From Evidence to Implementation: Investigating the Effects and Clinical Perspectives of Preoperative Exercise on Cognitive and Physical Outcomes in Older Adults

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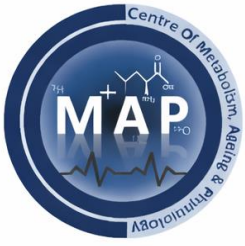



Abstract

Globally, people are living longer. The shift in population ageing means that more older adults are receiving surgical interventions for various health problems. Surgical interventions can cause negative cognitive and physical impacts and further effect the independence and quality of life of older adults. Cognitively, the risk of postoperative cognitive dysfunction (POCD) is higher in this age group, and postoperative cognitive impairment may even lead to more permanent impairment such as dementia. In addition to age-related loss of skeletal muscle mass, strength and neuromuscular system deterioration, postoperative physical dysfunction is more common in older adults. Preoperative physical exercises aimed at preserving cognitive and physical function in older adults are promising, but further investigation is needed to specifically examine the effects of preoperative motor control-based exercise interventions on cognitive and physical function.

In Chapter 2 of this thesis, a systematic review examining the effect of preoperative physical exercise interventions on postoperative cognition is presented. Only three studies met our inclusion criteria, which highlights the gap in the literature. Despite the limited and heterogeneous evidence base, the results of this review suggest that preoperative exercise training may be a viable strategy to mitigate postoperative cognitive impairment in adult patients undergoing elective surgery.

In Chapter 3, the methodology of a pilot study examining the effects of low-intensity unilateral upper limb motor control training (uMCT) on cognitive and physical functions in healthy older adults are presented. Chapter 4 and 5 present the results in detail. Twenty older adults (10 men, 10 women) exercised three days per week for four weeks using a custom-made arm rig, and assessments were conducted at three different time points (pre-training, post-training, and follow-up (4 weeks later)). Cognitive outcomes were determined by examining three different cognitive tests (Trail Making Test (TMT), Montreal Cognitive Assessment (MoCA) and Stroop Colour-Word Test (SCWT)) and blood biomarkers related to cognitive function (Interleukin-2 (IL-2) and Brain-Derived Neurotrophic Factor (BDNF)). Physical function outcomes were determined by muscle strength, handgrip, motor control, balance, dexterity, and physical performance battery.

Chapter 4 presents the cognitive results of this pilot study, while Chapter 5 presents the physical function results. uMCT had a protective or beneficial effect on cognitive function in older adults. There was no significant change in blood markers, which is attributed to the relatively short duration of the exercise programme. uMCT also resulted in improved physical function outcomes, including muscle strength, handgrip, motor control, balance, manual dexterity, and physical performance.

To follow on, in Chapter 6, a modified Delphi study was conducted to systematically explore consensus views of multidisciplinary medical staff regarding the effect of preoperative exercise training in the older adults on postoperative cognitive function. This study was conducted in three rounds, with 41 statements presented and 34 statements accepted. This study has reached a consensus on risk factors that may lead to significant cognitive clinical problems such as POCD, which can occur in older adults after surgery, and on prevention strategies that can be implemented. Although there was consensus that preoperative rehabilitation has positive effects on postoperative physical function, no consensus was reached regarding its effects on cognitive function, and it was emphasised that this area requires more comprehensive research.

Overall, uMCT has been demonstrated to be an effective, safe, and feasible exercise training for healthy older adults that can improve both cognitive and physical function. Future studies should investigate the effects of preoperative uMCT on postoperative cognitive and physical function in older adults undergoing surgery.

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Abbreviations

ACP	advance clinical practitioners
AD	Alzheimer's disease
ADAS-Cog	Alzheimer’s disease assessment scale–cognitive subscale
ADL	activities of daily living
AET	aerobic exercise training
ATP	adenosine triphosphate
BBB	blood–brain barrier
BDNF	brain-derived neurotrophic factor
BIC	biceps brachii muscle
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass grafting
CI	confidence interval
CNS	central nervous system
COP	centre of pressure
DT	distance travelled
EA	ellipse area
EEG	electroencephalogram
ELISA	enzyme-linked immunosorbent assay
EMG	electromyography
iEMG	intramuscular electromyography
EUGMS	European Geriatric Medicine Society
FAB	frontal assessment battery
FAT	force accuracy training
FES	functional electrical stimulation
GP	general practice
GRADE	grading of recommendations, assessment, development, and evaluation
HD-SEMG	high-density surface electromyography
HX	history
ICF	informed consent form
IGF-1	insulin-like growth factor 1

IL-2	interleukin-2
IL-6	interleukin-6
IQR	interquartile range
ISPOCD	international study of post-operative cognitive dysfunction
LMM	linear mixed-effects model
MCI	mild cognitive impairment
MDT	multidisciplinary surgical team
MMAT	mixed methods assessment tool
MCON	motor control
MMSE	mini mental state examination
MoCA	Montreal cognitive assessment
MPS	muscle protein synthesis
MU	motor unit
MVC	maximum voluntary contraction
NGT	nominal group technique
NIH	national institutes of health
NMJ	neuromuscular junction
NS	not significant
OR	odds ratio
OT	occupational therapist
PIS	participant information sheet
POCD	postoperative cognitive dysfunction
POD	postoperative delirium
PPI	patient and public involvement
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PROSPERO	international prospective register of systematic reviews
RCT	randomised controlled trial
RET	resistance exercise training
ROS	reactive oxygen species
SCD	subjective cognitive decline
SCWT	stroop colour word test
SD	standard deviation

SERCA	sarcoplasmic/endoplasmic reticulum calcium ATPase
SPPB	short physical performance battery
SR	sarcoplasmic reticulum
TA	tibialis anterior
TIVA	total intravenous anaesthesia
TMS	transcranial magnetic stimulation
TMT	trail making test
TNF-α	tumour necrosis factor-alpha
TRI	triceps muscle
TUG	time up and go
UK	United Kingdom
uMCT	upper limb motor control training
USA	The United States of America
WHO	World health organization

Chapter 1 Introduction

1.1 Ageing

Ageing is a natural physiological process that occurs in all living beings and progresses gradually. Over time, it leads to deterioration in the body's functional mechanisms, increases the risk of disease, and reduces the capacity to cope with physiological stress [1]. Although ageing is a universal phenomenon, its progression may vary from person to person depending on genetic factors, environmental conditions, daily habits, and lifestyle changes [2]. From a biological perspective, ageing is driven by a series of interconnected molecular and cellular processes. These mechanisms, termed the '*hallmarks of ageing'*, contribute to the gradual decline observed in various systems, including cognitive, cardiovascular, musculoskeletal, and immune functions [1]. López-Otín et al. (2013) [1] have defined nine fundamental biological mechanisms to explain ageing, which are genomic instability, telomere shortening, epigenetic alterations, loss of proteostasis, impaired nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Collectively, these mechanisms contribute to the progressive loss of physiological resilience observed with advancing age.

On a global scale, population ageing has contributed to one of the most profound demographic shifts of the 21st century. The number of people aged 60 years and older is increasing rapidly, with projections indicating 1.4 billion by 2030 and 2.1 billion by 2050 [3]. This rise in the older population is largely attributed to advances in healthcare, sanitation, public health, and overall living conditions. Although life expectancy has increased, this has not been accompanied by a parallel increase in the number of years spent in good physical and cognitive health among older adults [4].

Ageing has been found to be closely associated with chronic conditions such as type 2 diabetes, cardiovascular disease, sarcopenia, frailty, neurodegenerative disorders, cognitive decline, and geriatric syndromes. These conditions negatively affect the independence and quality of life of older adults and, consequently, place a significant burden on healthcare systems and caregivers. Individual differences in the ageing process result in accelerated decline in some adults, while others are able to maintain relatively preserved functionality. This heterogeneity underscores the importance of

identifying protective interventions that support healthy ageing [5,6].

1.1.1 Cognitive changes in advancing age

Cognitive ageing refers to the decline in cognitive processes that is a natural part of non-pathological ageing and occurs gradually over time [7]. Although certain neurodegenerative diseases may contribute to cognitive decline in later life, it is clinically important to distinguish between pathological conditions, such as Alzheimer's disease or mild cognitive impairment (MCI), which affect functional ability, and the more gradual changes that occur as part of the normal ageing process [8].

Cognitive changes observed in the normal ageing process are well documented in the literature. Crystallised intelligence refers to well-learned, familiar skills and knowledge, such as vocabulary and general knowledge, and may even improve with age [7, 9]. Since crystallised intelligence is based on an individual's life experiences, older adults tend to perform better than younger adults. Fluid intelligence, on the other hand, may show a notable decline with ageing. Fluid intelligence is defined as the ability to reason and solve problems in relation to less familiar tasks and independent of an individual's experiences. Executive function, processing speed, memory, and psychomotor skills are included in this group [10,11].

Cognitive ability is a complex term that can be divided into areas such as processing speed, attention, memory, and executive function or reasoning. Processing speed refers to the rate at which cognitive activities are performed, which begins to decline in the third decade of life and continues throughout life, and includes the speed of motor responses (8, 11, 12). Most cognitive problems reported in healthy older adults stem from slow processing speed, and this slowing is a parameter that can affect performance in other cognitive domains, such as verbal fluency, and can lead to declines in many neuropsychological test scores [7].

Attention is the ability to concentrate and focus on specific stimuli, and marked declines can be observed with age in complex tasks such as selective and divided attention [11, 13]. Selective attention is the ability to ignore irrelevant information and focus on relevant information, as in chatting in a noisy environment or driving a car. Divided attention refers to the ability to perform two tasks simultaneously, such as talking while

preparing food, and this ability declines with age [14].

One of the most common cognitive changes in older adults is the decline in memory. Age-related memory changes can be explained by a decrease in processing speed [15], a loss of the ability to ignore irrelevant information [16], and a reduction in the ability to use strategies to improve learning and memory [17, 18]. Executive function is defined as an individual's ability to perform independent, appropriate, and purposeful behaviours, encompassing skills such as planning, self-monitoring, organisation, problem-solving, and mental flexibility [19]. Research has shown that abstraction, concept formation, and mental flexibility decline significantly in older adults, particularly after the age of 70 [19- 22]. However, response inhibition, defined as the ability to suppress automatic responses in order to generate a new response, and executive functions requiring speed and motor components may also decline with ageing [23, 24].

Ageing can also cause changes in brain structure and function, such as a marked decrease in both grey and white matter volume. It has been shown that the reduction in neuron size, dendritic branching, and synaptic density is primarily related to grey matter loss. Grey matter loss is particularly pronounced in the prefrontal cortex and is also associated with a moderate decrease in the temporal lobe and a decrease in hippocampal volume [7, 25, 26]. In addition, a 16-20% loss in white matter can be observed in older adults [27, 28], which contributes to deterioration in hippocampal connections and memory decline (Figure 1.1) [29]. Another factor contributing to cognitive impairment is beta-amyloid accumulation, which can be observed in cognitively healthy older adults and is associated with cognitive decline in advanced age [30- 32]. Neuroimaging studies have also highlighted a decline in the integrity of the dopaminergic system with age, which may contribute to reduced cognitive flexibility and slower processing speed in older adults [33].

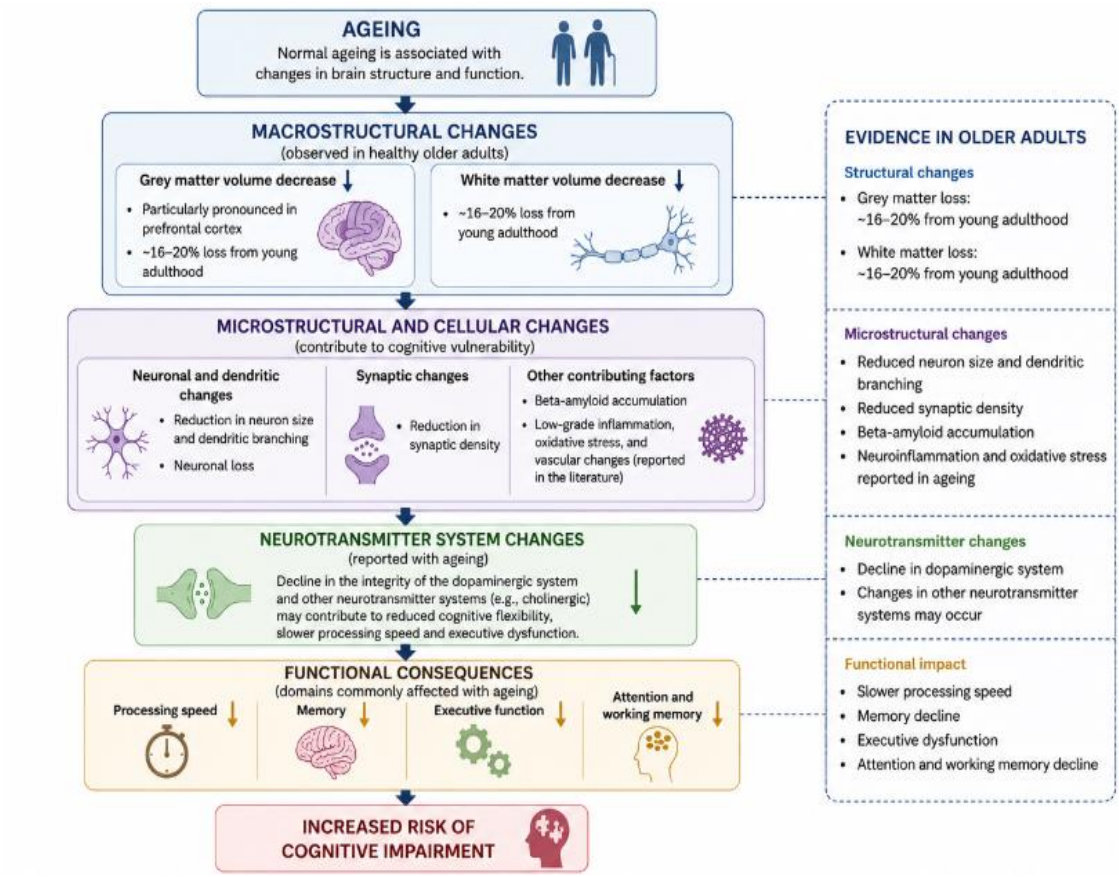


Figure 1.1: *Conceptual summary of age-related structural and neurophysiological changes associated with increased risk of cognitive impairment.*

Figure created using Biorender.

Genetic and environmental factors influence individual differences in the degree of cognitive decline. Factors such as a high level of education, intellectually demanding occupations, bilingualism, and active social participation have been demonstrated to increase cognitive reserve, delay the onset of cognitive decline, and reduce its severity [34]. Cognitive reserve refers to the brain's ability to cope with age-related or pathological changes while maintaining its function [34]. Some older adults may report a decline in memory and thinking skills despite performing within normal limits on standard cognitive assessments. This condition is known as subjective cognitive decline (SCD) and is considered a potential early indicator of MCI and dementia [35]. This cognitive decline can importantly negatively affect their ability to live independently and their quality of life [7].

Despite age-related decline, the ageing brain retains a degree of plasticity. Evidence

suggests that cognitive training, physical exercise, and combined multimodal interventions can support the maintenance, and in some cases the improvement, of cognitive function in older adults [36, 37]. However, the durability and generalisability of these benefits remain uncertain [38]. In conclusion, cognitive ageing is a heterogeneous and multifactorial process, with considerable variation between individuals.

1.1.2 Physical changes in advancing age

Physical ageing is a natural part of the ageing process, characterised by gradual and inevitable physiological changes in many organ systems [39]. These changes are characterised by loss of muscle mass and strength [40], decreased bone density [41], reduced cardiovascular [42] and pulmonary capacity [43], and reduced joint flexibility [44]. Collectively, these factors contribute to a progressive decline in physical function and resilience [39]. Physical ageing is not solely a biological process; environmental, behavioural, and socio-economic influences such as chronic diseases, physical inactivity, and inadequate nutrition are also involved, making it a multifaceted concept [45]. Declines in physical performance can significantly impair an older adult's ability to remain independent, perform daily activities, and maintain overall quality of life [46].

Frailty is defined as one of the most important consequences of ageing, characterised by the inability to maintain homeostasis sufficiently in older adults because of cumulative declines in various physiological systems that occur with ageing. Frailty is a state of vulnerability resulting from the body's diminished capacity to restore homeostasis as it ages [47,48]. Frailty can lead to disproportionate deterioration in health by reducing an individual's capacity to recover from stress and is associated with adverse outcomes in older age, such as loss of independence, falls, hospitalisation, low quality of life, and mortality [48]. Moreover, frailty is not limited to physical functional decline; cumulative reductions in metabolic, cardiovascular, immunological, and neuromuscular systems may also accompany this condition [49]. In addition, the intersection of frailty and multimorbidity can negatively affect surgical, rehabilitation and treatment outcomes in older adults [50, 51]. Therefore, identifying frailty at an early stage and planning appropriate interventions may be important for older adults.

