). Moreover, data show that although many older adults in the UK meet the general physical activity and muscle strengthening recommendations, a substantial proportion are not actually engaging in resistance-based exercises. Since the UK Biobank physical activity data included a broad range of activities, only one of which is resistance training, it is likely that many participants were not regularly performing resistance exercise. Therefore, incorporating resistance training such as home-based resistance exercise into RCTs study design in chapter 3 were necessary to confirm its specific effects.

Our results in chapter 3 align with previous evidence from a review (Phillips et al., 2024), which indicates that LCn-3 PUFA supplementation can lead to small but clinically meaningful improvements in lower limb muscle strength, but not in muscle size or physical function, in response to resistance exercise training. These benefits may be attributed, at least in part, to concomitant improvements in neuromuscular function (Phillips et al., 2024). This finding is also consistent with the results from chapter 2, where no association was found between n-3 fatty acid intake and muscle mass index in older adults. Although the findings from chapter 3 did not show a statistically significant improvement in grip strength with krill oil supplementation combined with resistance exercise, it is worth noting that the krill group experienced a 2.7 kg increase in grip strength (SD = 0.76 kg) over 16 weeks, compared to a 0.3 kg increase (SD = 0.58 kg) in the control group (p=0.07). This may suggest a potential effect, but the relatively small sample size meant the study lacked statistical power to detect a significant difference. Importantly, the 2.7 kg increase in grip strength is roughly equivalent to the decline typically observed over a five-year age span (from age 60 to 65), based on previous data (Dodds et al., 2014). Thus, this change may still be considered clinically meaningful, even though the MCID for grip strength has been reported to be around 5–6.5 kg (Bohannon, 2019). These results may support the findings from chapter 2, where n-3 fatty acid intake was positively associated with handgrip strength index in older women. However, in contrast to chapter 2, the results from chapter 3 included both men and women. While sex differences have been observed in previous studies, it is important to note that most randomized controlled

trials to date (including the one in chapter 3) have not reported sex-specific differences in the effects of LCn-3 PUFA supplementation on muscle strength (Alsowail et al., 2024). Moreover, none of these trials have been adequately powered to examine such differences (Alkhedhairi et al., 2022; Smith et al., 2015).

The current thesis also investigated the underling mechanism of the improvement in muscle strength by LCn-3 PUFA. As mentioned previously LCn-3 PUFA may lead to improvements in neuromuscular function which in turn may results in improvements of muscle strength (Gray, Mittendorfer, 2018, Phillips et al., 2024). This thesis has demonstrated that krill oil supplementation with home-based resistance exercise can improve firing rate variability which in turn may enhance muscle strength. We speculate that the improvement in firing rate variability may result from the effects of LCn-3 PUFAs on enhancing the strength of common synaptic input and reducing synaptic noise. It is worth noting that other mechanisms are likely involved, as it is doubtful that the change in firing rate variability alone accounts for all the observed increases in muscle strength. Taken together, the findings in chapter 3 may highlight the importance of adding of LCn-3 PUFA supplementation, such as krill oil, alongside home-based resistance exercise to prevent or counteract the adverse effects of sarcopenia in muscle strength. Furthermore, the choice of krill oil in the current thesis can be explained by several factors since most previous studies used fish oil. There is a key difference in molecular form between krill oil and fish oil. In fish oil, omega-3 fatty acids are mainly bound to triglycerides. However, in krill oil, 30-65% are bound to phospholipids (Ulven & Holven, 2015). Phospholipids can be directly incorporated into cell membranes, whereas triglycerides require breakdown before absorption. Studies on absorption have shown better LCn-3 PUFA absorption from krill oil at lower doses. Indeed, a network meta-analysis of 26 studies found that at dosages under 2000 mg daily, krill oil showed better absorption, with phospholipid formulations showing the highest values (Hoang et al., 2024). Schuchardt et al. (2011) reported that following a 1680 mg EPA+DHA dose, krill oil showed the highest incorporation into plasma phospholipids compared to fish oil. This enhanced absorption has important implications. Phospholipid-bound LCn-3 PUFA may more effectively modify membrane composition, which may influence receptors, ion channels, and signalling pathways relevant to muscle function. Furthermore, phosphatidylcholine may support neuromuscular function by contributing to acetylcholine synthesis Hayman et al.,

2024). This may also be relevant to the motor unit firing rate variability improvements observed in Chapter 3.

Although no statistically significant differences were found between the krill oil group and the control group in measures of physical function (such as chair rise, gait speed, and cadence) and muscle control, such as force steadiness, a significant time effect was observed for several measures of strength, physical function and force steadiness. This highlights the importance and effectiveness of resistance exercise as an intervention to counteract sarcopenia, particularly in improving physical function and muscle control in older adults, regardless of supplementation, since resistance exercise alone can lead to meaningful improvements over time.