Sarcopenia is one of the most prominent consequences of neuromuscular ageing. Its underlying mechanisms include the loss of motor neurons, chronic low-grade inflammation, mitochondrial dysfunction, reduced anabolic signalling, and hormonal decline, which are elaborated on in the section on skeletal muscle ageing [52, 53]. These muscular changes are often accompanied by age-related deterioration in bones and joints, such as reduced bone mineral density and compromised cartilage integrity. These conditions contribute to an increased risk of fractures, joint stiffness, impaired mobility, and falls in older adults [54, 55].

Physical ageing also affects the cardiovascular and respiratory systems, leading to arterial stiffening, reduced lung function, and decreased cardiac output. These physiological changes can reduce physical endurance and cause older adults to experience fatigue more quickly during daily activities [42, 43]. Such changes may compromise independence and diminish overall quality of life. However, evidence suggests that these age-related physical declines can be delayed, or in some cases prevented, through regular physical activity, resistance training, and appropriate nutritional support [39, 56, 57].

1.1.2.1 Skeletal muscle ageing

Skeletal muscle is one of the structures that must be preserved to increase health span [58, 59], given its role in muscle strength, mass, and physical performance [60]. Skeletal muscle constitutes approximately 40% of the human body and is a complex tissue [61] responsible for numerous functions, including contraction for movement, thermogenesis, and metabolism [58]. The main change associated with skeletal muscle ageing is muscle atrophy. Progressive muscle mass loss begins physiologically around the age of 40 and is estimated to increase by approximately 8% per decade until the age of 70. After the age of 70, this rate can rise to 15% per decade [62].

There are underlying structural and biochemical changes in skeletal muscle ageing in older adults. First, muscle cross-sectional area may decrease by approximately 30% by the age of 70, and this is often associated with intramuscular fat accumulation [63, 64]. A study investigating intramuscular fat infiltration revealed that intramuscular fat can significantly reduce specific muscle strength even when muscle cross-sectional area is equal [65]. Furthermore, another study conducted on sarcopenic older adults revealed that an increase in intramuscular fat may be associated with impairments in muscle

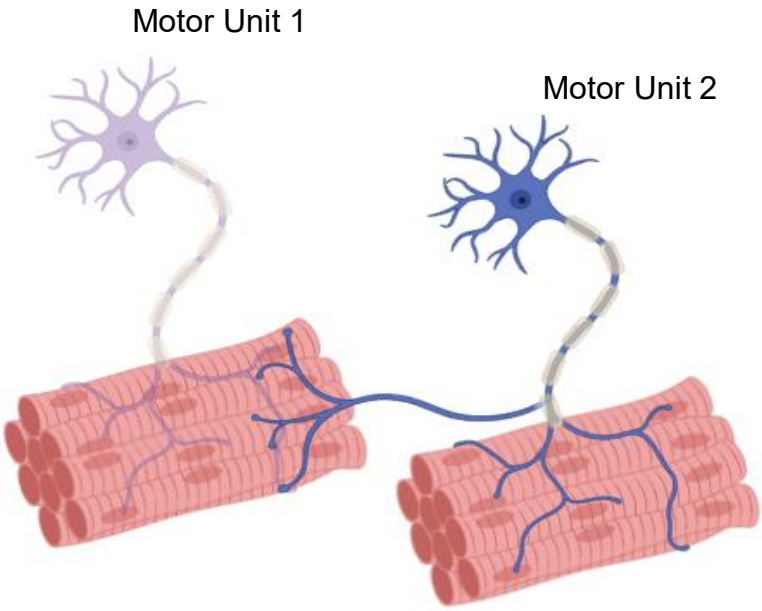
contraction efficiency and metabolic functions, thus it has been demonstrated that the concept of '*muscle quality'* should be evaluated not only in terms of mass but also in terms of tissue and functional qualities [66]. In addition to age-related alterations in muscle fibres, skeletal muscle in older adults undergoes several morphological and metabolic changes, including intramuscular fat infiltration (myosteatosis), increased fibrosis, capillary rarefaction, and a decline in satellite cell activity. These structural and cellular modifications contribute to reduced muscle quality and impair the efficiency of muscle contraction [67, 68]. Based on these findings, we can say that although muscle volume can be preserved in older adults, function may deteriorate, and muscle quality is an important variable in ageing.

Ageing is also associated with a reduction in fast-twitch glycolytic (Type II) fibres and a shift in muscle fibre composition [46, 69]. Furthermore, important changes in motor neurons may be observed. A decrease in motor unit number and activity is evident, which can result in impaired motor control [70, 71]. When Type II myofibres are reinnervated by Type I motor neurons, changes in fibre type occur [70]. It has not been conclusively determined whether this reinnervation is the cause of sarcopenia or an adaptive response that compensates for it [72]. As explained in Section 1.3, sarcopenia is a neuromuscular sign of ageing characterised by progressive loss of muscle mass, strength and functional capacity. It typically begins in the fourth decade of life and accelerates with advancing age. In older adults, sarcopenia contributes to reduced mobility and decreased independence in activities of daily living [52, 73].

The central biological mechanism underlying skeletal muscle atrophy is the loss of motor neurons, particularly those innervating fast-twitch type II muscle fibres. This selective denervation leads to muscle fibre disorganisation and, over time, contributes to muscle atrophy. Although the remaining motor neurons can partially compensate through reinnervation, the efficiency of this process diminishes with age, resulting in a net decline in the number of functional motor units [74]. The motor unit (MU), composed of a motor neuron, its axon, distal axonal terminals, neuromuscular junctions (NMJs), and the innervated skeletal muscle fibres, represents the final common pathway of the neuromuscular system and plays a critical role in muscle contraction and force generation. MUs are the primary determinants of muscle strength, with their contribution modulated through changes in firing rate and recruitment patterns [75]. The relationship between muscle strength and MU firing behaviour is closely linked to

the force produced by individual MUs, and fluctuations in firing rate have been identified as a key mechanism in the fine control of muscular output [76].

Progressive declines in skeletal muscle mass, strength, and physical performance seen in the ageing process may lead to a range of adverse physiological and psychosocial outcomes, including loss of independence, increased frailty, heightened risk of falls, physical inactivity, depression, and cognitive impairment [77]. As highlighted in a review by Wilkinson et al. (2018) [78], the decline in age-related muscle strength and function can be primarily attributed to two interconnected mechanisms. The first is anabolic resistance, defined as the diminished sensitivity of skeletal muscle to anabolic stimuli such as exercise or protein intake. This impaired anabolic signalling plays a crucial role in accelerating skeletal muscle ageing and may hinder the potential benefits of interventions aimed at preserving muscle mass and function in later life [53, 79]. This impaired responsiveness contributes to reduced muscle protein synthesis and, over time, leads to muscle fibre atrophy and loss, ultimately promoting motor unit remodelling and neuromuscular dysfunction. The second mechanism contributing to age-related decline in muscle function involves the interplay between muscle size and neuromuscular control. Loss of muscle fibres disrupts this interaction, resulting in MU remodelling [78] (Figure 1.2).



Motor Unit Remodelling

Figure 1.2 *Age-related motor unit remodelling.*

In response to motor unit loss, some muscle fibres (motor unit 1) can be reinnervated by surviving axons (motor unit 2). (Figure created using Biorender)

Age-related motor unit remodelling reflects a compensatory response to progressive motor neuron loss. Surviving axons undergo collateral sprouting and reinnervate muscle fibres that have lost their original neural input. While this adaptive process may partially preserve muscle mass, it can often contribute to decreased neuromuscular efficiency, impaired force sensitivity, reduced fine motor control, and subsequent functional decline in older adults [78].

Another factor that may adversely affect skeletal muscle function in older adults is "*inflammaging*", a chronic low-grade systemic inflammation associated with ageing. This inflammatory state contributes to catabolic activity within skeletal muscle, accelerating tissue degradation. Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), have been shown to increase protein breakdown and impair muscle regeneration, thereby promoting skeletal muscle ageing [80]. Nonetheless, current evidence suggests that resistance training and adequate protein intake can counteract these physiological and molecular changes by enhancing muscle mass, strength, and physical performance in older adults [57, 81, 82].

1.1.2.2 Neuromuscular ageing

Neuromuscular ageing refers to progressive deterioration in muscle and nerve components that occurs with ageing and is characterised by impaired communication between skeletal muscles and the motor neurons that innervate them. Neuromuscular ageing typically manifests as a decrease in muscle strength, impaired motor control, and limitations in voluntary movements [74, 83, 84]. At the physiological level, neuromuscular ageing may manifest as several interrelated changes, including

remodelling of muscle fibre structure, degeneration of the neuromuscular junction, gradual loss of motor neurons, and marked atrophy of type II (*fast-twitch*) muscle fibres. Collectively, these changes may cause functional impairment in neuromuscular performance during ageing [85, 86].

Age-related neuromuscular decline significantly contributes to balance disorders, increased risk of falls, reduced mobility, and the development of sarcopenia. These outcomes can diminish older adults' independence and quality of life. Therefore, neuromuscular ageing is considered a key determinant of declining physical performance in older age [52, 87, 88]. A comprehensive understanding of the underlying mechanisms and clinical effects of neuromuscular deterioration is a key parameter for targeted interventions. Such approaches may help preserve functional capacity, support autonomy, and increase care independence in the ageing population [57, 89, 90].

1.1.2.2.1 The mechanistic basis of age-associated changes in neuromuscular structure and function

One of the most prominent changes observed in neuromuscular ageing is the progressive loss of alpha motor neurons, leading to a decline in neural transmission and muscle activation. The surviving neurons may attempt to reinnervate denervated muscle fibres through collateral branching, but the performance of this compensatory mechanism may gradually decline with age. As a result, motor units become larger but functionally less efficient, which may cause impaired muscle coordination and reduced physical performance in older adults [86].

Age-related deterioration of synaptic transmission at the NMJ results from a combination of structural and molecular changes. These include fragmentation of the postsynaptic membrane, mitochondrial dysfunction, and a decline in acetylcholine receptor density, all of which impair the efficiency of neuromuscular signalling [74]. Furthermore, increased oxidative stress and chronic low-grade inflammation associated with ageing can further disrupt the delicate balance between muscle breakdown and renewal, reducing the muscle's capacity for adaptation and repair [80].

MU is a term encompassing the alpha motor neuron and the muscle fibres it supplies [91]. To ensure equal force distribution in muscles, the fibres that form the MU spread

throughout the muscle, forming a MU region [70, 92]. In addition to the physiological changes that may develop with ageing, neurological changes that may occur can also affect the MU. Within the scope of muscle changes that can occur with ageing, important changes in MU size and number may occur, and this situation can directly affect muscle function. In ageing muscles, the number of MUs decreases and MU size may increase; these changes in MU are generally associated with the loss of motor control commonly seen in older adults [86].

1.1.2.2.2 Clinical implication of age-associated changes in neuromuscular structure and function

In addition to physiological changes in many organs and systems, ageing can also be associated with disorders in the neuromuscular system. Along with ageing in the cardiovascular, musculoskeletal, and cognitive systems, neuromuscular ageing is a condition that can affect motor unit function, muscle strength, balance, gross motor control, and fine motor control [93, 94]. All these systemic changes that occur with ageing can result in loss of mobility, reduced independence, and ultimately a decline in quality of life [95]. Motor unit loss with decreased synaptic density, delayed motor responses, and muscle fibre degeneration associated with ageing as described in more detail in the previous section, can lead to weakened postural control and reduced independence in activities of daily living in older adults [93]. Therefore, neuromuscular ageing is not merely a physiological process but can result in negative clinical consequences for older adults.

Along with neuromuscular ageing, there may be a decrease in motor control, a decrease in motor sensitivity, a slowing of walking speed, and an increased risk of developing postural instability [93]. These changes in this age group can lead to balance and coordination disorders and contribute to an increased risk of falls, which are among the most important causes of morbidity and mortality associated with injury in the older adults [96, 97]. Secondly, decreased neuromuscular function can cause a decline in hand–eye coordination, fine motor skills, and dexterity [98] which are functions that may limit older adults in many areas, from self-care skills to social participation. The mechanism underlying upper extremity dexterity loss with ageing is linked to age-related motor unit atrophy in muscles, the transformation of fast-twitch motor units into slow-twitch units, increased co-activation between agonist and antagonist muscles, and

variability in motor unit firing rate [93, 99- 101].

One of the most important non-pharmacological strategies against neuromuscular ageing is exercise. The literature has consistently demonstrated the benefits of different exercise modalities in this area. Studies in older adults indicate that resistance exercise programmes can increase muscle mass and strength [102], balance exercises can improve postural control [97, 103], and combined aerobic, strength, and balance training can enhance neuromuscular performance [104].

In a randomised controlled trial, Monti et al. (2023) [104] investigated the effects of a multi-component exercise programme involving aerobic, resistance, and balance training over two years in older adults with low muscle function. The results showed that exercise performed two to three times per week can preserve both muscle strength and neuromuscular connections (e.g. motor unit number and NMJ stability) in older adults. Furthermore, this study demonstrated that improvements in walking speed and overall physical performance can be achieved in this population. Long-term, regular exercise was also shown to slow down neuromuscular degeneration associated with ageing and to increase functional independence. In a systematic review, Wang et al. (2020) [105] examined the effects of exercise on NMJ degeneration, a marker of neuromuscular ageing. Their findings highlighted that aerobic and resistance exercise can support NMJ morphology, maintain synaptic connections, and contribute to sustaining nerve-muscle communication.

Such studies exist, but most have been conducted in healthy older adults who are able to live independently in the community, while the literature on the effects of exercise in frail or multimorbid older adults is limited and the findings are inconsistent [106]. Another point is that improvements in motor control and fine motor skills may not always translate into the same degree of functional independence [107, 108]. Although research findings demonstrate that exercise interventions are effective for outcomes requiring neuromuscular function, such as falls, there are limitations due to restricted access to exercise programmes, insufficient healthcare resources, low motivation among older adults, and low levels of physical activity [109, 110]. Therefore, these limitations pose important challenges to the sustainable implementation of exercise programmes for older adults in general.

1.2 Ageing and surgery

The increase in the older population has led to a rise in the need for surgical interventions, which has necessitated developments in surgical techniques and anaesthesia practices [111, 112]. It has been reported that approximately half of adults aged 65 and over have undergone at least one surgical procedure during their lifetime [113] and evidence shows that surgical procedures performed on older adults have increased from the year 2003 onwards [114, 115]. This demographic trend is also associated with longer life expectancy, technological advances in diagnostic methods, and changing healthcare expectations. The growing demand for surgery has stimulated research and new developments in anaesthesia practices and perioperative care models [116, 117]. In this context, epidemiological trends in the surgical needs of older adults may directly influence clinicians' surgical decision-making processes and perioperative care protocols.

The increase in the frequency of surgical interventions in the older population cannot be attributed solely to demographic factors; increased life expectancy and the associated rise in the prevalence of chronic diseases in later life are important contributors to the growing need for surgery [114, 118]. Furthermore, increasing expectations for maintaining independence, mobility, and quality of life in older age have contributed to a greater demand for healthcare services, including surgical interventions aimed not only at prolonging life expectancy but also at preserving daily function and improving quality of life [117, 119]. Advances in anaesthesia and surgical techniques, together with the development of minimally invasive surgical protocols, are additional reasons for the increased frequency of surgical interventions [113, 116]. In addition, technological developments have enhanced imaging methods and contributed to the introduction of new screening programmes [120, 122]. Artificial intelligence-based decision support systems, alongside advances in imaging, have made it possible to detect many diseases in older adults at an earlier stage and to perform surgical interventions [114, 123]. Advancing age is associated with an increased need for surgical intervention [114], but individual health and functional status are also important factors in deciding whether to have surgery in older adults.

Technological advances, improvements in diagnostic methods, and access to healthcare are important factors contributing to the increase in surgical rates. However, these are

not the only influences, as social and economic variables are also important determinants that can affect surgical rates [124]. Healthcare financing, inequalities between countries, and insurance coverage can influence older adults' access to surgery and have a considerable impact on surgical rates [125]. Furthermore, factors such as health literacy, education, and socioeconomic status can influence both the treatment-seeking process and the decision to undergo surgery. Health policies in different countries, the organisation of health systems, and budgets allocated to health are other factors that can affect older adults' access to surgery and the quality of surgical care [126]. Consequently, when these variables are considered, surgical rates depend on biomedical as well as socioeconomic and political issues.

Age-related physiological changes can affect an individual's ability to tolerate surgical stress, anaesthesia, and post-operative recovery, thereby increasing the risk of complications in the older population [127]. Ageing is accompanied by a range of physiological alterations, including diminished cardiovascular and pulmonary reserve, compromised immune function, altered pharmacokinetic and pharmacodynamic responses, including slower drug metabolism and increased sensitivity to anaesthetic agents, and an increased prevalence of frailty [47, 116, 128]. Frailty is often characterised by loss of muscle strength, slow walking, decreased levels of physical activity, reduced reserve capacity, and exhaustion in older adults [129]. Among age-related physiological changes, frailty is a critical factor in postoperative recovery, as it is associated with postoperative mortality, complications, and prolonged hospital stays [130, 131].

Considering the effects of frailty, it would be inadequate to evaluate ageing solely as a demographic process. Frailty is a condition that must be systematically assessed, and to this end, strategies such as prehabilitation programmes [132, 133] (e.g. preoperative aerobic and resistance exercises), cardiac [134] and pulmonary rehabilitation approaches, and frailty scoring systems (Clinical Frailty Scale, Edmonton Frail Scale, etc.) have been developed [135]. These interventions aim to reduce complication rates and support functional recovery. However, limitations may be observed in these interventions due to cost, resource constraints, time limitations, and low participation motivation among older adults [136]. Therefore, although their effects on surgical outcomes have been theoretically defined, it can be said that difficulties persist in translating them into clinical practice.

1.2.1 Cognitive changes after surgery in older adults

When examining the relationship between ageing and surgery, it is evident that the consequences can be critical not only physically but also cognitively. Preoperative cognitive exercises have been shown to be effective in older adults for reducing postoperative delirium and cognitive dysfunction [137, 138]; however, studies on exercise-based prehabilitation remain limited. In a systematic review conducted by Ekici et al. [139], the effect of exercise-based prehabilitation on postoperative cognition was examined, and it was reported that such interventions may have a protective effect. Nevertheless, due to the limited number of studies included in this review, the heterogeneity of exercise protocols, and the use of different cognitive assessment methods, the results should be interpreted with this in mind [139]. This review is also one of the studies conducted within the scope of this thesis and is presented in detail in Chapter 2.

Cognitive decline that may develop physiologically with ageing becomes more pronounced in the postoperative period. The most common cognitive complications in adults over 65 that contribute to postoperative morbidity, mortality, and loss of independence are postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) [140, 141]. The consequences of these complications can be as damaging as physical complications and can adversely affect the independence and quality of life of older adults in the long term [142].

POD and POCD are common age-associated postoperative neurocognitive complications in older adults, with incidence rates varying considerably across surgical populations and assessment periods [143]. These cognitive complications can importantly impact older adults, leading to prolonged hospitalisation, increased postoperative complications, reduced quality of life, and, in some cases, long-term cognitive decline, dementia, and elevated mortality risk [143- 145]. While POCD tends to resolve over time in many individuals, a subset of patients may experience persistent impairments with lasting consequences [146]. Although POD and POCD have traditionally been defined as separate postoperative cognitive states, emerging evidence suggests that these two conditions may represent points on a broader spectrum of postoperative neurocognitive fragility, and that acute delirium may more prolonged cognitive decline. POD is generally viewed as the more acute and transient

manifestation; however, cognitive impairments have been reported to persist in 10–30% of patients and may progress to POCD [147, 148]. The focus of this thesis is on POCD rather than POD.

1.2.1.1 Postoperative Delirium (POD)

POD is defined as a neuropsychiatric syndrome in older adults that develops immediately after surgery and is characterised by attention and awareness disorders with a fluctuating course [149, 150]. The incidence of this postoperative complication, which is more common in the older population, may vary depending on the type and urgency of the surgery and whether the patient requires intensive care [151]. Its prevalence in older adults can reach up to 60% (particularly after hip surgery) [152, 153] and has been associated with poor functional recovery, prolonged hospital stays, increased healthcare costs (exceeding $150 billion annually), and high mortality [154]. This complication, which is more common in older adults, is preventable in up to 40% of cases [155, 156]. Despite its prevalence, it is important to develop preventative strategies for older adults, as this condition often goes undiagnosed or is identified too late.

The pathophysiology of POD is not fully understood, but it is considered to be multifactorial. Alterations in neurotransmitter systems such as acetylcholine, serotonin, glutamate, γ-aminobutyric acid, and norepinephrine, together with stress, inflammation, neuronal damage, blood–brain barrier disruption, and melatonin deficiency, contribute to this complex condition [151].

The aetiology of POD is also multifactorial and includes predisposing factors (e.g. cognitive impairment/dementia, poor overall health, low body mass index (BMI), hypoalbuminaemia, frailty, depression) and precipitating factors (e.g. acute medical conditions or infections, abnormal leukocyte levels, anaemia, blood transfusion, prolonged hospitalisation, sleep deprivation) that increase the likelihood of POD [151]. These factors may reduce the brain's resistance to surgical and anaesthetic stress factors and thus reduce its defence against cognitive impairment in the postoperative period [157, 158]. Older patients who develop POD are at increased risk of POCD, which often presents with persistent memory impairment in the days or weeks following surgery [143, 159, 160].

1.2.1.2 Postoperative Cognitive Dysfunction (POCD)

Based on Bedford's (1955) early observations regarding potential anaesthesia-related cognitive problems in older individuals, the findings of the first study in this field revealed post-surgical cognitive changes. This study followed 251 cases and focused on "definite cases showing the most severe degree of dementia" (18 cases) [161]. However, this study relies largely on subjective reports from patients and their relatives and provides limited information on the underlying mechanisms of cognitive impairment. Dijkstra et al. (2002) [162] conducted a review focusing on the differences between POCD and patients' subjective cognitive complaints, demonstrating that long-term changes in cognitive function are not solely attributable to subjective perception but must also be confirmed by objective neuropsychological tests. Research conducted since Bedford's early observations has highlighted that POCD is a complex process associated not only with the direct effects of surgery and anaesthesia, but also with multidimensional mechanisms such as preoperative cognitive reserve, neuroinflammation, and vascular factors [162]. Supporting this view, there is research indicating that POCD may be associated with neuroinflammatory response, impairments in blood-brain barrier integrity, oxidative stress, and reduced synaptic plasticity [163]. Furthermore, it has been demonstrated that hospital stay duration, mortality rate, and functional independence are negatively affected in patients experiencing POCD, which may lead to significant clinical and socio-economic consequences for older adults [164]. Based on this evidence, we can say that POCD is not merely a transient cognitive impairment but may also be a trigger for long-term neurodegenerative processes in older adults.

Although cognitive impairment was initially thought to occur more frequently after cardiac surgery, the ISPOCD1(International Study of Post-Operative Cognitive Dysfunction) study [165] (1218 patients, ≥60 years of age, 13 centres, 8 countries) demonstrated that POCD can also develop after non-cardiac surgery. A study investigating the incidence of POCD following minor surgery in older adults showed that it was 6.8% in the early period and 6.6% at three months, with a significant increase in risk particularly in individuals over the age of 70 [166]. Long-term follow-up studies remain limited. In the ISPOCD1 subgroup, the POCD rate was 10.4% after one to two years, with no difference compared to the control group [167]. These results suggest that POCD may be common in the early postoperative period, more persistent in older

adults, and that long-term studies are needed to characterise the trajectory. Furthermore, POCD has been associated with an increased risk of mortality within three months after non-cardiac surgery [168]. The incidence of POCD ranges from 30% to 80% in the initial weeks following cardiac surgery and declines to approximately 10% to 60% at three to six months postoperatively [169]. For non-cardiac surgery, POCD is reported in 19% to 47% of patients, often contributing to long-term declines in functional ability and independence [170, 171].

POCD is a clinical condition characterised by impairments in attention, information processing, orientation, perception, and memory. It may also present with disturbances in consciousness, mood alterations, and personality changes [172]. POCD is typically defined as a decline in cognitive function that persists beyond 30 days after surgery, as earlier changes may be influenced by acute stress, pain, and medication effects [159]. The diagnosis of POCD using cognitive tests may be insufficient to capture its impact on individuals' daily lives, making the assessment of quality of life important. In a five-year postoperative follow-up study, Newman et al. reported that poorer cognitive performance was associated with poorer overall health and reduced work productivity [173]. Similarly, Steinmetz et al. followed the ISPOCD subgroup for 8.5 years and showed that POCD may be associated with increased mortality, the need for social support, and early loss of work capacity [174].

1.2.1.2.1 Pathophysiology of POCD

POCD is a multifactorial condition with a complex pathophysiology involving several interrelated biological processes. One of the primary contributors to its development is neuroinflammation. Surgical trauma can induce a systemic inflammatory response, leading to the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α). These circulating cytokines can cross the blood–brain barrier (BBB), where they activate microglial cells and trigger a cascade of neuroinflammatory events. This inflammation disrupts synaptic transmission and plasticity, contributing to the cognitive impairment observed in the postoperative period [175, 176].

Another important factor in the development of POCD is oxidative stress. Surgical procedures can disrupt the balance between reactive oxygen species (ROS) and

antioxidant defences, leading to neural damage. Moreover, anaesthesia and surgical stress can cause mitochondrial dysfunction [177] and indirectly contribute to cognitive slowing [151]. Older adults are more susceptible to oxidative stress, which may increase their risk of developing POCD [177, 178].

Other mechanisms implicated in the pathophysiology of POCD include disruptions in cholinergic neurotransmission, tau hyperphosphorylation, and the accumulation of amyloid-beta peptides, changes that mirror those observed in neurodegenerative diseases such as Alzheimer's disease [140, 179]. Findings also highlight the role of the gut–brain axis, with postoperative alterations in gut microbiota potentially triggering systemic inflammation and contributing to cognitive impairment [180]. The gut microbiota plays an active role in neuroendocrine and immune regulation and has been shown to influence cognitive function [181]. Surgery and anaesthesia can disrupt gut microbiota homeostasis and, for this reason, may contribute to cognitive impairment [181]. According to Liufu et al. [181], this disruption may be associated with decreased microbial diversity and changes in beneficial bacterial populations. Such dysbiosis can increase systemic inflammatory responses and trigger neuroinflammatory processes via the gut-brain axis by increasing the release of pro-inflammatory cytokines. Consequently, hippocampal inflammation and disruption of neuronal homeostasis may contribute to postoperative cognitive decline in older adults.

Furthermore, it has been demonstrated that abnormal gut microbiota caused by surgical anaesthesia is age-related, with a marked decline in both the abundance and diversity of microbiota observed with advancing age [181]. Based on this evidence, surgical interventions that further disrupt gut microbiota may increase the risk of POCD in older adults, who are already at a disadvantage in terms of microbial diversity and resilience.

1.2.1.2.2 Risk Factors for POCD

Although the relative contribution of individual risk factors remains unclear, several preoperative, intraoperative, and postoperative variables have been identified as contributing to the development of POCD. Among these, advanced age is recognised as a primary risk factor, with individuals aged 75 and over facing approximately a threefold increased risk of developing POCD compared with younger adults [157, 182]. Additionally, patients with comorbid conditions such as hypertension, cardiovascular

disease, or diabetes may be particularly vulnerable. These chronic conditions are thought to elevate POCD risk by negatively affecting vascular health and cerebral perfusion, which in turn may compromise the maintenance of cognitive function in the postoperative period [157, 182]. Educational level, associated with insufficient "cognitive reserve", has also been shown to influence POCD risk, with higher educational attainment offering a protective effect [183]. Other patient-related factors linked with POCD include frailty [168], a history of cerebrovascular disease [184], and chronic pain [185].

The role of surgery itself in POCD development is unclear, but surgical stress and inflammation are thought to affect brain function [175, 186, 187]. Although clinical data are conflicting, some studies indicate that major surgery may increase POCD risk [165, 188]. Conversely, other studies suggest that the size and type of the procedure may not importantly influence risk [189]. Cardiac surgery, particularly procedures involving cardiopulmonary bypass, is particularly associated with POCD [173, 190]. However, in patients with coronary artery disease, it may be that cognitive impairment may be more closely related to underlying cerebrovascular pathology rather than the surgery itself [191]. Furthermore, postoperative inflammatory responses are highly individual, and susceptibility to POCD may also be influenced by patient-specific immune conditions [151].

Pre-existing cognitive impairment, including mild cognitive impairment and dementia, is a well-established risk factor for POCD. Age-related reductions in neuronal number and brain volume may contribute to diminished memory capacity and slower response times, thereby increasing vulnerability to the cognitive stressors of surgery and anaesthesia. Older adults with pre-existing cognitive deficits are therefore more likely to experience postoperative cognitive decline. Supporting this, a study of patients undergoing hip replacement surgery found a higher incidence of POCD among those with pre-existing cognitive impairment [192].

It remains unclear whether anaesthesia alone constitutes a risk factor for POCD. While animal models suggest that anaesthesia can impair cognition in older subjects, clinical findings remain inconsistent [193, 194]. A study comparing general and regional anaesthesia found no difference [195], and another examining the association between deep anaesthesia and POCD also failed to establish a clear relationship [196]. A large-

scale study in Denmark [197] involving twin participants showed that previous major surgeries were associated with an important decline in cognition. However, this decline was not considered clinically important. In a subgroup analysis of 211 twins, one of whom had undergone surgery, and the other had not, no effect of surgery on cognitive function was found. Nevertheless, this study may have been influenced by selection bias due to the homogeneity of the population and the dropout of subjects with selective mortality and/or higher risk [197].

1.2.1.2.3 Prevention and Management of POCD

There is currently no universally accepted treatment for POCD; however, several strategies have been explored to reduce its incidence and severity. Non-pharmacological approaches are at the forefront of these strategies. Cognitive exercise programmes, regular physical activity, and sleep hygiene implemented before and after surgery may be effective interventions for preserving cognitive reserve by reducing neuroinflammatory processes [163, 198].

In addition to non-pharmacological interventions, certain pharmacological agents may also reduce the risk of POCD. A systematic review by Zeng et al. evaluated the relationship between commonly used anaesthetics and POCD, and found that dexmedetomidine and sufentanil, in comparison to other commonly used anaesthetic medication, may lessen the risk of postoperative cognitive decline [199].

Given the potential contribution of anaesthesia to POCD, efforts have also been made to minimise anaesthetic-related risks. The use of total intravenous anaesthesia (TIVA), combined with electroencephalogram (EEG)-guided depth of anaesthesia monitoring, may help preserve cognitive function by reducing exposure to excessive anaesthetic agents and limiting intraoperative cerebral hypoperfusion [200]. In the prevention and management of POCD, non-pharmacological approaches, along with strategies targeting the preoperative and perioperative periods, play an important role. Physical, cognitive, and psychological preparation programmes in the preoperative period are defined as prehabilitation. It has been demonstrated that prehabilitation may be an effective intervention for cognitive reserve in older adults [201] .

Although both perioperative management and prehabilitation are important in reducing the risk of POCD, perioperative management focuses on maintaining physiological

stability during and immediately after surgery, whereas prehabilitation aims to improve the patient's cognitive and physical reserve before surgery. Kotekar et al. (2018) [127] have demonstrated that factors such as neuroinflammation, hypoxaemia, hypotension, and anaesthetic agent selection are decisive in the development of POCD and that, therefore, maintaining oxygenation and haemodynamic stability, appropriate anaesthesia management, and early mobilisation may be fundamental protective strategies. However, He et al. (2024) [202] systematic review and narrative synthesis indicated that preoperative cognitive prehabilitation has the potential to reduce the incidence of POCD and post-operative cognitive decline in older adults; however, it was demonstrated that the current evidence is uncertain due to the limited number of studies and low methodological certainty. These findings suggest that non-pharmacological strategies are promising in preventing POCD, but stronger evidence is needed.

1.3 Skeletal muscle and physical activity

1.3.1 Skeletal muscle structure and function

Skeletal muscle is a highly organised and metabolically active tissue that plays a central role in maintaining posture, facilitating voluntary movement, and regulating whole-body metabolism. Structurally, it comprises bundles of muscle fibres encased within layers of connective tissue: the endomysium, perimysium, and epimysium, which provide mechanical support and enable the efficient transmission of contractile force [203].

Each muscle fibre contains numerous myofibrils, which are subdivided into sarcomeres, the fundamental contractile units of skeletal muscle. These sarcomeres are composed of precisely organised actin (thin) and myosin (thick) filaments, which interact through the sliding filament mechanism to generate force. The process of excitation–contraction coupling begins with the propagation of an action potential along the sarcolemma and into the transverse (T) tubules. This electrical signal triggers the sarcoplasmic reticulum (SR) to release calcium ions, which are essential for initiating and sustaining muscle contraction [204, 205].

In addition to its primary role in facilitating voluntary movement through contraction

and relaxation, skeletal muscle also functions as a metabolically active endocrine organ. It is capable of releasing myokines, such as interleukin-6 (IL-6), which influence systemic processes including metabolism, and inflammation [206]. Furthermore, skeletal muscle plays a critical role in insulin-mediated glucose uptake, reinforcing its contribution to metabolic regulation in a manner similar to that of traditional endocrine organs [207]. Skeletal muscle exhibits a remarkable degree of plasticity, enabling it to adapt in both size and fibre composition in response to various physiological stimuli, including disuse, ageing, and mechanical loading. This adaptive capacity is fundamental to preserving mobility, functional independence, and metabolic health throughout the lifespan [208].