However, as mentioned earlier, many older adults do not participate in such exercises (Strain et al., 2016). Several barriers contribute to this low participation rate, including limited access to gyms, lack of equipment, and a general dislike of the gym environment (Burton et al., 2017; Dismore et al., 2020). Thus, the home-based resistance exercise program used in chapter 3 can be considered a pragmatic and feasible solution. Therefore, in chapter 4, the enablers and barriers experienced by older adults toward such exercise were investigated. This thesis found that the flexibility and simplicity of home-based resistance training, along with perceived benefits such as receiving feedback on their results and a sense of commitment, were key enablers for participation. Conversely, learning home-based resistance exercise as well as indolence and procrastination were barriers to participating in home-based resistance exercises. However, these barriers can be overcome. Thus, the data from the thesis support a recommendation that healthcare providers, such as physiotherapists and other exercise specialists, focus on promoting home-based resistance exercise by incorporating body weight movements, resistance bands, and portable tools like grip strength measuring devices when designing or prescribing programs. This approach may enhance engagement and adherence among older adults.

5.1 Limitations

This thesis has several clear limitations. First, in chapter 2, although UK Biobank participants may represent the general United Kingdom population, there is a

possibility of a ‘healthy volunteer’ selection bias, as participants tend to have a lower frequency of disease and are less likely to be obese (Fry et al., 2017). Second, causality cannot be established in chapter 2 due to the cross-sectional design. Third, participants’ dietary intake was not controlled during the exercise intervention period in chapter 3. Fourth, there is a potential for reporting bias, as participants performed the exercises at home and self-reported their activity using exercise logs in chapter 3. Finally, an important limitation of the present thesis is that the studies were conducted in healthy older adults rather than individuals diagnosed with sarcopenia. This approach was influenced by several practical considerations. Recruitment of individuals with sarcopenia can be challenging, as this population often presents with multiple comorbidities, mobility limitations, and reduced capacity or willingness to participate in research studies. Indeed, previous research has reported difficulties in recruiting participants with sarcopenia for intervention-based studies (Phu et al., 2019). Second, the time constraints of a PhD limited the feasibility of recruiting a sufficient number of individuals with sarcopenia within the available timeframe. Therefore, the present thesis focused on healthy older adults as a preventative approach. It is important to acknowledge that prevention is a key strategy in the context of sarcopenia (Dent et al., 2018). Indeed, once sarcopenia is established, reversing muscle loss becomes more difficult due to anabolic resistance and other age-related physiological changes (Breen & Phillips, 2011). Therefore, targeting healthy older adults before substantial losses in muscle strength and mass occur is essential for the prevention of sarcopenia. The current findings suggest that krill oil supplementation combined with home-based resistance exercise may be a potential prevention strategy to counteract sarcopenia and prevent older adults from developing the condition. However, whilst the findings from healthy older adults provide evidence for prevention strategies, the magnitude of effects in individuals with established sarcopenia remains uncertain.

5.2 Future studies

There are several important areas for future research that have emerged from the findings and limitations of this thesis. First, large RCTs in different populations, such as older adults diagnosed with sarcopenia, are needed to confirm the effects of home-based resistance exercise combined with krill oil supplementation on muscle strength, size, physical function, and motor unit function. Second, large RCTs with sufficient power are needed to investigate potential sex differences in the effects of LCn-3 PUFA

supplementation on muscle strength. Third, further studies are required to confirm the role of neuromuscular function, particularly motor unit function, underlying improvements in muscle strength resulting from LCn-3 PUFA supplementation and to investigate other potential mechanisms involved. Fourth, studies with larger sample sizes and adequate statistical power are necessary to detect meaningful differences in grip strength. Finally, future research should explore the use of home-based resistance exercise programs with portable devices for measuring strength or physical function, in order to investigate adherence to such interventions.

5.3 Conclusion

This thesis has demonstrated that the magnitude of the association between n-3 fatty acid intake and grip strength index in older women, regardless of their activity status, was unlikely to be clinically relevant. Thus, supplementation with LCn-3 PUFAs, particularly krill oil, combined with home-based resistance exercise may offer small but clinically meaningful improvements in muscle strength and motor unit function. This thesis also provides further insight into the underlying mechanisms of neuromuscular function in relation to muscle strength. Furthermore, home-based resistance exercise was found to be both feasible and motivating for older adults. These findings support the implementation of combined LCn-3 PUFA supplementation and home-based resistance exercise as a potential strategy to counteract the adverse effects of sarcopenia.