1.3.1.1 Skeletal muscle contraction

The mechanism of skeletal muscle contraction is a finely regulated physiological process that converts electrical signals into mechanical force, underpinning voluntary movement and postural stability. It is initiated by an action potential in an alpha motor neuron, which triggers the release of acetylcholine (ACh) at the neuromuscular junction [209]. ACh binds to receptors on the sarcolemma, inducing depolarisation that propagates through the transverse tubules and activates ryanodine receptors (RyR1) on the sarcoplasmic reticulum, leading to the rapid release of calcium ions. Calcium then binds to troponin C, causing a conformational change in the troponin–tropomyosin complex and exposing myosin-binding sites on actin [210]. The ATP-dependent (Adenosine triphosphate) cross-bridge cycle facilitates sarcomere shortening and muscle contraction. Relaxation occurs when calcium is actively re-sequestered into the sarcoplasmic reticulum by Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase (SERCA) pumps, allowing tropomyosin to return to its inhibitory position [209, 211].

Ageing is associated with a progressive decline in the efficiency of skeletal muscle contraction mechanisms. Piasecki and colleagues investigated the impact of ageing on fast motor units, reporting a marked loss of these units alongside important remodelling of slow-twitch motor units. Such neuromuscular adaptations contribute to diminished contractile power, particularly during rapid or high-force movements [86, 212]. Moreover, age-related impairments in calcium handling and reduced efficiency of excitation–contraction coupling further compromise both the speed and strength of

muscle contractions. Although these physiological changes are generally at the root of the decline in muscle performance with ageing [213], individual variability affects the severity of this process. Factors such as genetics, nutritional status, chronic disease, physical activity level, and lifestyle are important determinants of age-related muscle performance [58, 214- 216].

1.3.1.2 Exercise and skeletal muscle structure

Exercise refers to physical activities performed in a planned, structured, and repetitive manner to improve or maintain health and enhance an individual's physical fitness [217]. It can provide numerous cardiovascular and metabolic benefits, as well as benefits for skeletal muscle structure and function [218]. Different types of exercise, such as aerobic and resistance training, will be discussed in detail in this section, as they exert distinct yet complementary effects on muscle mass, fibre composition, and overall physical performance.

Exercise induces structural and functional adaptations that enhance force production, fatigue resistance, and metabolic efficiency. Furthermore, it is recognised as a key regulator of skeletal muscle [218, 219]. The physiological and morphological changes elicited by exercise vary depending on the type, intensity, and duration of training. In response to resistance exercise, muscle hypertrophy develops, characterised by an increase in muscle fibre cross-sectional area. This process is mediated by mechanical loading, which activates intracellular signalling pathways and promotes protein synthesis and muscle growth [220].

Resistance training has been shown to stimulate myofibrillar protein synthesis and expand the myonuclear domain, thereby contributing to the structural integrity and functional maintenance of skeletal muscle across the lifespan [221]. These adaptations reinforce muscular resilience and mitigate age-related deterioration, supporting long-term physiological function. Resistance training elicits important functional adaptations in both young and older adults, including enhanced myofibrillar protein synthesis, improved motor control, and increased tendon stiffness, all of which contribute to greater muscle function and a reduced risk of falls in ageing populations [221, 222].

Aerobic exercise also induces both structural and metabolic adaptations in skeletal muscle and has been shown to stimulate muscle protein synthesis, predominantly

through the upregulation of mitochondrial protein fractions rather than substantial myofibrillar protein accretion [223]. Regular aerobic training has been demonstrated to increase mitochondrial biogenesis, thereby enhancing oxidative capacity and energy production efficiency in muscle cells [223]. Aerobic exercise primarily promotes mitochondrial biogenesis, enhances capillary density, and supports a shift towards more oxidative type I muscle fibres, improving fatigue resistance without increasing muscle mass [218, 224]. The structural plasticity of skeletal muscle is further evident in fibre-type composition, as training induces a transition from type IIx to the more metabolically efficient type IIa fibres, optimising contractile function [225]. Moreover, endurance exercise increases capillary density within muscle tissue and enhances oxygen transport and utilisation, thereby improving fatigue resistance [226].

In addition, physical exercise plays a pivotal role in preserving the NMJ, the critical interface between muscle and nerve communication. Regular exercise is associated with the maintenance and remodelling of NMJ morphology, potentially counteracting age-related degeneration and delaying the progression of sarcopenia [86, 212, 227]. In summary, aerobic exercise is a fundamental training modality that maintains and enhances cardiovascular health as well as the structural and functional integrity of skeletal muscle. The physiological benefits of resistance exercise extend beyond improving muscular strength, to improving mobility, balance, and overall independence, particularly in older adults.

1.3.1.3 Exercise and skeletal muscle adaptation in advancing age

Despite the gradual decline in skeletal muscle mass, strength, and function associated with ageing, skeletal muscle also possesses an extraordinary capacity for adaptation that supports the maintenance of function [228]. Evidence suggests that regular physical activity, particularly resistance training, may be effective against age-related muscle fibre atrophy, motor unit remodelling, and mitochondrial dysfunction, and may reduce the functional decline typically associated with ageing [221, 222]. Through resistance training, muscle protein synthesis and hypertrophy can be stimulated via anabolic signalling pathways, while regenerative capacity can be supported through increased satellite cell activation and increased capillary density [221, 228, 229]. Collectively, these adaptations help preserve muscle function and increase metabolic resistance in

older adults, thereby preventing the harmful physiological effects of ageing.

Exercise can act as a partially compensatory mechanism for MU loss that develops with ageing [84, 230, 231]. This mechanism is based on surviving motor neurons expanding the area they innervate through collateral reinnervation. Such adaptation leads to the formation of large motor units, which may result in reduced fine motor control [86]. In contrast, regular and individually tailored resistance training increases muscle mass, muscle strength, and neuromuscular efficiency in older adults. These improvements support mobility, balance, and functional independence [57, 232 ,233]. Clinically, the World Health Organization (WHO) recommends that older adults perform resistance training involving major muscle groups at least twice a week, in addition to 150 minutes of moderate-intensity aerobic exercise per week [234]. These strategies aim to slow age-related MU loss and preserve muscle function through exercise.

When considering the metabolic effects of physical activity, it can support healthy ageing by increasing insulin sensitivity, improving mitochondrial function, and reducing chronic low-grade inflammation. Collectively, these adaptations support the metabolic health of older adults [218, 235, 236]. Although physiological changes associated with ageing are largely inevitable, regular physical activity can support skeletal muscle adaptation, reduce frailty, and is arguably one of the most effective non-pharmacological strategies for extending the healthy lifespan of the older population.

However, there are limitations to the application of these exercises in older adults, as they are more likely to experience cardiovascular disease, musculoskeletal problems, and a higher risk of injury [237]. In addition, factors such as lack of motivation, low awareness, and insufficient facilities or professional support for participation in regular exercise programmes can hinder adherence in this population [238]. For this reason, when planning exercise interventions for older adults, it is important to develop strategies that address not only the benefits but also the potential barriers and disadvantages.

1.4 Physical activity and cognitive function in advancing age

Cognitive decline is well known to occur alongside deterioration in cognitive domains such as memory, executive function, and processing speed. However, physical activity

is also known to be a modifiable factor that may mitigate age-related cognitive decline. Both aerobic and resistance exercises have been shown to support brain health by increasing cerebral blood flow, promoting neurogenesis, and modulating neurotrophic factors that are critical for neuronal survival and synaptic plasticity, including brain-derived neurotrophic factor (BDNF) which is critical for neuron survival and synaptic plasticity, thereby contributing to brain health [239].

A systematic review and meta-analysis [240] examined the effect of resistance training on cognitive function in older adults with mild cognitive impairment and showed that cognitive improvements are possible. Although various types of exercise are beneficial for general cognitive function, resistance training appears to have a stronger effect on cognition [240]. Furthermore, aerobic exercise has also been shown to have a significant effect on improving attention, processing speed, and overall cognitive performance in older adults [239, 240]. However, resistance training has been found to have the greatest effect on cognition, and it is thought that this may be due to its ability to increase BDNF through mechanical loading, improve insulin sensitivity, and preserve neuromuscular connections.

Furthermore, unlike aerobic training or walking, which are often recommended after cardiac surgery, resistance training targets specific muscle groups and may enhance cognition through its direct effects on these muscles. Greater muscle engagement during resistance exercise requires increased neuromuscular activation and cortical input, which may augment blood flow to the frontal cortex responsible for executive functions. This could represent another mechanism underlying its effectiveness on cognition [241]. In addition, unlike aerobic exercise, resistance training requires conscious learning of new movements and tasks, a process that may promote both neurogenesis and neuroplasticity [242, 243] .

Resistance-based exercise programmes have been shown to improve overall cognitive health in older adults and may be effective in improving specific cognitive parameters such as executive function and memory [240]. Supportive evidence for the cognitive benefits of resistance exercise has also been reported in surgical populations. A pilot randomised controlled trial involving 38 patients who had undergone cardiac surgery assessed the effect of 12 weeks of resistance and aerobic exercise on cognition using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). The

findings of this study are noteworthy, as they indicate that resistance training may lead to greater cognitive improvements compared to aerobic exercise in older adults following cardiac surgery. This may be explained by the higher neuromuscular demands of resistance training, which could enhance central nervous system activation and promote neuroplastic adaptations. Such mechanisms may contribute to improvements in cognitive domains such as executive function and memory. These results highlight the importance of exercise modality when considering interventions aimed at supporting cognitive recovery. [244].

1.5 Motor control

1.5.1 Motor Control

Motor control refers to the complex process by which the central nervous system (CNS) organises and executes purposeful movements. The production of coordinated movement requires the simultaneous regulation of multiple components, including sensory input integration, motor planning, neural transmission, and muscle activation. With advancing age, structural and functional impairments in the brain, spinal cord, peripheral nerves, and musculoskeletal system increase the risk of motor control deterioration. Such impairments can adversely affect the precision and coordination of movement, leading to compromised balance and reduced functional independence. Consequently, the decline in motor control can have a profound impact on the overall quality of life in older adults [89, 245].

Other neurophysiological changes that may develop with age include reduced corticospinal excitability, diminished proprioception, diminished intermuscular coordination, and delayed reaction times [246]. These changes can increase the risk of falls, limit function, and reduce quality of life for older adults, so motor control is an important factor for older adults. Based on this, motor control training was developed as a targeted therapeutic approach that aims to improve movement precision, neuromuscular coordination and muscle activation patterns in neurorehabilitation and geriatric exercise programs [247].

1.5.2 Motor Control Training

Motor control training is a targeted exercise approach that aims to enhance quality of life by improving neuromuscular control, inter-joint coordination, and postural stability. These programmes typically incorporate a range of tasks involving focused attention, proprioceptive feedback, and precisely controlled movements performed under varying conditions [248].

Evidence suggests that motor control exercises can enhance performance in both healthy individuals and those with neurological or musculoskeletal impairments. Research has shown that such training can modulate motor unit recruitment patterns, reduce inappropriate co-contractions, and optimise the timing of muscle activation [249]. This form of intervention is particularly pertinent for older adults, who may experience motor decline in the absence of important muscle atrophy, an issue increasingly recognised as a central contributor to functional deterioration in later life. In support of this, Piasecki et al. [70, 86, 212] have demonstrated that ageing is associated with motor unit remodelling and loss, yet physical activity and targeted interventions such as resistance or motor control training can help preserve motor unit function through collateral reinnervation and enhanced neuromuscular activation. These findings highlight the relevance of motor control strategies in maintaining functional capacity and delaying age-related motor impairments.

Ageing is associated with a reduction in the number and function of MUs, impairing neuromuscular transmission [78]. Although resistance exercise training (RET) has been shown to increase MU firing rates, it may not be feasible for all individuals due to its physical demands. As an alternative, neuromuscular training protocols have been proposed to enhance motor control under submaximal conditions [250]. In a pilot study, ten healthy participants underwent a four-week neuromuscular training programme targeting the knee extensors. The intervention involved randomised sinusoidal oscillation tasks at 10%, 25%, and 40% of maximal voluntary contraction, with a frequency of 8 Hz and an amplitude of ±4%. Participants tracked these oscillations via a visual interface while engaging their knee extensors. Intramuscular electromyography (iEMG) assessments revealed a reduction in MU firing rate variability in the trained limb, suggesting improved neuromuscular control and potential benefits for MU remodelling [250]. Although this protocol was laboratory-based and required specialised visual feedback and electromyographic assessment, its underlying principle

of low-load precision motor control training may still be clinically transferable. Similar movement-tracking, force-matching, or visually guided submaximal contraction tasks could potentially be adapted into simplified outpatient rehabilitation settings.

1.5.2.1 Motor Control Training in the Upper Limbs

Upper limb motor control is essential for performing functional tasks such as grasping, writing, reaching, and object manipulation. However, neurological impairments resulting from conditions such as stroke or age-related decline can lead to deficits in coordination, motor planning, and movement precision [251]. To address these impairments, upper limb motor control training can be implemented using various exercise modalities. These typically consist of individually tailored, task-specific activities, including grip modulation exercises, mirror therapy, goal-directed reaching tasks, and sensorimotor training involving visual and tactile feedback [251, 252, 253].

Concerning its mechanism of action, motor control training involving repetitive, goal-directed upper limb tasks has been shown to induce neuroplastic changes within cortical motor regions, thereby enhancing voluntary motor control [252]. In addition, adjunctive technologies such as electromyographic (EMG) biofeedback, functional electrical stimulation (FES), and robotic-assisted devices have been found to further support improvements in upper limb motor function [254]. Notably, in older adults, motor control training has been associated with enhanced manual dexterity and reduced movement variability, contributing to improved motor performance and functional ability [89, 255].

1.5.2.2 Motor Control Training in the Lower Limbs

Physiological changes associated with ageing, such as neuromuscular deterioration, reduced proprioceptive acuity, motor unit loss, and delayed neuromuscular responses, can importantly compromise lower limb control [86]. One of the most critical age-related adaptations involves motor unit remodelling, particularly reinnervation or permanent loss, which is commonly observed in major locomotor muscles such as the quadriceps and tibialis anterior. Studies [86, 212] have demonstrated that although compensatory reinnervation occurs following motor unit loss in the ageing lower limb, this process is often incomplete. As a result, persistent muscle fibre denervation may

occur, potentially impairing motor coordination and contributing to functional decline in older adults. Age-related neuromuscular degeneration contributes to reduced power output and diminished movement precision, thereby increasing the risk of falls in older adults [256]. In this context, lower limb motor control training represents a valuable intervention aimed at enhancing postural stability, preserving mobility, and improving functional balance, particularly in older individuals who are at elevated risk for movement disorders and fall-related injuries.

Lower limb motor control training aims to address functional impairments by targeting neuromuscular performance and inter-joint coordination. These interventions typically involve structured activities such as dynamic balance exercises, perturbation-based stepping, ankle and hip strategy training, and task-specific gait exercises. Such training approaches have been shown to enhance individuals' ability to adapt to unexpected postural disturbances, improve reactive stepping responses, and support more efficient sensorimotor integration [256- 258].

The integration of progressive resistance and neuromuscular training has been shown to enhance intermuscular coordination and joint control, particularly when paired with proprioceptive feedback and functionally relevant tasks [246]. The efficacy of such interventions may be further augmented with technology-assisted feedback mechanisms, including EMG biofeedback and force platform-based training systems, which provide real-time information to guide and refine motor performance [259].

In conclusion, lower limb motor control training has the potential to enhance not only dynamic balance and mobility but also overall functional independence in older adults. The effectiveness of motor unit reorganisation and neuromuscular plasticity in ageing muscle is largely contingent upon targeted activation and load-specific recruitment strategies, which are best achieved through individualised and structured motor control interventions [86].

1.6 Cross-Education and Neural Adaptation

Cross-education refers to the phenomenon whereby unilateral strength or motor training results in performance gains in the contralateral, untrained limb. This effect is primarily attributed to neural adaptations occurring at both cortical and subcortical levels,

including increased interhemispheric communication and changes in motor cortex excitability [260].

From a mechanistic perspective, cross-education is thought to involve increased excitability in the ipsilateral motor cortex, which promotes interhemispheric communication via the corpus callosum. This neural interaction results in bilateral activation of motor networks, even during unilateral training. Neuroimaging and neurophysiological studies employing functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) have consistently demonstrated that unilateral strength or motor training enhances cortical activation bilaterally [260, 261].

One of the key advantages of cross-education in older adults lies in its ability to preserve strength and neuromuscular control during periods of limb immobilisation, such as following injury or surgery. By engaging the unaffected limb in targeted training, it is possible to attenuate the effects of disuse and prevent the progression of motor impairment in the contralateral, immobilised limb. This neural transfer effect is particularly beneficial in early rehabilitation scenarios, including hemiparesis, postoperative limb disuse, or instances where bilateral training is not feasible [260, 262].

Moreover, integrating motor control training with cross-education principles may enhance neuroplasticity and contribute to the reduction of interlimb asymmetries in motor performance among older adults. This combined approach has the potential to maximise neural adaptations by targeting both cortical reorganisation and interhemispheric facilitation, thereby supporting more balanced and effective motor function [262, 263].

1.7 Aims and Purpose of the Current Study

The study that is presented within this thesis will explore the impact of preoperative exercise and motor control interventions on postoperative cognitive and functional outcomes in older adults. Considering the growing concern surrounding postoperative cognitive disorders, specifically POD and POCD, this research aims to address key gaps in the literature by integrating clinical evidence, experimental data, and expert consensus regarding both cognitive decline and its neuromuscular correlates.