Appendices:

Appendix 1:

In the United Kingdom, a very large general-population cohort study, known as the UK Biobank (http://www.ukbiobank.ac.uk), was conducted. Over 500,000 participants, aged 37 to 73 years, were recruited from the general population after approximately 9.2 million invitations were mailed, response rate of 5.5% [1]. Recruitment was carried out through mailed invitations sent to people residing within a 25-mile radius of any of the 22 assessment centres located in England, Scotland, and Wales [2]. The baseline assessment for these participants took place at these study centres and data collection involved self-completed touch-screen questionnaires, verbal interviews, biological sample collection and a series of physical and functional measurements performed by trained staff [3,4]. The ethical approval of the UK Biobank was obtained from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820) [5] and written informed consent was received from all the participants before the baseline assessment [5]. This research has been conducted using the UK Biobank resource under application number 71392.

“The Oxford WebQ was first administered at the assessment centre to participants who made their initial assessment centre visit between April 2009 and September 2010. As this was towards the end of the participant recruitment period, Oxford WebQ was completed in clinic by 70,000 participants. The Oxford WebQ was not administered at participants’ repeat assessment centre visits which took place from 2012 onwards, however from February 2011, participants with a known working email address (~320,000) were invited on four separate occasions over approximately one year to complete the questionnaire, as per the following schedule:

First e-mail invitations: February 2011-April 2011

Second email invitations: June 2011-August 2011

Third email invitations: October 2011–December 2011
Fourth email invitations: April 2012–June 2012" [6].

These are the number of people with data available for n3 fatty acid intake across different time points:
Assessment 1, 2006: baseline n=70,681
Assessment 2, April 2011: n=100,569
Assessment 3, Sept 2011: n=83,236
Assessment 4, Dec 2011: 103,756
Assessment 5, June 2012: 100,215

210,914 participants have at least 2 assessments of n3 fatty acid intake.

Appendix 1 references

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Appendix 2:

Title: Relationship of Multimorbidity, Demographic Factors and Mortality: Findings from UK Biobank Cohort

Additional file 1

Table S1 List of self-reported long-term conditions considered for multimorbidity count

Long term condition grouping	Conditions included as reported by participants
Painful conditions	Back pain Joint pain Back pain Joint pain Headaches (not migraine) Sciatica Plantar fasciitis Carpal tunnel syndrome Fibromyalgia Arthritis Shingles Disc problem Prolapsed disc/slipped disc Spine arthritis/spondylitis Ankylosing spondylitis Back problem Osteoarthritis Gout Cervical spondylosis Trigeminal neuralgia Disc degeneration Trapped nerve/compressed nerve
Hypertension	Hypertension Essential Hypertension
Depression	Depression Postnatal Depression
Asthma	Asthma
Atrial Fibrillation	Atrial Fibrillation
Coronary Heart Disease	Heart attack/Myocardial Infarction Angina
Dyspepsia	Gastro-oesophageal reflux (GORD)/gastric reflux Oesophagitis /Barrett's oesophagus Gastric stomach ulcers Gastric erosions/gastritis

	Duodenal ulcer Dyspepsia/indigestion Hiatus hernia Helicobacter pylori
Diabetes	Diabetic nephropathy Diabetic neuropathy/ulcers Diabetes Type 1 diabetes Type 2 diabetes Diabetic eye disease
Thyroid disorders	Thyroid problem (not cancer) Hyperthyroidism/thyrotoxicosis Hypothyroidism/myxoedema Grave's disease Thyroid goitre Thyroiditis
Connective tissue disorders	Myositis/myopathy Systemic Lupus Erythematosus Connective tissue disorder Sjogrens syndrome/sicca syndrome Dermatopolymyositis Scleroderma/systemic sclerosis Rheumatoid arthritis Psoriatic arthropathy Dermatomyositis Polymyositis Polymyalgia Rheumatica Malabsorption/coeliac disease
Chronic Obstructive Pulmonary Disease (COPD)	COPD/chronic obstructive airways disease Emphysema/chronic bronchitis Emphysema
Anxiety	Anxiety/panic attacks Nervous breakdown Post-traumatic stress disorder Obsessive compulsive disorder Stress Insomnia Psychological/psychiatric problem

Irritable bowel syndrome	Irritable bowel syndrome
Alcohol problems	Alcohol dependency Alcoholic liver disease/alcoholic cirrhosis
Other psychoactive substance abuse	Opioid dependency Other substance abuse/dependency
Treated constipation	Constipation
Stroke/Transient Ischaemic Attack (TIA)	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke
Chronic kidney disease	Polycystic kidney Diabetic nephropathy Renal/kidney failure Renal failure requiring dialysis Renal failure not requiring dialysis Kidney nephropathy Immunoglobulin A (IgA) nephropathy
Diverticular disease	Diverticular disease Diverticulitis
Peripheral vascular disease	Peripheral vascular disease Leg claudication/intermittent claudication
Heart failure	Cardiomyopathy Hypertrophic cardiomyopathy Heart failure/pulmonary oedema
Prostate disorders	Prostate problem (not cancer) Enlarged prostate Benign prostatic hypertrophy
Glaucoma	Glaucoma
Epilepsy	Epilepsy
Dementia	Dementia Alzheimer's disease Cognitive impairment
Schizophrenia/bipolar disorder	Schizophrenia Mania/

	Bipolar disorder Manic depression
Psoriasis/eczema	Eczema Dermatitis Psoriasis
Inflammatory Bowel Disease	Inflammatory Bowel Disease Crohn's disease Ulcerative colitis
Migraine	Migraine
Chronic sinusitis	Chronic sinusitis
Anorexia or bulimia	Anorexia Bulimia Other eating disorders
Bronchiectasis	Bronchiectasis
Parkinson's disease	Parkinson's disease
Multiple Sclerosis	Multiple Sclerosis
Viral Hepatitis	Infective/viral hepatitis Hepatitis B Hepatitis C Hepatitis D Hepatitis E
Chronic Liver disease	Oesophageal varices Non infective hepatitis Liver failure/cirrhosis Primary biliary cirrhosis
Osteoporosis	Osteoporosis
Chronic fatigue syndrome	Chronic fatigue syndrome
Endometriosis	Endometriosis
Meniere's disease	Meniere's disease
Pernicious Anaemia	Pernicious Anaemia
Polycystic ovary	Polycystic ovary
Cancer	Lifetime diagnosis

Appendix 3:

Fish consumption Log

Please note every time you consume any fish (oily or non-oily) by writing in these boxes. For example, one salmon fillet or portion haddock.

Weeks	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week 1							
Week 2							
Week 3							
Week 4							
Week 5							
Week 6							
Week 7							

The example above shows only weeks 1 to7 of the 16 week fish consumption log provided to participants. The full log followed the same structure for the remaining weeks.

Appendix 4:

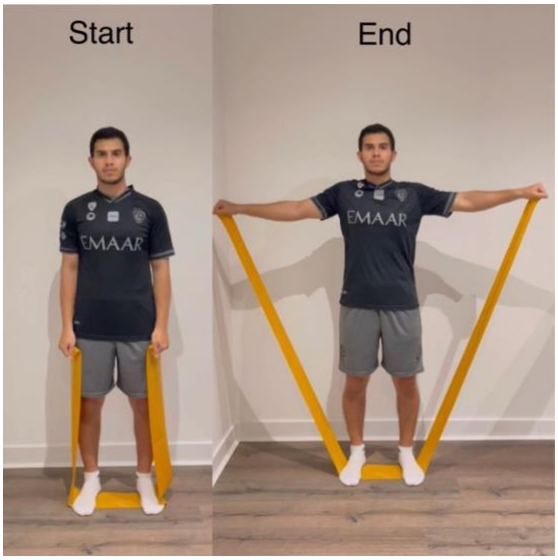
Chest Press

- Body weight

- Resistance band

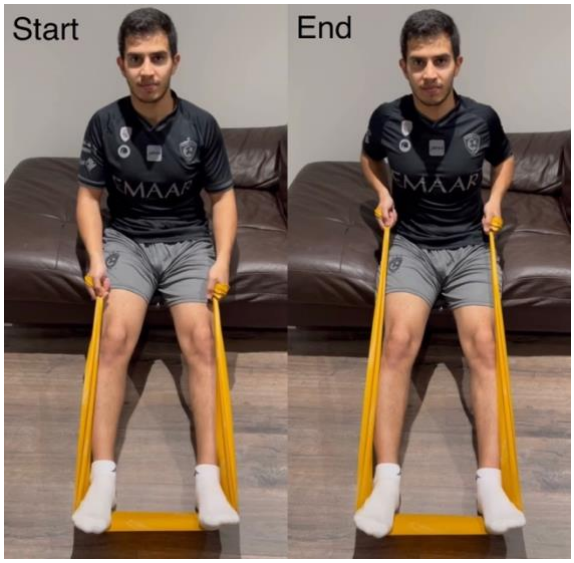
Lateral raise

- Resistance band



Seated rows

- Resistance band



Leg press

- Resistance band

Squats

- Body weight

- Resistance band

Calf Press

- Body weight

- Resistance band

Appendix 5:

Exercise Guideline

The effects of krill oil supplementation on adaptations in muscle strength, size, physical function, and neuromuscular function to a pragmatic home-based resistance exercise intervention in older adults

Short title – Krill Oil exeRcisE Ageing (KOREA study)

School of Cardiovascular and Metabolic Health, University of Glasgow, G12 8QQ.

ABOUT THIS MANUAL

This manual contains the details of the exercises we will ask you to perform during this study.

A member of the research team will guide you through this manual, during an initial meeting and if there is anything you do not understand, then please let them know. The meeting will be in person.

We will also check in with you from time to time by phone to see how you are getting on with the exercises and to give any help required.