The thesis comprises three interrelated empirical chapters, the first of which is a systematic review examining the effects of preoperative exercise training on postoperative cognitive function [139]. This review synthesises current evidence to determine the efficacy of such interventions in preserving or enhancing cognitive performance in the perioperative context.

The second study is an experimental investigation conducted with a cohort of healthy older adults. In this study, twenty participants underwent a motor control training programme targeting the dominant upper limb. Moreover, upper limb tasks are associated with higher demands on fine motor control and cortical involvement, making them particularly suitable for investigating the interaction between motor control and cognitive function. The primary aim was to evaluate the effects of this intervention on cognitive performance, upper limb motor control, and physical function. In addition, the study assessed the cross-education effect by examining whether unilateral training elicited functional improvements in the contralateral, untrained limb.

The final study adopts a modified Delphi design involving multidisciplinary medical experts. This consensus-building exercise aims to explore clinicians' perspectives and levels of agreement concerning the feasibility and implementation of preoperative exercise interventions, with a particular focus on addressing cognitive vulnerability in older adults.

The overarching objective of this study is to contribute to a comprehensive understanding of the current gaps in exercise-based prehabilitation strategies, particularly those targeting cognitive resilience, the promotion of healthy ageing, and their integration into clinical practice. By employing a mixed methods approach that combines evidence synthesis, empirical investigation, and expert consensus, this thesis aims to inform the development of proactive and integrative strategies to optimise surgical outcomes in the ageing population.

Chapter 2 The effect of pre-operative exercise training on post-operative cognitive function: a systematic review

2.1 Introduction

Due to population ageing across the globe [264], the number of adults undergoing surgery continues to rise each year [114, 265, 266], with a higher risk of POCD observed in older age groups [163, 267]. The most performed procedures in older adults include orthopaedic surgeries such as hip and knee replacements, cardiovascular procedures, and abdominal surgeries [114]. As a result, there is a growing need for strategies to prevent cognitive decline during the preoperative period, although cognitive outcomes are influenced across the wider perioperative pathway. While physical exercise interventions have been shown to enhance cognitive function across various clinical populations [268] and age ranges [269], the specific impact of such interventions during the preoperative phase remains unclear within the context of surgery. This chapter presents a systematic review of the current literature exploring the effects of preoperative physical exercise training on postoperative cognition [139]. The objective of this chapter is to synthesise available evidence, highlight critical gaps in knowledge, and subsequently make suggestions on what research is needed to inform the future development of prehabilitation strategies aimed at improving cognitive recovery following surgery in individuals at increased risk of POCD.

As outlined in the section above, the number of individuals aged 60 and over is rapidly increasing worldwide, and this number is projected to reach 1.4 billion by 2030 and 2.1 billion by 2050 [270]. Advances in anaesthesia and surgical techniques have facilitated surgery for older individuals [114, 271]. It is known that with advancing age, the likelihood of health problems requiring surgery can almost double [114, 272, 273] meaning that older adults constitute an increasingly large proportion of the surgical patient group. Due to frailty and the prevalence of multiple health problems, older adults may experience difficulties that increase the risk of adverse outcomes before, during, or after surgery [114, 273].

POCD is a significant complication that may arise following surgical procedures [159, 274, 275]. POCD is characterised by impairments in various cognitive domains, including attention span, processing information, orientation, perception,

consciousness, and memory. Considering that emotional stress, pain, and pharmacological agents may each have adverse effects on cognitive functions during the early stages of the postoperative period, POCD is generally defined as cognitive impairment that persists for 30 days after surgery (i.e., not just in the initial recovery period) [159]. It is important to distinguish POD, which is acute and fluctuating and can last for several weeks, from POCD. POCD is not a term that encompasses POD, but prolonged POD can sometimes blur the temporal distinction between these two separate conditions. POCD not only causes a decline in cognitive performance but can also lead to a picture of psychiatric symptoms such as personality changes and mood disorders [276]. Approximately one-quarter of patients over the age of 65 experience significant cognitive decline after major surgery, and approximately half of these cases may result in permanent cognitive impairment [127]. Various studies in the literature have shown that POCD may be associated with long-term functional impairment in activities of daily living [165, 277], and can significantly affect quality of life.

The European Geriatric Medicine Society (EUGMS) have recently published their collaborative international guideline on "Physical activity and exercise for the prevention and management of mild cognitive impairment and dementia". Derived from a literature review, reported using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework, and discussions by community experts to reach a consensus, these guidelines strongly recommend the use of physical activity and exercise for the prevention and management of MCI and dementia. These guidelines discuss that although the evidence base for the positive cognitive effects of physical activity and exercise may be weak, overall beneficial effects, on both physical and psychological function, have been demonstrated [278].

Outside the perioperative context, numerous studies [279- 283] have demonstrated that exercise training may have positive effects on various aspects of cognitive function in both young [284] and older individuals [285]. Additionally, studies exist supporting the notion that physical exercise may be effective in preventing age-related cognitive decline [286, 287]. In this context, the term 'exercise' refers to a general term encompassing various types of structured physical activity, such as aerobic exercise, resistance exercise, and balance-focused activities (e.g., Tai Chi). The literature suggests that each of these exercise types may be effective through unique physiological mechanisms that can support maintenance of cognitive function [282].

Evidence from studies examining the independent effects of exercise suggests that several physiological mechanisms may contribute to cognitive function, including increased brain plasticity [288, 289], elevated levels of neurotrophic substances such as BDNF and IGF-1, regulated inflammatory cytokine responses [290, 291], increased cerebral blood flow [292], and reduced oxidative stress [293]. However, despite these findings and these mechanical suggestions regarding the cognitive benefits of exercise, no comprehensive evidence synthesis has yet been conducted to systematically examine the effects of physical exercise training administered in the preoperative period on postoperative cognitive functions.

2.2 Methods

2.2.1 Search strategy and inclusion criteria

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines on reporting for systematic reviews and meta-analyses (Appendix 9.3). The review protocol was prospectively registered with PROSPERO (International Prospective Register of Systematic Reviews) (Registration ID: CRD42022370648) prior to the commencement of data extraction. In May 2024, six electronic databases were systematically searched: Medline (OVID), EMBASE (OVID), EMCARE (OVID), CINAHL (EBSCOhost), Cochrane Library, and PubMed. The search utilised a combination of keywords, including terms such as cognitive* impair*, cognitive function, surgery, operation, exercise, and exercise therapy. No date limit was applied in this study. Detailed database-specific search strategies are provided in Appendix 9.3.

Duplicate records were identified and removed using Rayyan software. The titles and abstracts of the remaining studies were independently reviewed by two reviewers (H.S.E. and A.H.K.). In cases where there was any uncertainty between the evaluations, a decision was made in consultation with a third reviewer (A.L.G.). Full-text articles were then assessed by two independent reviewers (H.S.E. and M.C.Y.), and any disagreements were resolved by consulting a third reviewer (A.L.G.).

This systematic review is a compilation of all English-language studies investigating the effect of preoperative physical exercise interventions on postoperative cognitive

function in adults aged 18 years and older undergoing emergency or elective surgery, as age-specific studies focusing exclusively on older adults were limited. Studies that only included cognitive training interventions were excluded from the review. Study types included randomised controlled trials (RCTs), cluster randomised trials, cohort studies, case-control studies, mixed-method studies, and cross-over trials. Case reports, editorial articles, reviews, opinion pieces, educational theses, and conference abstracts were excluded.

2.2.2 Quality Assessment (Risk of bias)

The methodological quality of the included studies was independently assessed by two reviewers (H.S.E. and A.H.K.) using the Mixed Methods Assessment Tool (MMAT, 2018 version). The reviewers conducted the assessments separately and were blinded to each other's ratings. Any discrepancies were discussed between the two reviewers, and if consensus could not be reached, a third reviewer (A.L.G.) was consulted to make the final decision. In this assessment process, factors such as randomisation, baseline differences between groups, data integrity, blinding practices, and adherence to the intervention were considered. Studies scoring 4 or 5 on the MMAT scale (0–5) were classified as high quality, while those scoring below 3 were classified as low quality [294].

2.2.3 Data extraction

Data extraction was completed by two independent researchers (H.S.E. and M.C.Y.) using a pre-prepared structured data extraction form (Table 2.7). The data extraction form included the first author's name, year of publication, country where the study was conducted, study purpose, study design, participant characteristics, interventions and comparisons applied, type of surgery, POCD assessment method, time points at which tests were administered relative to surgery, and results obtained. Data from the three included studies were synthesised and presented comparatively.

Table2. 1: *Study demographics*

First author, year	**Country**	**Study aim [synopsis)**	**Study design**	**Participants**	**Interventions [Exercise type/duration) Comparator**	**Type of surgery**	**Cognitive assessment method**	**Post-surgery test time & Outcomes**
Kim et al., 2021[295]	USA	-To examine the effect of a preoperative aquatic exercise intervention on postoperative outcomes in older adults undergoing total knee arthroplasty	Pilot randomized clinical trial	-N=43 (19F, 24M) ->50 years old -Mean age: 67.2±6.1 years -Scheduled for elective total knee arthroplasty.	**Intervention group (N=20):** -Standard care plus 4–8 weeks of aquatic exercise: Three times/week, 60 min/session (10 min warm-up, 20 min flexibility & strength, 20 min low-intensity aerobic, 10 min cool down). **Control group (N=23):** Standard care only.	Total knee arthroplasty	Montreal Cognitive Assessment (MoCA)	-4–6 weeks after surgery. -MoCA score improved by 1.7 and 2.1 points (post-intervention/ postoperatively). -No change in control group.

Rengel et al., 2021[296].	USA	-To investigate the postoperative outcomes of home-based combined physical and cognitive prehabilitation on non-cardiac surgery patients.	Open label, randomized, controlled pilot feasibility trial.	-N=25 ->18 years old -Major non-cardiac surgery, ≥3 days hospitalisation -Mean age: 62 -Control group (N=8), Mean age: 56.	**Intervention group (N=17):** 10–21 days of computerised cognitive training (tablet, PositScience). Resistance exercise plan with daily schedule. **Control group:** Same cognitive game. General health information. Weekly phone calls.	Non-cardiac surgery.	National Institutes of Health (NIH) Cognitive Battery: Dimensional Change Card Sort, Pattern Comparison, Flanker Inhibitory Control.	-1 month after surgery. -88% adherence in intervention group. -Improvement in cognitive scores [not statistically significant).

Trubnikova et al., 2021[297].	Russia	-To determine how a physical prehabilitation program affected cognitive function, EEG, and neurovascular markers in patients undergoing coronary artery bypass grafting.	Prospective randomized study.	-N=103 -≥45 years old, no depression/dementia -Intervention (N=50), Mean age: 59 -Control (N=53), Mean age: 58.	**Intervention group:** 5–7 days/week aerobic exercise (40 min/session) Warm-up (5 min), main (30 min), cool down (5 min). **Control group:** Standard preoperative preparation.	Coronary artery bypass grafting.	Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Extended neuropsychological testing.	-7–10 days after surgery. -POCD: 58% (intervention) vs 79.5% (control). -Attention scores improved only in intervention group. -No difference in psychomotor/executive function. - Incidence of POCD decreased in the intervention group only.

2.3 Results

2.3.1 Study selection

The initial database search yielded 3,983 records, which were reduced to 3,066 after removing duplicates. Following a screening of titles and abstracts, 43 articles met the inclusion criteria for full-text review. The reasons for excluding the 40 articles from the systematic review were as follows: lack of cognitive outcome measures (n=9), inappropriate study design, including study types such as case reports, editorials, and conference abstracts that were not eligible according to the predefined inclusion criteria (n=8), incomplete or ongoing studies (n=5), interventions applied only in the postoperative period (n=10), and absence of a physical exercise component in the intervention (n=8). Ultimately, 3 studies met the inclusion criteria and were incorporated into the final review [295- 297]. This is summarised in a PRISMA diagram below (Figure 2.1).

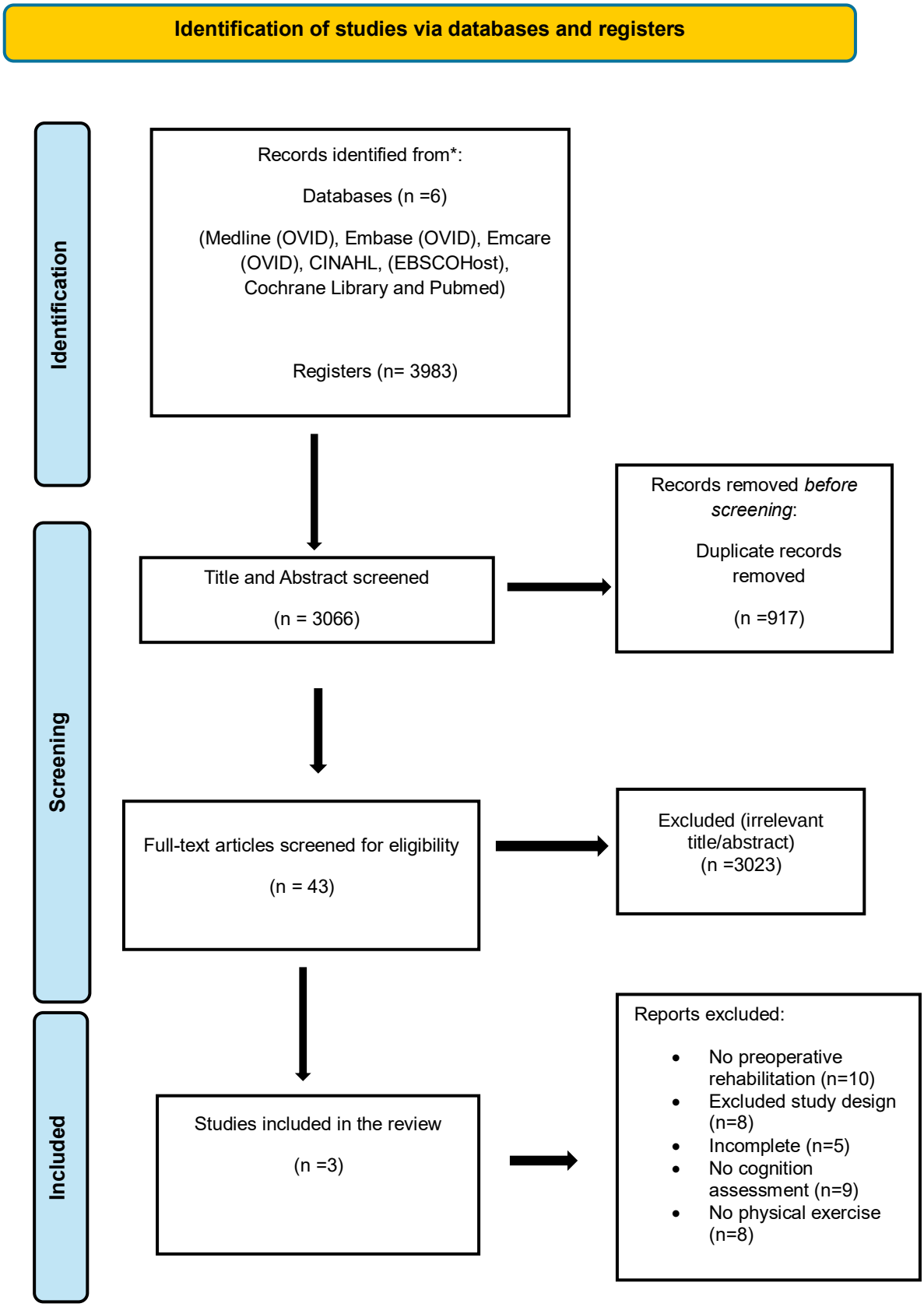


Figure 2.1 *PRISMA diagram of study selection.*

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. DOI: 10.1136/BMJ.n7

2.3.2 Study Characteristics

The mean age of participants in the included studies ranged from 44 to 73 years, and the sample size ranged from 25 to 103. Two of these studies were conducted in the United States [295, 296], and one was conducted in Russia [297]. In terms of study types, two of the studies were designed as pilot randomised controlled trials [295, 296], while one was conducted as a prospective randomised controlled trial [297].

2.3.3 Quality Assessment (Risk of Bias)

MMAT (2018 version) was used to assess quality, considering factors such as randomisation, baseline differences, completeness of data, blinding, and adherence to the intervention. Two of the included studies were assessed as having high methodological quality, with MMAT scores of 5 [297] and 4 [295], respectively, while the other study was classified as having low methodological quality, with an MMAT score of 3 [296]. The lack of evaluator blinding [295] and deficiencies in data management including a small pilot sample size, limited statistical power, and insufficient detail regarding missing data handling [296] were the main factors contributing to the low-quality rating (Table 2.8).

Table2. 2: *Quality Assessment (MMAT)*

	Is randomization appropriately performed?	Are the groups comparable at baseline?	Are there complete outcome data?	Are assessors blind to the intervention?	Did participants adhere to the intervention?	MMAT Score
Trubnikova et al., 2021 [297]	Yes	Yes	Yes	Yes	Yes	5 (100%) High-quality
Kim et al., 2021 [295]	Yes	Yes	Yes	No	Yes	4 (80%) High-quality
Rengel et al., 2021 [296]	Yes	Yes	No	No	Yes	3 (60%) Low-quality

2.3.4 Study Findings

Kim et al. [295] investigated the impact of a preoperative aquatic exercise programme on postoperative cognitive outcomes in adults undergoing knee arthroplasty. In this study, the participants' mean age was 67.1 (SD = 6.2), and 44% of the participants were women. The intervention, lasting four to eight weeks, was implemented in the form of fully supervised water exercise sessions three times a week, with the primary focus of these sessions being to improve flexibility, muscle strength, and cardiovascular fitness. Assessment sessions were conducted prior to intervention (post-surgery) and between four- and six-weeks post-surgery. The control group received standard care along with a brochure on perioperative nutrition. Cognitive performance was assessed using the MoCA, a 30-point tool with proven validity and reliability that measures various cognitive abilities, including memory, visual-spatial skills, executive function, attention, working memory, language, and orientation [298]. Improvements in MoCA scores were observed exclusively in the intervention group, with mean scores rising from 25.5 ± 2.2 at baseline to 27.2 ± 0.4 post-intervention (p=0.0008), and to 27.6±0.4 at the postoperative timepoint (p = 0.033). The overall effect of the intervention was statistically significant, with a mean increase of 1.46 (95% CI: 0.46 – 2.45, p = 0.005). This represents a large effect size relative to typical findings in the literature.

Trubnikova et al. [297] investigated the effect of preoperative aerobic exercise training on patients undergoing coronary artery bypass grafting (CABG). All patients included in this study were male, with a mean age of 58 (interquartile range: 52–65). The intensity of the aerobic exercise to be performed was individually adjusted based on the cardiopulmonary exercise test administered to patients prior to the intervention. The exercise training was administered in the form of supervised daily treadmill sessions lasting 40 minutes, including 5-minute warm-up and cool-down periods. These sessions targeted a perceived exertion level of 12 to 15 on the modified (0-20) Borg scale, corresponding to ‘somewhat hard’ to ‘hard’ exertion levels [299]. The control group did not participate in any exercise training. Cognitive function was assessed using a neuropsychological test battery measuring domains such as attention, psychomotor speed, executive function, and short-term memory, administered via the Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB), and ‘Status PF’ software within 7 to 10 days post-surgery [297]. The incidence of postoperative cognitive decline was significantly lower in the intervention group (58%) compared to

the control group (79.5%) (OR = 2.74, 95% CI: 1.11 – 6.81, p = 0.029). Attention scores were significantly higher in the exercise group than in the control group (p = 0.048) and showed a significant improvement from baseline after surgery (p = 0.04). In contrast, declines in attention scores were recorded in the control group after surgery (p=0.03). No differences were observed between groups in psychomotor or executive functions, parameters of cognitive performance; however, both groups showed significant improvement in these areas postoperatively (p = 0.0008 and p = 0.0001, respectively). Overall cognitive improvement was only achieved in the intervention group, but this was not statistically significant (p = 0.06). No power calculation was reported, and the small sample size may have limited the ability to detect statistically significant effects.

In a study conducted by Rengel et al. [296] the effect of multimodal exercise training, which included preoperative cognitive and physical training, on postoperative cognitive functions in patients undergoing major non-cardiac surgery was investigated. The median age of patients in the intervention group was 62, while the median age of patients in the control group was 56. All participants were given general health information and electronic tablets for daily use. Participants in the control group, referred to as the “active attention” group, played a trivia-based electronic game, while participants in the intervention group played an adaptive, progressively difficult game designed to improve cognitive performance. In addition, the intervention group was given an exercise plan that could be performed using resistance bands. Weekly telephone calls were made to both groups for guidance and support, and participants' cognitive performance was assessed one month after surgery using subtests selected from the National Institutes of Health (NIH) Cognitive Battery. Although patients in the intervention group showed a trend towards improvement in executive function and cognitive flexibility (dimensional change card sorting), inhibitory control and attention (flanker task), and processing speed (pattern comparison), these differences were not statistically significant (p > 0.05).

There was significant heterogeneity among the three studies included in this review in terms of intervention protocols and cognitive outcome measures used, and therefore a meta-analysis could not be performed. The studies differed in terms of exercise method, duration and implementation, as well as the tools used to assess cognitive function, which did not allow for a meaningful quantitative synthesis of the findings.

2.4 Discussion

This systematic review investigated the effect of preoperative exercise training on postoperative cognitive outcomes. The existing literature in this field is limited, and only three studies met the inclusion criteria. The included studies utilised different exercise interventions, such as water exercise, aerobic exercise, and a combination of cognitive and physical approaches, along with various cognitive assessment tools. Despite these methodological differences, the three studies included in the systematic review demonstrated that prehabilitation may have positive effects on post-operative cognitive functions, although one study did not report a statistically significant improvement [296].

Cognitive function plays a vital role in maintaining independence in daily life [300] and ensuring effective interpersonal communication [301, 302]. Age-related cognitive decline has been linked to both structural and functional brain changes [303]. Although such decline is often considered a normal aspect of ageing [304], surgical interventions, being acute physiological stressors, can significantly accelerate cognitive decline and contribute to the development of POCD [159]. Considering the growing population of older adults undergoing surgery [272, 273] and the significant adverse effects POCD can have on both clinical outcomes and patient well-being [274, 275], greater emphasis should be placed on identifying and implementing effective preventive strategies.

One of the studies included in this review examined the effect of preoperative water exercises on postoperative cognitive function and reported cognitive improvements measured by the MoCA [295]. Supporting these findings, a more recent systematic review published in 2021 and analysing 16 studies [285] has shown that water exercises may have beneficial effects on various neuropsychological outcomes, including cognitive functions, in older adults. This review encompassed a broad spectrum of participant groups, including healthy community-dwelling older adults [305- 309], and included older adults with mild-to-moderate Parkinson's disease [310], a history of falls [311], and musculoskeletal conditions such as osteoporosis, osteopenia, or osteoarthritis [307-309, 312-314], illustrating the wide applicability of this exercise modality.

Compared to land-based exercises, aquatic exercises may help overcome serious barriers commonly reported in older adults, such as fear of falling, which can hinder

physical activity. The aquatic environment provides a supportive setting where balance and postural control difficulties can be safely addressed, potentially enhancing balance reactions and postural stability [315- 318].

However, water exercises may not be suitable for all older adults. This is because issues such as access to appropriate facilities and feelings of insecurity in the water can pose barriers for this age group. Furthermore, a further randomised controlled trial conducted in older adults demonstrated that water-based exercise was effective in improving cognitive performance, body composition, and functional fitness [319]. In particular, this study emphasised that variations in a single type of exercise, such as differences in training format, can influence specific outcomes. While continuous (e.g., steady-paced aquatic walking or cycling) and intermittent (e.g., interval-based high-intensity water aerobics) water exercises are shown to be the most effective methods for improving functional fitness, their combination appears to be more beneficial for improving cognitive function and body composition [319].

In addition to aquatic exercise, there may be substantial evidence supporting the benefits of land-based exercise training on cognitive function in both younger [284] and older adults [285] as documented in multiple systematic reviews [279, 281]. Nevertheless, as this review has identified, there remains a lack of robust evidence specifically addressing whether preoperative exercise training can enhance postoperative cognitive outcomes or reduce the risk of developing POCD. Although the included study involving a combined cognitive and resistance exercise intervention [296] reported only a signal of effect (i.e., a non-significant numerical improvement) towards cognitive improvement, more comprehensive findings have been presented in a recent systematic review and meta-analysis from 2021 [320]. This analysis, which encompassed 47 randomised controlled trials (41 of which were included in the quantitative synthesis), concluded that combined cognitive and physical interventions were more effective than single-modality approaches for improving cognitive function. Combined training was found to be the most effective format for improving cognitive outcomes when compared to sequential approaches or exergaming. Notably, the physical elements of these interventions commonly included aerobic, resistance, and balance-based exercises components that align with current physical activity guidelines for older adults [321], due to their capacity to promote distinct physiological adaptations [322, 323]. These findings suggest that a preoperative training programme

combining these exercise methods with cognitive training may be effective in enhancing the physiological and cognitive resilience of older adults prior to surgery.

The study focusing solely on aerobic exercise training [297] demonstrated a significant improvement in cognitive function within the exercise group. However, cognitive assessments in this study were conducted only 7 to 10 days after surgery, a period earlier than standard POCD definitions, the observed cognitive function improvement may still be relevant, as cognitive vulnerability is often greatest in the immediate postoperative phase. In this early postoperative period, various factors such as emotional stress, pain, and medication use [159] can impair cognitive performance, and declines observed at this stage are less likely to affect long-term quality of life or the ability to return to normal daily activities.

A possible reason for the difference in outcomes between the aquatic [295] and aerobic [297] exercise study and the study that incorporated combined training [296], aside from the variation in sample size, may relate to the level of exercise supervision. Although good compliance was reported in all three studies and each received a score for this in the MMAT quality assessment, the first two studies (water and aerobic) used fully supervised training sessions, whereas in the combined intervention, participants were monitored only by weekly telephone calls at home. Supervised exercise has been found to result in greater adherence and compliance in a range of studies involving different exercise modalities and populations [324- 326]. However, evidence regarding whether this increases physiological adaptation is unclear. For example, supervision was found to have no effect on physiological adaptation outcomes in older adults who completed a four-week high-intensity interval training programme [327].

In the study by Trubnikova et al.[297] the level of attention increased in the intervention group and decreased in the control group as expected However, unexpectedly, significant increases were reported in both the intervention and control groups in cognitive domains such as psychomotor speed and executive function, which is quite noteworthy. Considering the factors that could cause this situation, several possible effects are considered. The first of these effects is the practice effect of test repetition [328]. Due to this effect, the control group may have shown significant improvement in the second postoperative assessment because they were familiar with the test. Secondly, general postoperative recovery and the positive effects of standard care may

have led to positive developments in cognitive areas. In addition, positive effects may have been obtained in the control group due to the Hawthorne effect, that is, participation in the study and follow-up [329].

2.4.1 Strengths and Limitations

The primary strength of this systematic review lies in its comprehensive synthesis of existing evidence examining the effect of preoperative exercise interventions on postoperative cognitive impairment. The review was conducted according to a pre-specified protocol and employed a systematic approach to assess the risk of bias across the included studies. Furthermore, the findings were reported in accordance with recognised PRISMA guidelines, thereby enhancing the transparency and reproducibility of the review process.

However, several limitations must also be acknowledged. One of the three included studies was found to be of low methodological quality, which may have affected the overall certainty of the evidence. Another study included only a specific male patient population who had undergone CABG, which limits the generalisability of the findings to broader surgical populations. Finally, although our systematic search strategy was rigorous, the exclusion of grey literature and non-English language studies may have limited the scope of the evidence obtained.

2.4.2 Conclusion

In conclusion, this systematic review has demonstrated that preoperative exercise training may be a promising strategy for alleviating POCD in adult patients undergoing elective surgical procedures. Although the evidence base is limited, the findings of the included studies suggest potential benefits. However, the small number of existing studies, each using different exercise interventions and various cognitive assessment tools, clearly highlights the need for more robust and standardised research in this area. The objectives of future research should be as follows: (i) adopting standardised and validated cognitive assessment methods to enable meaningful comparisons between studies; (ii) specifically targeting older adults at high risk of POCD who are most likely to benefit from preventive strategies; and (iii) using larger and more representative samples to facilitate reliable statistical analyses and increase generalisability. Furthermore, with the growing interest among researchers, clinicians, and health

policymakers in the role of exercise-based surgical prehabilitation, investigating how such interventions can be integrated into perioperative care pathways is crucial for the implementation of preoperative exercise interventions. Studies should examine how preoperative physical activity affects cognitive outcomes in older populations, with the aim of contributing to the development of evidence-based, feasible, and effective exercise protocols that are compatible with current clinical practice.

This systematic review is valuable in addressing a critical gap in the existing literature, specifically the lack of studies examining the effects of preoperative physical exercise interventions on postoperative cognitive function in older adults (i.e., those aged 65 and above). Furthermore, only three relevant studies were identified in the broader adult population, reinforcing the limited scope of current research in this area. Based on the findings of this review, it is suggested that preoperative physical activity may contribute to reducing the risk of postoperative cognitive decline; however, it is important to note that the strength of this evidence is limited due to methodological heterogeneity, underrepresentation of older adults, and small sample sizes.

In response to these limitations, the findings of an experimental study involving older individuals living in the community are presented in Chapters 3, 4, and 5 of this thesis. This study investigated whether a structured upper limb motor control training (uMCT) programme, administered three times a week for four weeks, affected the cognitive and physical functions of healthy older adults. This approach was selected to provide a novel and more accessible intervention targeting neural mechanisms and potential cross-education effects, addressing limitations of previous protocols that focused predominantly on lower limb or whole-body exercise. Targeting a specific and relevant cohort, this study aims to provide preliminary evidence supporting the potential of uMCT as a feasible prehabilitation strategy to enhance resilience and optimise outcomes in older surgical candidates.

Chapter 3 Methodology and methods for "The effect of low-intensity unilateral upper limb motor control training (uMCT) on cognitive and physical function in healthy older adults: a pilot study"

3.1 Introduction

This chapter presents the methodology and methods of a pilot study conducted to examine the effects of low-intensity unilateral uMCT on cognitive and physical functions in healthy older adults. It outlines the rationale for the research design and explains the methodological framework for the selection of the study approach. Subsequently, participant characteristics, intervention protocols, outcome measures, data collection process and data analysis methods are reported in detail.

3.2 Methodology

This study was planned and implemented as a pilot study design. The aim of this study was to test the feasibility, safety, and potential effect size of low intensity unilateral uMCT in healthy older adults in a small, controlled sample; hence, it was conducted as a pilot study. Pilot studies are recommended to determine the practical feasibility of different components of the research process, such as participant recruitment, adherence to the intervention protocol, and data collection procedures, particularly for new and limited interventions [330, 331]. The limited number of studies in the literature examining the effect of uMCT on cognitive and physical functions in older adults made an exploratory approach methodologically appropriate.

The pilot study enables the collection of preliminary findings from the intervention and allows for the estimation of the sample size required for the design of a future large-scale clinical study (such as a randomised controlled trial) [332, 333]. The pilot study design, which ensures the reliability of data collection tools and prevents potential waste of resources, has been determined to be a rational choice that reduces research risk, is ethically justifiable, and provides a strong preliminary assessment for subsequent research studies.

3.3 General Methods

3.3.1 Regulatory approval and participant recruitment

This study was reviewed and approved by the Nottingham University Faculty of Medicine and Health Sciences Research Ethics Committee (FMHS 331-0723). It was registered at www.clinicaltrials.gov (NCT06962722) and conducted in accordance with the declaration of Helsinki. Twenty healthy older adults (10 male, 10 female) were recruited to this study via posters in the local community, on social media platforms, and via the University of Nottingham research groups Patient and Public Involvement and Engagement (PPI-E) community. Prior to eligibility screening, all potential participants gave their written informed consent (ICF) to participate in this study after provision of a participant information sheet (PIS) and the opportunity to ask questions.

3.3.2 Eligibility assessment

After asking any questions and providing written informed consent to participate all potential participants underwent a screening session to assess their eligibility for the study. In this session, participants medical history was reviewed, and their height, weight, alcohol and tobacco use recorded. Blood pressure (BP) measurements were performed. An ECG was performed to screen for clinically significant cardiac abnormalities such as arrhythmias, conduction disturbances, or signs of ischaemia that could increase participation risk before participants were included in the study, and participants with abnormal findings were excluded from the study.

The inclusion criteria for this study were:

Participants were community-dwelling, generally healthy older adults without clinically diagnosed cognitive impairment or major medical conditions.

- Willing and able to give informed consent for participation in the study
- Aged between 65-85 years,

with exclusion criteria of:

- Body mass index (BMI) <18 or >35 kg/m²
- Clinically confirmed diagnosis of cognitive impairment or dementia
- Current or recent (< 5y) malignancy

- History of, or current psychiatric illness
- History of, or current neurological condition (e.g., epilepsy, Parkinsons disease, cerebrovascular disease)
- Severe respiratory disease (e.g., uncontrolled asthma, COPD, pulmonary hypertension)
- Active cardiovascular disease: Uncontrolled hypertension (BP > 160/100mmHg); Recent (< 12mo) cardiac event; Heart failure (Class III/IV); Significant arrhythmia; Unstable angina
- Metabolic disease: Untreated hyper/hypo-parathyroidism; Cushing's disease; Type 1 or 2 diabetes
- Significant musculoskeletal disorder [based on clinical opinion)
- Family history of early (< 55y) death from cardiovascular disease

All information obtained during screening sessions was reviewed by a clinician to confirm eligibility for participation in the study. The maximum duration between screening and first assessment visit was stated as 3-months, as per research group policy, however all participants completed this first assessment visit within 2-weeks of screening.