Contact details: If you have any questions then please contact the study team using the details below.

Researcher _____ Tel _____ Email _____

Contents

Background

Study details

A key aspect of normal ageing is the loss of muscle mass of 0.5-2% per year and a loss of muscle strength at a rate of 2-4% per year. This is termed sarcopenia and it has been estimated that in the UK 5-8% of older adults suffer from sarcopenia.

Several adverse outcomes are known to be associated with sarcopenia such as poor lung function, falls and fractures, cognitive impairment, sleep disorders, poor quality of life, and premature mortality. There is also evidence that sarcopenia may increases the risk of admission to hospital in older people.

However, it has been found that resistance exercise (lifting weights) interventions are effective and appropriate for treating these adverse outcomes – although there are many barriers to performing such exercise – such as access to equipment and the complexity of the exercises. We have, therefore, developed some simple exercises that you can do to try and increase your muscle mass and strength and we will also investigate whether

krill oil can enhance the beneficial effects of this exercise programme.

We invite you to perform home-based resistance exercises for the duration of the study (16 weeks).

Summary of the resistance training exercises

Resistance exercise will performed using body weight and elastic resistance band exercises. The elastic-band colour indicates the elasticity and thus the resistance level (tan, yellow, red, green, blue, black, silver and gold– in increasing order of resistance).

Every week you will be asked to perform 3 to 6 sets of 6 different exercises with between 8 and 20 repetitions of each exercise. These exercises can be performed throughout the week at your chosen time, ie in discrete sessions or split throughout the week. You will be asked to perform these exercises where you score 8-9 (4-5 in the first week) out of 10, on the exercise effort scale, and adjust the difficulty of the exercise to reach this effort score in 8-20 repetitions. If you can perform more than 20 repetitions at a score of 8 to 9 on the exercise effort scale, you can move to the next difficulty level.

The order of these exercises is up to you. The exercises will be upper body exercises (chest press, lateral raises, seated rows) and lower body exercises (squat, leg press and calf raise). Each exercise below has pictures and a QR code to scan to remind you how to safely perform these exercises.

Don’t over do it!

Whilst we will encourage you to progress and make the exercises a bit harder over time we don’t want you to try exercises you are not ready for. So don’t try to push and progress to more difficult exercises when these are too challenging for you.

Keeping track of your exercises

We will ask you to log each time you perform your exercises in the exercise diary provided. If you can’t manage any of the exercises or find them painful/sore, don’t worry just stop that exercise and let us know.

Progressing during the programme

Ideally during the programme we want to reach the required effort level after around 8-20 repetitions of each exercise. If you find you are doing more, or less, repetitions to reach this effort level then you can try to move up or down a level.

Taking care if using exercise bands

To avoid injury, if you are using the exercise band please see guidance below.

- Before starting your exercises:

- Always check the condition of your band before using.
- Do not place the resistance band handles over your feet. They can easily slip off and strike the user
- Avoid jerking the band
- Do not stretch a band over 2 ½ times their length
- Begin all exercises slowly to ensure band strength
- Do not release a resistance band while under tension
- Never exercise with resistance bands on uneven surfaces
- Resistance bands should only be used for the specific exercises they were designed for and not as toys
- Avoid placing bands in hot areas or in direct sunlight

Keeping in touch during the programme

You can contact the study team at any time throughout the programme using the contact details given at the beginning of the manual. From time to time a member of the research team will contact you by phone to see how you are getting on with the exercises and to give any help required.

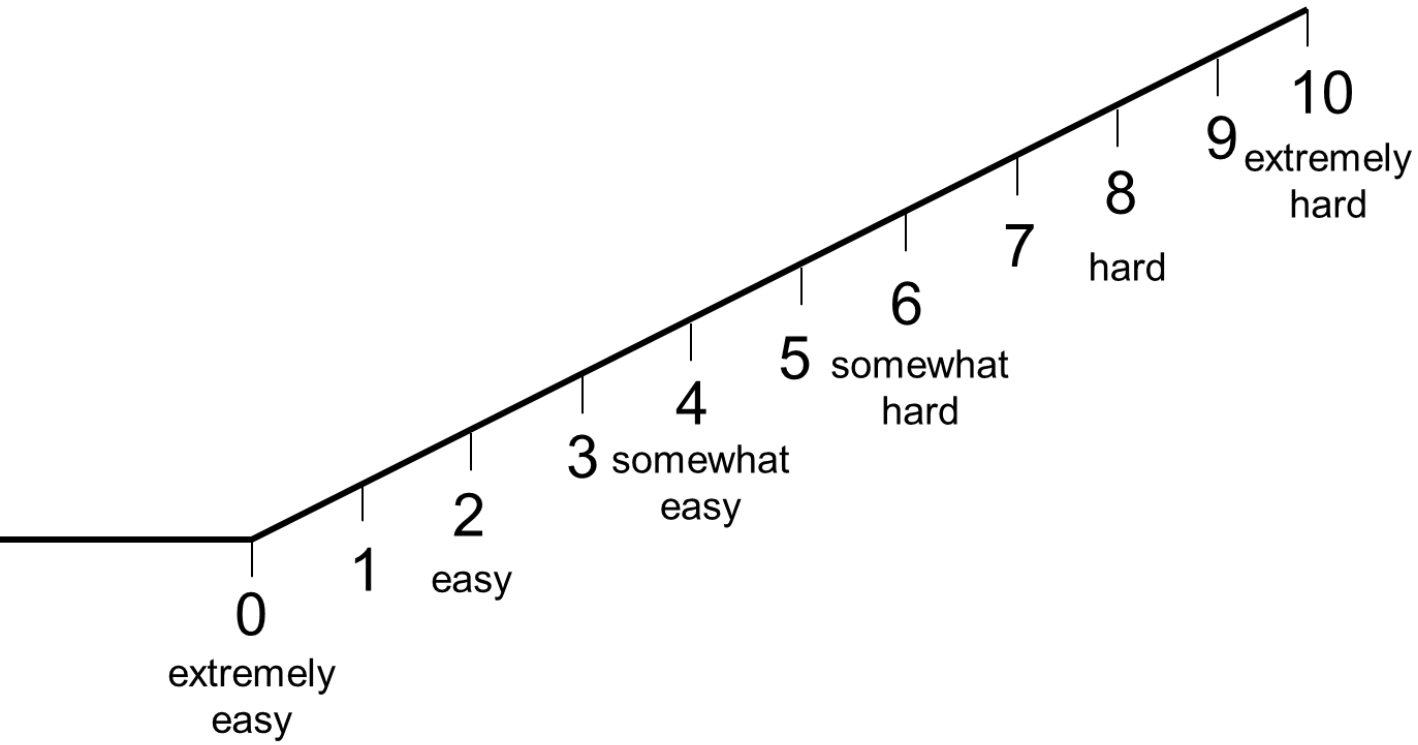
Exercise Effort Scale

Instructions for use

Definition: The perception of physical effort is the level of effort, strain, discomfort, and/or fatigue that you feel during exercise.

Instructions: We would like you to use the scale below to describe how your body feels during the exercises. You are going to perform muscle strengthening exercises using your upper and lower body. If you feel that the exercises are EXTREMELY EASY then you would rate this as number zero. If you feel like the exercises are EXTREMELY HARD then you rate this as number 10. If you feel somewhere in between Extremely Easy (0) and Extremely Hard (10), then you can rate this anywhere between 0 and 10. Remember, there are no right or wrong numbers. Use the words to help select the numbers. Use

any of the numbers to describe how you feel when performing the resistance exercises.



Upper body exercises

Chest Press

Body weight https://youtu.be/5WEChYX0bAM

Begin with your arms shoulder height and just a bit wider than shoulder width apart, against the surface chosen from the options below based on your abilities. Bend your elbows as you lower your upper body toward the surface in a slow controlled manner, keeping your feet planted in position. Slowly push yourself back until your arms are straight but don't lock your elbows. Repeat.

This exercise can be made harder via the following stages

1. Press up against wall
2. Incline press up on kitchen worktop
3. Press up on knees
4. Press ups on the floor

Resistance band https://youtube.com/shorts/auu6Mxn6ag8

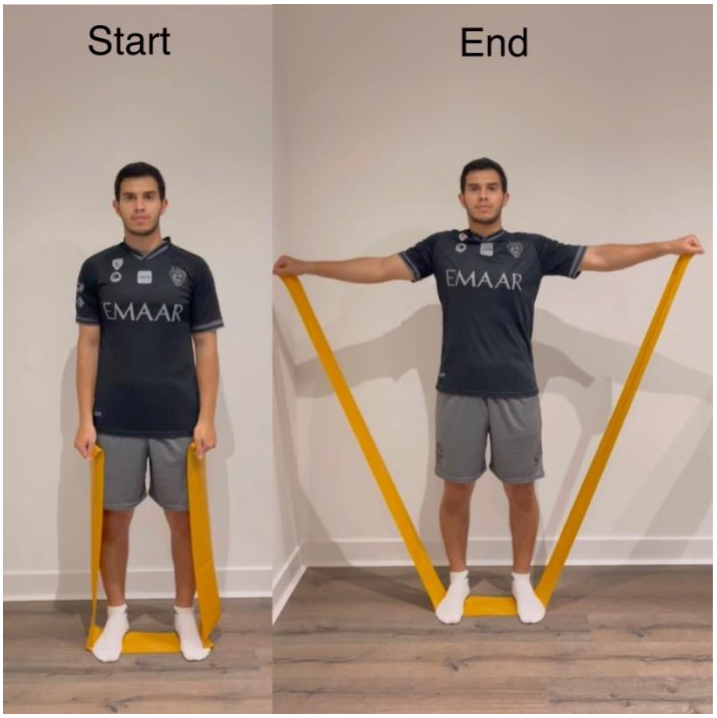
Sit or stand and put the resistance band behind your back and hold each end of it. Stretch both arms out in front of your chest, then return to your starting position. Repeat.