3.3.3 Experimental Protocol

After screening, eligible participants were invited to undergo their first (pre-training) assessment visit. This assessment session was repeated twice more: once after the uMCT training and once 4-weeks after cessation of uMCT (follow-up). All assessment sessions and details of the uMCT intervention applied are shown in Figure 3.1.

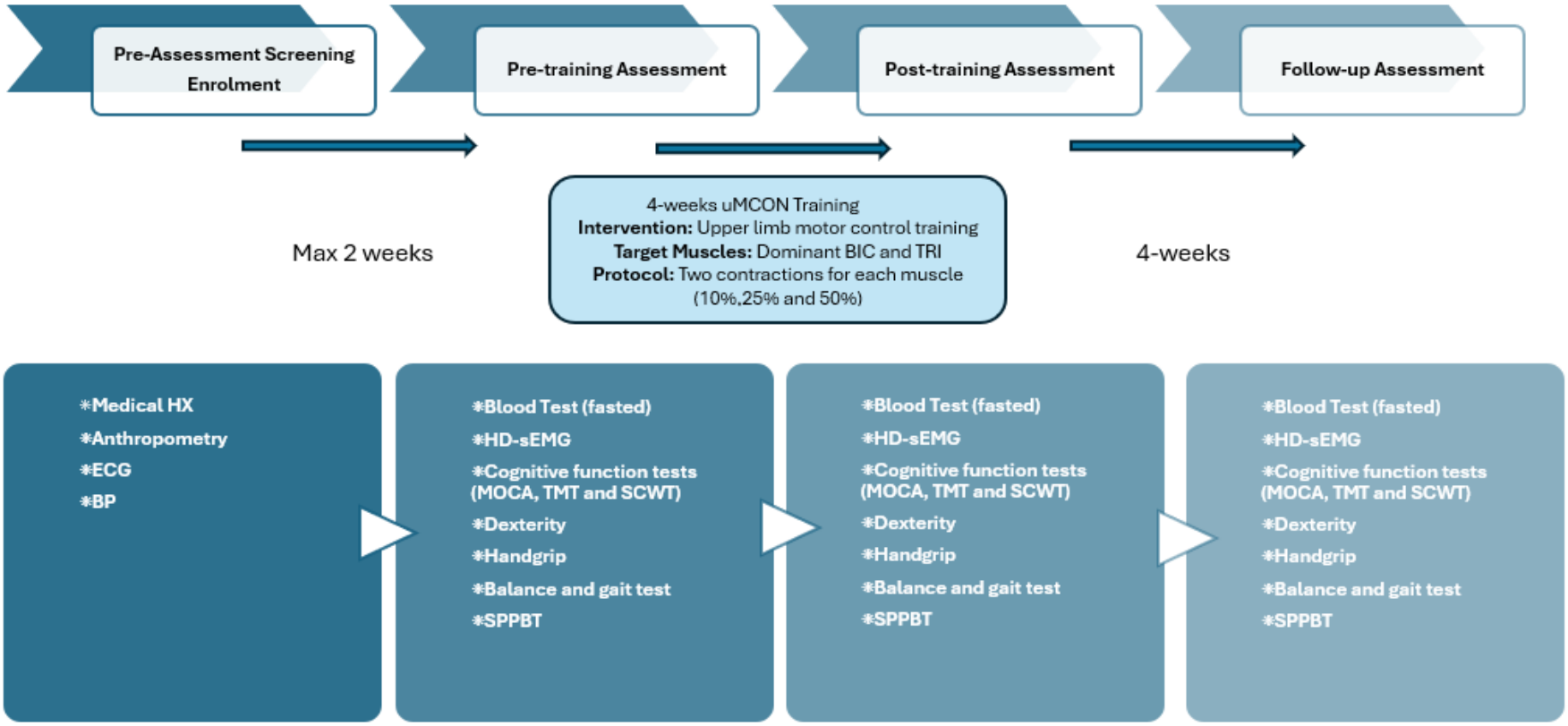


Figure 3.1 *Schematic diagram summarising the experimental protocol.*

Abbreviations: uMCT: Upper limb motor control training; HX: history, ECG: Electrocardiogram; BP: Blood pressure; HD-sEMG: High-density surface electromyography; BIC: Biceps brachii muscle; TRI: Triceps muscle; SPPB: Short Physical Performance Battery tests; MoCA: Montreal Cognitive Assessment; TMT: Trail Making Test; SCWT: Stroop Colour Word Test.

3.3.4 Outcome measures

3.3.4.1 Cognition assessment

To assess participants' cognitive functions, the Montreal Cognitive Assessment MoCA, Trail Making Test (TMT), and Stroop Colour Word Test (SCWT) were used. In addition, a single fasted blood sample was taken at the start of each of these assessment visits via venepuncture (antecubital vein) to determine systemic (plasma) levels of Interleukin-2 (IL-2) and BDNF. Since a fasted blood sample was required to minimise the influence of recent food intake on circulating biomarker levels, all assessment sessions were performed in the morning following an overnight fast (minimum 10h) with water *ad libitum*. Prior to all cognitive tests, participants were given a detailed explanation of each task in the test and confirmed full understanding before starting. Cognitive assessments were conducted in a quiet, private room. Blood samples were centrifuged immediately after collection to facilitate collection of plasma, with plasma stored at -80°C until analysis.

3.3.4.1.1 Montreal Cognitive Assessment (MoCA)

The MoCA is a test developed to screen for early-stage cognitive decline and MCI in older adults and is capable of assessing different cognitive domains. These domains include executive function, language, visual-conceptual skills, calculation, attention and concentration, memory, and abstract thinking [298].

The MoCA test is administered individually in a quiet environment and takes approximately 10-15 minutes to complete. It is a test that includes visual/executive drawing, naming, memory, attention, language (sentence repetition and verbal fluency), abstraction through similarity, delayed recall of five words, and orientation instructions [298]. The maximum score that can be obtained in the MoCA is 30, with a score of 26 or above generally indicative of normal cognitive function [334, 335].

In the study by Nasreddine et al., (2005), the MoCA has demonstrated to be more sensitive and specific than the MMSE, another widely used test for detecting mild cognitive impairment [298]. Further, the validity and reliability of this test have also been confirmed in clinical settings across different patient groups. For example, MoCA has been shown to differentiate between healthy older adults, adults with mild cognitive impairment, and individuals with Alzheimer's disease based on score differences [298].

Furthermore, this test has been demonstrated to have good test-retest reliability and high sensitivity and specificity [298, 336]. To contextualise these scores, the average MoCA score in healthy older adults was 27-28, a group of individuals with MCI had a mean MoCA score of 22-24, and individuals with Alzheimer's disease reported scores below 20 were reported.

In relation to exercise interventions, the MoCA is one of the tests frequently used to assess the effects of exercise interventions on cognition in older adults. Studies have reported that aerobic exercise, resistance training, and multi-component exercise training can improve MoCA performance. Randomized controlled trials and systematic reviews have demonstrated that both short-term and long-term exercise interventions can produce significant improvements in memory, executive functions, and general cognition, as measured by the MoCA [337, 338]. Based on these study results, MoCA is sufficiently sensitive to detect exercise-induced global cognitive changes in older adults.

3.3.4.1.2 Trail making test (TMT)

TMT is a test that can measure cognitive function and has been shown to do so in many patient populations including those with MCI, neurodegenerative diseases, and brain injury [339]. It is an appropriate test for the evaluation of visual scanning, graphomotor speed, visuomotor processing speed, working memory, and executive function in older adults [339]. Each of these components of cognition are important for older adults to independently perform activities of daily living (ADL) [340, 341], with one study showing a direct relationship between executive function and quality of life (QoL) in those over the age of 65 [342]. TMT is a short and practical test that consists of two parts (A and B) and can be used in older adults [339]. In TMT-A, participants attempt to connect numbers from 1 to 25 in the correct order, while in TMT-B, they must connect numbers and letters alternately (e.g., 1-A-2-B-3-C...). The TMT is a brief assessment, typically completed within 5–10 minutes, and was selected to minimise participant burden when used in combination with other cognitive tests within the assessment battery.

TMT scoring is based on recording the total time in seconds it takes for the participant to complete the task after explaining the test and ensuring that they are ready. According to Sánchez-Cubillo et al. (2009), longer times are associated with poorer cognitive

performance, while shorter times are associated with better cognitive performance [343]. If any errors are made during the test, the participant is notified and asked to correct the error and continue the test. For TMT Part A, the average score is 29 seconds, >78 seconds reflecting "deficient," and this section must be completed by participants in no more than 90 seconds. For TMT Part B, the average score is 75 seconds, >273 seconds reflecting "deficient," and this section must be completed by participants in no more than 3 minutes [343].

In the context of exercise intervention studies, the TMT has been used as a measure of executive functions. Studies investigating the effects of both aerobic and multicomponent exercise interventions on cognitive performance have shown that exercise interventions can produce significant improvements in TMT performance [344, 345].

3.3.4.1.3 Stroop Colour-Word Test (SCWT)

The SCWT is a neuropsychiatric test that can assess cognitive components such as cognitive inhibition, information processing speed, selective attention, and executive function in older individuals, with good test-retest reliability and validity previously reported [346, 347]. In this test, a conflict is created between the words and the colour of the text, and the participant is asked to say the colour of the text rather than the word. This process involves unconscious reading [347].

The SCWT consists of three parts. In the first part, participants are asked to read the names of colours written in black as fast as they can in 45 seconds, and the number of words they read is recorded. In the second part, participants are asked to name the colours of "XXXX" letters written in coloured ink within 45 seconds, and the number of words they read is recorded. In the final part, participants are asked to name the colours of colours written in different ink colours (for example, "GREEN" written in red ink), ignoring the word itself, and the number of words they read in 45 seconds is recorded.

As for SCWT analysis, both the Interference Raw Score and the Interference T Score from the SCWT are designed to assess inhibitory control, a fundamental component of executive functioning. In this test, inhibition control is measured in the final part. In this part, the automatic response to reading the word is suppressed and the ability to

correctly name the ink colour is assessed. It reveals the individual's capacity to focus their attention on the appropriate target and to respond appropriately when faced with stimulus conflict. The Interference T Score is a standardised measure adjusted for demographic factors such as age and gender, allowing for comparison with normative data. The Interference T Score can be used to show how well a participant conforms to expected norms. Interference Raw Scores represent the direct difference in response times between compatible and incompatible conditions (e.g., Word and Colour-Word). The SCWT Colour score obtained in the Colour Naming condition primarily assesses attention control, psychomotor speed, and basic information processing; therefore, improvements in this measurement indicate the development of basic executive functions.

The Colour T Score reflects basic information processing speed and attention efficiency. In this test, the SCWT Colour score obtained in the Colour Naming condition primarily assesses attention control, psychomotor speed, and basic information processing; therefore, improvements in this measurement indicate the development of basic executive functions. The Raw Word Score reflects the automatic verbal fluency and processing speed of cognitive function, while the Word T Score reflects a standardised measurement of these abilities [347]. The SCWT Colour-Word Raw Score is a direct measure of executive functions, particularly inhibitory control and cognitive flexibility, and in this test, participants must suppress the tendency to read a word and instead say its ink colour [348]. Thus, in this test, the prefrontal cortex comes into play to manage the effects of competing stimuli.

The SCWT is a test used in clinical and experimental studies and is considered the gold standard for assessing inhibition and executive functions [349]. In this study, the Stoelting Stroop Colour & Word Test Normative Update, Adult Kit was used, a format analysed using Adult, Computerised Scoring. The Interference T score calculated in this analysis is a measure reflecting the participant's level of cognitive control in the face of conflicting stimuli, and high T scores indicate stronger response inhibition and attentional regulation skills. This score is considered a sensitive indicator of executive function in the context of ageing, neuropsychiatric disorders, and cognitive impairments [350, 351].

In the context of exercise/physical activity intervention studies, the SCWT is a widely

used cognitive test to assess inhibition and attention control in adults and to evaluate executive functions. A systematic review and meta-analysis [352] examining the effect of exercise programmes on cognitive functions in older adults specifically showed that exercise may positively contribute to Stroop performance in this age group by reducing SCWT scores, suggesting that it may increase inhibition speed and processing speed.

3.3.4.1.4 Plasma IL-2 concentrations

Plasma IL-2 concentration was determined using a commercially available enzyme-linked immunosorbent assay (ELISA) (Invitrogen Human IL-2 High Sensitivity ELISA kit (via ThermoFisher, Catalogue Number: BMS221-2HS)) performed according to manufacturer's instructions. This is a solid-phase sandwich ELISA designed to detect and quantify the level of human IL-2 in cell culture supernatants, plasma, and serum.

3.3.4.1.5 Plasma BDNF concentrations

The BDNF ELISA was performed using the Invitrogen (ThermoFisher) Human BDNF ELISA Kit (Catalogue Number: EH42RB) according to manufacturer's instructions. As with the IL-2 ELISA kit, the BDNF kit is a solid-phase sandwich ELISA designed to detect and quantify the level of human BDNF in cell culture supernatants, plasma, and serum.

In this study, plasma IL-2 and BDNF analyses were conducted by the researcher in laboratory conditions. Assays were performed according to standardised procedures in accordance with the manufacturer's protocols. Detailed laboratory steps, sample preparation processes, and quality control procedures for ELISA tests are presented in detail in the thesis appendices to ensure reproducibility (see Appendix 9.4).

In brief, both ELISA tests performed involved the mechanism of antigen-antibody binding to a specific epitope. In the sandwich ELISA format used in this study, the capture antibody is immobilised on the plate (following a specific series of steps for each test) and recognises a specific epitope on the target antigen (e.g., BDNF or IL-2). The sample is then added, the antigen binds to this antibody, and a second detection antibody targeting a different epitope on the same antigen is added, which increases the specificity of the double binding and reduces cross-reactivity. The final step is the

measurement of fluorescence at 450 nm according to a standard curve of known concentrations.

3.3.4.2 Physical Function Assessment

Participants underwent a series of functional assessments in each assessment session. Muscle strength was measured for both arms and both legs using maximum voluntary contraction (MVC). Furthermore, hand strength was measured using a handgrip dynamometer. Hand dexterity was assessed via the 9-hole peg test, with balance, the Short Physical Performance Battery (SPPB), and the Timed Up-and-Go (TUG) test also performed. Each of these assessments are detailed below.

3.3.4.3 Strength Assessments

3.3.4.3.1 *Maximum voluntary isometric contraction force (MVC)*

Elbow flexor strength was assessed with participants seated, elbows positioned at 90° of flexion, and the forearm secured to a force transducer placed just above the wrist. Prior to the main assessment, a submaximal contraction trial was performed to familiarise participants with the equipment and to warm up the target muscles.

During the test, maximal isometric elbow flexion contractions were performed while participants received verbal encouragement and visual force feedback. Each contraction was repeated three times with 60-second rest intervals. The highest recorded value was accepted as the MVC.

Elbow extensor strength was assessed using the same dynamometer and seating position as for the flexor strength assessment. Participants performed isometric elbow extension by pressing against the fixed rig, following the same testing protocol used for elbow flexion (Figure 3.2).

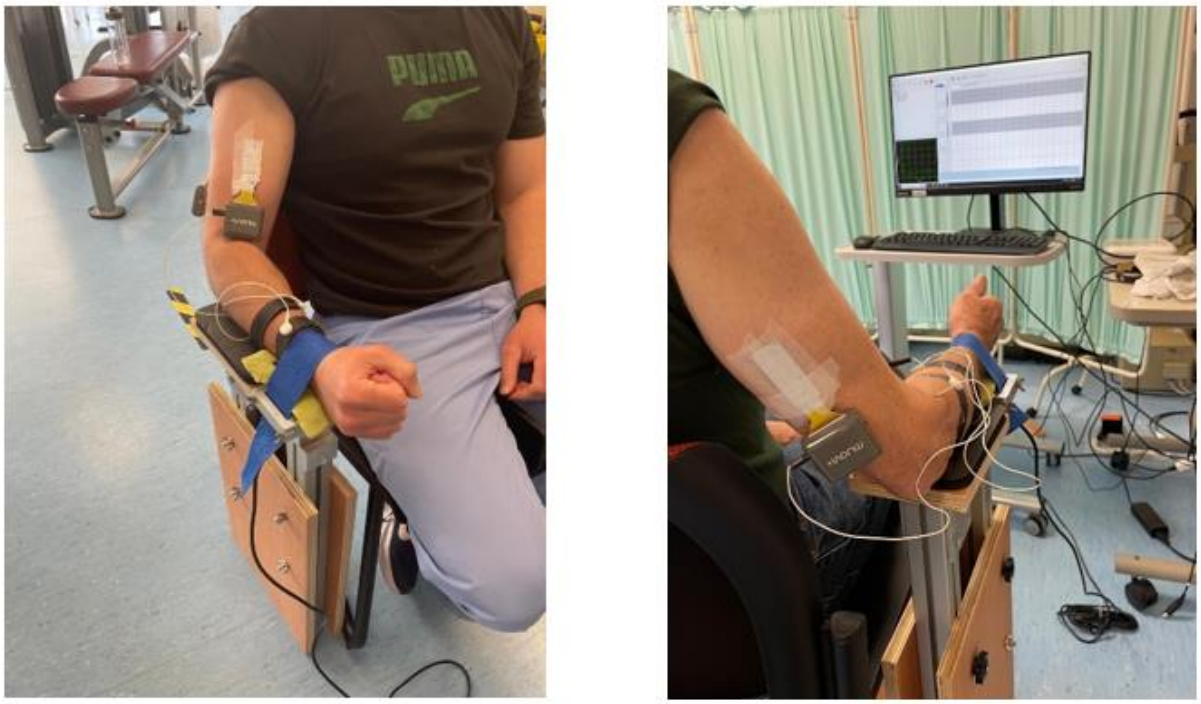


Figure 3.2: *Upper limbs MVC assessment position.*

Abbreviation: MVC (*maximum voluntary contraction).*

Ankle dorsiflexion strength was assessed using a custom-made dynamometer specifically designed for the lower limb. The participant's foot was secured to the device, which was fixed just above the metatarsals (Figure 3.3). The leg rig (dynamometer), designed to assess the tibialis anterior, measured dorsiflexion MVC for both the right and left feet.