Lateral raise

Resistance band https://youtube.com/shorts/Jgyq9wClaOE

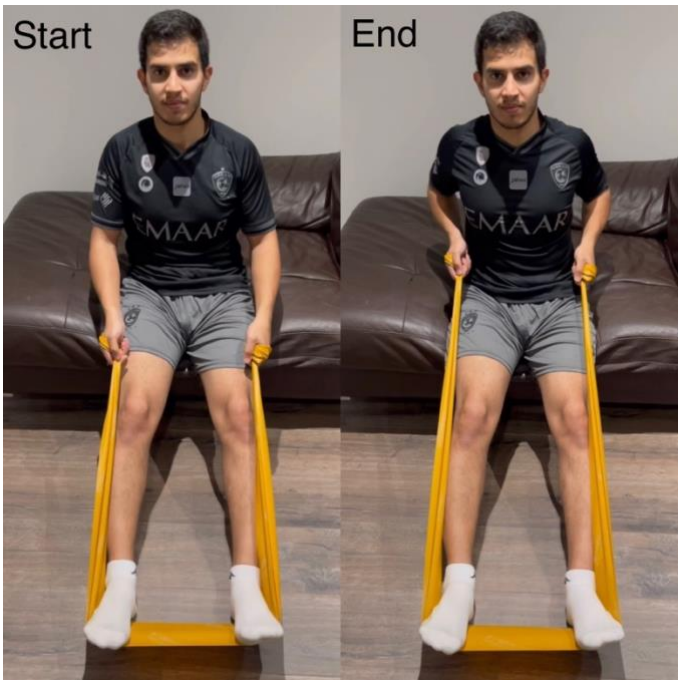
Stand up, place both feet on the middle of the resistance band and hold each end of it with your hands.

Raise both arms to the side, until they reach shoulder height, then return to your starting position. Repeat.



Seated rows

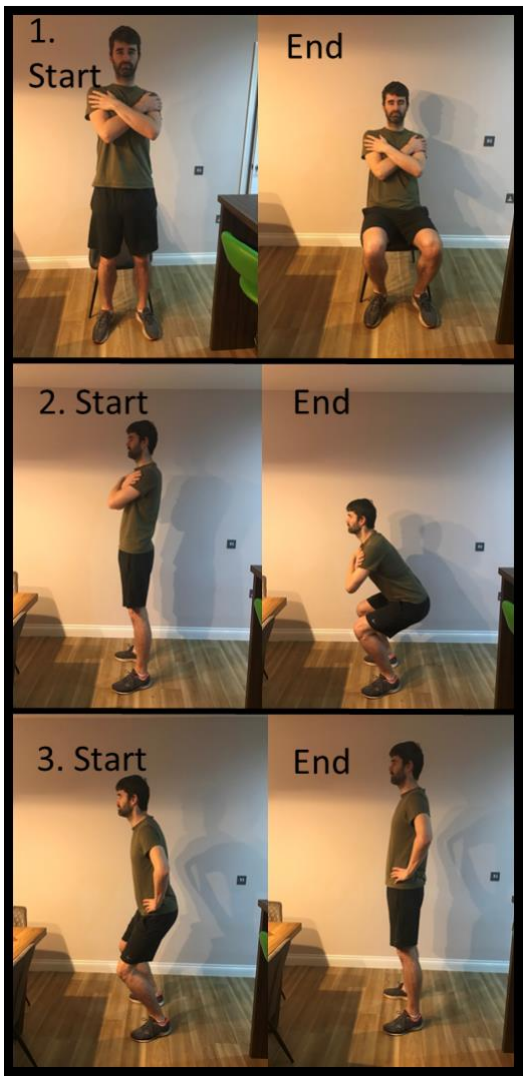
Resistance band https://youtu.be/qjf947SuAww



Sit with feet firmly planted on the ground. Hold an end of the exercise band in each hand. Lower the middle section of the band to the floor. The band should be flat, not twisted. Step on the band with both feet. Sit up tall and hold the band in each hand; it doesn't have to be at the end of the band. Start with the arms straight, hands near the outside of the lower thighs. Pull hands back toward the waist, tightening muscles between the shoulder blades. Be sure to keep your wrists straight and in line with your forearm. Slowly lower hands back to starting position. Repeat.

Lower body exercises

Squats



Body weight (https://youtu.be/j9Ym9hr40RI)

Stand up straight with your feet shoulder width apart. Squat down as far as you can, aiming to get your legs parallel to the ground. Pause for a second and then stand up again. Repeat.

This exercise can be made harder via the following stages

1.Rise up and down from chair (arms folded across chest)

2.No chair and slow on way down (arms folded across chest)

3.No chair and add a small jump in to the squat

Resistance band https://youtu.be/8NozXOkjrHQ

Place both feet on the middle of the resistance band and hold each end of it with your hands. Slowly bend your knees into a squatting position, then return to your starting position. Repeat.

Leg press

Resistance band https://youtu.be/GQu4TZSnr1M

Sit on a chair with your back straight. Place one foot in the middle of the resistance band and hold both ends of it with your hands. Bend your knee towards you, then straighten it back out in front of you before returning to your starting position. Repeat.

Calf Press

Body weight (https://youtu.be/rUZ0Ec529G0)

Stand up straight with your feet shoulder width apart and your hands on your hips or balancing yourself against a wall or a chair. Push through the balls of your feet and raise your heel until you are standing on your toes. Return to starting position and repeat.

Three options you have when performing exercises (see pictures, with 1 being the easiest and 3 the hardest):

1. On floor both feet
2. On step both feet
3. On step single foot

Resistance band https://youtu.be/g6xUSojeHgU

Sit on a chair with your back straight. Place one foot in the middle of the resistance band and hold both ends of it with your hands.

Extend your leg and point your toes towards the ceiling, then point your toes forwards towards the ground. Return to the starting position. Repeat.

Appendix 6:

Exercise Log

Please indicate each set you completed in each week of the study by ticking the box of each exercise. You can add any comments you have each week too.

Weeks	Sets	Chest Press	Lateral raise	Seated rows	Squats	Leg press	Calf Press
Week 1	SET 1						
	SET 2						
	SET 3						
	SET 4						
	SET 5						
	SET 6						
Comments							
Week 2	SET 1						
	SET 2						
	SET 3						
	SET 4						
	SET 5						
	SET 6						
Comments							
Week 3	SET 1						
	SET 2						
	SET 3						
	SET 4						
	SET 5						
	SET 6						

The example above shows only weeks 1 to 3 of the 16 week exercise log provided to participants. The full log followed the same structure for the remaining weeks.

Appendix 7:

Interview topic guide

Questions	Information
Experience and Attitude	
Q1. Have you ever tried to do RT exercises before? **If Yes: A) Why?**	We would like to know past experience of performing RT exercises.
Q2. If answered Yes to Q1: A) What type of RT exercises have you done? **B) Where?** **C) How did you find it?** **D) how and when you did the exercises? ie all in one go, broken up throughout the day, whilst watching tv**	We would like to see what type of RT exercises the participants have done previously and if there are any barriers in order to compare it with home-based RT exercises.
Q3. On the home based exercise A) Which exercises did you manage to do? **B) Where did you do them?** **C) How did you find the exercises?** **D) how and when you did the exercises? ie all in one go, broken up throughout the day, whilst watching tv**	
Q4. How would do describe your overall experience with home-based exercise intervention?	We would like to see the participants experience and attitude toward home-based exercises intervention.
Q5. What could we have done to improve your experience in the study?	We want to know what could be improved in this study to enhance related future studies.
Q6. How useful do you think home-based RT exercises is for your muscle health? Why do you say this?	We would like to know the participants' opinion about the beneficial effect of home-based RT exercises.
Motivators and Barriers	
Q7. Can you tell me what you liked or enjoyed about the study intervention? **Prompts: Is there anything that you consider as motivator?)**	We would like to find out what factors might motivate participants to keep performing Home-based RT exercises.
Q8. Can you tell me what you disliked or found difficult about the study intervention?	We would like to know if the participants facing any difficulties or barriers.

Prompts: Is there anything that you consider as barrier?)	
Q9. We asked you to take krill oil every day during the study period, have you found any difficulty about it?	We would like to know if the participants facing any difficulties or barriers.
Adherence to the intervention after the study completion	
Q10. How often did you keep performing home-based RT exercises after the study finished?	We want to know to what extent participants adhere to home-based RT exercises.
Q10. Do you find any difficulty to adhere to the exercises?	We would like to find out any barriers toward the adherence of home-based RT exercises.
Q11. If answered Yes to Q: A) What do you think could enhance your adherence to the exercises OR what could we do to encourage older adults to engage in such exercises?	We want to know the motivators toward the adherence of home-based RT exercises.
Q12. How often do you think you would be willing to do home-based RT exercises now that you have tried it? If not, why not?	We want to know about the participants' perceptions of doing Home-based RT exercises regularly
Q13. Before we draw this discussion to a close, is there anything else you would like to add?	

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