The measurement procedures and testing protocol for the lower limbs were identical to those used for the upper limb strength assessments.

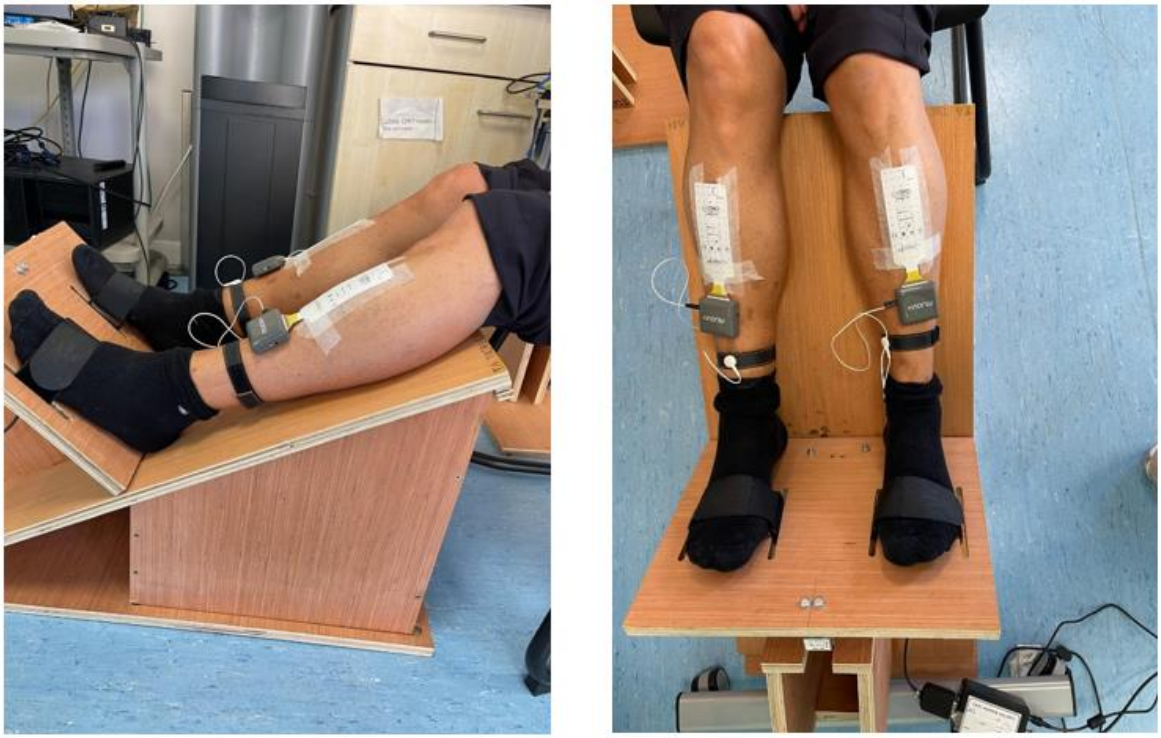


Figure 3.3:*Lower limbs MVC assessment position.*

Abbreviation: MVC (maximum voluntary contraction).

3.3.4.3.2 *Handgrip Strength*

Handgrip strength was assessed using a handgrip dynamometer (Grip-D, Takei, Japan) to measure the grip strength of both the dominant and non-dominant hands. Before testing, the width of the dynamometer handle was individually adjusted for each participant. During the assessment, the dynamometer indicator was held facing outwards while the participant's arms were positioned alongside the body with the elbows fully extended. The grip position was set so that the interphalangeal joint of the index finger was flexed at approximately 90 degrees. Participants stood naturally with their feet placed hip-width apart and were instructed to grip the dynamometer with maximum force without allowing contact with the body or clothing Each participant performed three maximal voluntary contractions, each lasting three seconds, with short rest intervals between attempts. The highest force value recorded from the three trials was taken as the maximal handgrip strength. The Takei hand dynamometer has been shown to be a reliable and valid tool with high test-retest reliability for measuring

handgrip strength in older adults [353].

3.3.4.4 Motor control (MCON) assessment

Motor control of the upper limb (elbow flexion and extension) was assessed using surface high-density electromyography (sHDEMG- HD04MM1305) recordings of the biceps and triceps muscles, obtained with the Muovi+ wireless probe system and Synchstation base (OT Bioelettronica, Turin, Italy). Participants were positioned in a specially designed arm rig, with the elbow flexed at 90° and the wrist stabilised using a strap (Figure 3.2). Motor control of the lower limb (dorsi flexion) was assessed using sHDEMG (HD08MM1305)) recordings of the tibialis anterior muscles, obtained with the Muovi+ wireless probe system and Synchstation base (OT Bioelettronica, Turin, Italy). Participants were positioned in an especially lower limb rig and the participant's foot were secured to the device, which was fixed just above the metatarsals (Figure 3.3).

Prior to testing, the procedure was explained in detail, and participants were instructed to perform isometric contractions following the target line displayed on the computer screen using their muscle strength. The MCON task consisted of a 5-second rise phase up to 25% MVC, followed by a 30-second sinusoidal wave with six oscillations at ±4% amplitude, and a 5-second fall phase leading to relaxation. Participants were given the opportunity to practise before the actual recording (Figure 3.4).

The coefficient of variation (CoV) of the force signal was calculated as an indicator of force stability. In addition, correlation coefficients between the target force and the generated force signals were computed to evaluate motor control.

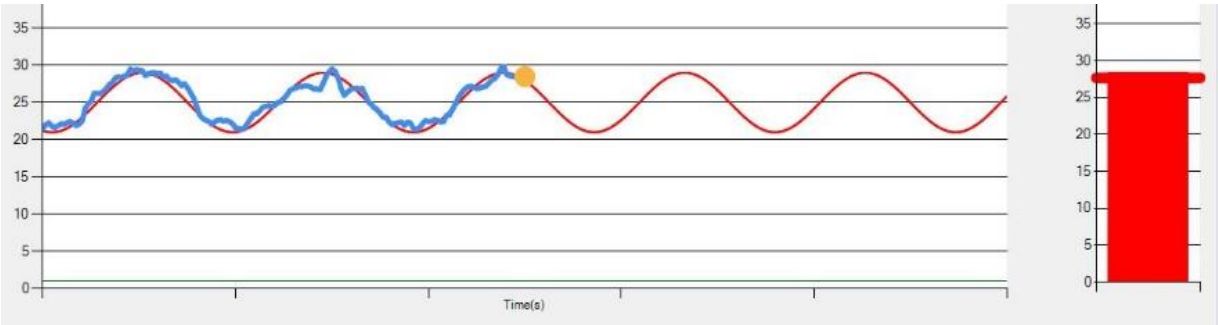


Figure 3.4: *MCON waves screen image.*

Abbreviation: MCON (Motor control).

3.3.4.5 Short Physical Performance Battery (SPPB)

The SPPB, consisting of three components, was completed by all participants under the supervision of a trained assessor qualified in its correct application. The sections of this test are 1) progressive standing balance test (side-by-side, semi-tandem, tandem), 2) 4-metre walk at normal speed, 3) standing up from a chair five times without using arms [354]. Participants were familiarised with each subtest before assessment and were given the opportunity to practise if necessary. The walking test was performed twice, and the best time was recorded. Performance on each component was scored on a 0–4 scale, with higher scores indicating better performance. The total SPPB score ranged from 0 to 12, obtained by summing the scores of all three components [355].

3.3.4.6 Dexterity (9- Hole Peg Test)

In this study, the 9-hole peg test, a valid and reliable test for assessing dexterity in adults, was used [356, 357]. Participants were asked to take the pegs one by one from a container and place them in the holes on the board as quickly as possible in any order they wished. Then, without pausing, the participant was asked to remove the pegs from the holes one by one and put them back in the container. The evaluator started the stopwatch when the participant touched the first peg and stopped it when the last peg was placed in the container, recording the time. This test was administered to participants twice for each side, using both their dominant and non-dominant hands.

3.3.4.7 Time up and go (TUG)

The TUG test is a simple, valid, and reliable test for assessing the dynamic balance, strength, and mobility of the lower extremities in older adults [355]. The test begins with the participant sitting on a standard chair and requires them to walk three metres without running and without using their upper limbs, turn around, and return to the chair. Participants were asked to perform this test in the shortest time possible and, if necessary, practised before the test. The TUG test was administered twice per session, and the best score recorded in seconds was used. Reis et al (2025) demonstrated excellent reliability (ICC = 0.82) and strong agreement (r = 0.716) of the TUG test in adults aged 50 years and older [358].

3.3.4.8 Balance

A Footscan plate (Footscan, 200 Hz, RScan International, Belgium) was used to measure balance. In this study, postural sway was assessed on both legs, with eyes open and closed, and on one leg (right and left legs), with eyes open and closed. Participants were asked to stand barefoot on the platform and focus on the target point in front of them during the test (30 seconds). In the single-leg tests, participants were asked to lift their leg, followed by a 5-second countdown, and the distance travelled (DT) and ellipse area of the centre of pressure (COP) were recorded. The COP elliptical area was calculated based on the set of ellipses covering 95% of the total area covered by the COP trajectory in the anterior-posterior and medial-lateral directions.

3.3.5 Upper motor control training (uMCT)

The uMCT training involved unilateral isometric elbow flexion and extension using a custom-made dynamometer on each individual's dominant side (Figure 3.5A). Each training session lasted ~20 minutes, and all sessions were fully supervised. Based on their pre-training MVC, each participant underwent a 4-week unilateral uMCT programme, tailored to their strength, consisting of 3 sessions per week. The training intensity was standardised across the intervention period, with force targets set relative to baseline MVC and maintained throughout the 4-week programme.

During the sessions, participants were instructed to follow a visual on-screen cue across six to ten different force-tracking waveforms relative to their MVC using isometric elbow flexion and extension. Each waveform lasted between 20 and 30 seconds, with 60-second rest intervals between each (Figure 3.5B). Six to ten different force tracking wave forms were performed during each session at 10%, 25%, or 50% of MVC with an amplitude of ±2%, ±4%, or ±8%. Different amplitude percentages were designed to allow participants to practise by varying their control and precision. That is, the sinusoidal waveform shown in Figure 3.5B indicates that the target force level (10%, 25%, or 50% of MVC) oscillates above and below the specified amplitude. For example, at ±4% amplitude at 25% MVC, the participant must modulate the force signal between 21% and 29% MVC. Therefore, it can be said that larger amplitudes represent greater fluctuations around the target force and require greater precision and control from participants.

A B

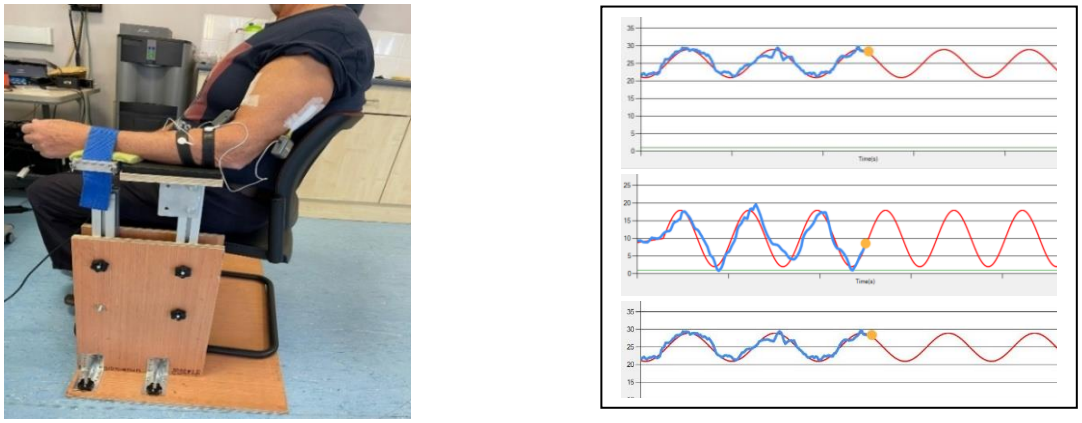


Figure 3.5: *A) Custom made arm rig (dynamometer) used for uMCT training; B) Example computer screen during uMCT.*

On the screen, the red line represents the force target and the blue shows an example trace from a participant. The top trace is at 25% MVC with an amplitude of ±4%. The middle trace is at 10% MVC with an amplitude of ±8%, hence the 'steeper' waves.

Abbreviations: uMCT (upper limb motor control training), MVC (maximal voluntary contraction).

3.4 Data Analysis

3.4.1 Statistical Analysis

GraphPad Prism (v10, San Diego, CA, USA) was used for statistical analysis with significance assumed at $p < 0.05$. Given the relatively small sample size, the normality of data was assessed using the Shapiro–Wilk test [359]. Descriptive statistics for variables showing a normal distribution are reported as mean ± standard deviation (SD), while median and interquartile range (IQR) are used for variables not showing a normal distribution. Similarly, parametric statistical methods were applied when the assumptions of normal distribution were met; and non-parametric analyses when the assumptions of normal distribution were not met. A formal a priori power calculation was not conducted due to the exploratory nature and small sample size of this pilot study.

Data for all cognitive outcome measures (TMT, MoCA, SCWT, IL-2, BDNF) were not

normally distributed; therefore, non-parametric statistical methods were applied. The Friedman test was applied to evaluate differences for repeated tests at three different time points. For a more detailed analysis, Dunn's multiple comparisons test was conducted with adjusted p-values. All p-values were two-tailed, and effect sizes are reported when appropriate. All graphs were created using GraphPad Prism.

Balance and SPPB data did not show a normal distribution, and as such non-parametric statistical methods were used. For these data sets the differences between the three time-points (pre-exercise, post-exercise, and follow-up) were analysed using the Friedman test, a non-parametric alternative to a repeated measures ANOVA. In contrast, TUG data were normally distributed, and changes across the time-points were analysed using a one-way analysis of variance (one-way ANOVA). Dunn's multiple comparison test was used for non-parametric data, and Tukey's test for parametric data to perform pairwise comparisons. Dexterity, MVC, and handgrip strength data were normally distributed, and changes across the time-points were analysed using a two-way ANOVA with Šidák post-hoc multiple comparisons.

All p-values were calculated using a two-tailed approach, and effect size was calculated where appropriate. All graphs were created using GraphPad Prism. The MCON data collected from participants were first converted to. mat format using the OT Biolab+ (v1.3.2, OT Bioelettronica) application for analysis in MATLAB. Data in this format were then analysed in MATLAB using the MCONforce script. In this analysis, correlation coefficient (CC) data were obtained. All statistical analyses were performed in R (v4.5.1) using the lme4 package for linear mixed-effects modelling.

A linear mixed-effects model (LMM) was used to examine the effects of time, training side, and muscle on the cross-correlation of the target and achieved force. The fixed effects included Time (three levels: Pre, Post, Follow-Up), Trained (Ipsilateral, Contralateral), and Muscle (Biceps Brachii, Triceps Brachii, Tibialis Anterior), as well as all interaction terms (Time × Trained × Muscle). A random intercept for Subject was included to account for within-subject repeated measures.

The results of the cognitive and physical functions of the healthy volunteer study, in which the methodology and methods are described in this chapter, will be presented in Chapters 4 and 5.

Chapter 4 Results for "The effect of low-intensity unilateral upper limb motor control training (uMCT) on cognitive function in healthy older adults: a pilot study"

4.1 Introduction

With the rapid increase in older adults worldwide, cognitive decline associated with ageing has become a significant public health issue. As people age, structural changes occur in the brain, such as a reduction in white matter volume and a decrease in synaptic complexity, along with functional changes that include a loss of activity in the brain regions responsible for cognitive and memory functions [360, 363]. During the ageing process of the brain, significant declines can be observed, particularly in processing speed, memory, and executive functions [362, 364, 365). In addition, a bidirectional relationship exists between age-related declines in muscle mass and function and cognitive decline, whereby impairments in one domain may exacerbate deterioration in the other. Physical impairment can negatively affect cognitive capacity, while cognitive decline can negatively affect participation in physical activity [366, 368]. Traditional exercise types such as aerobic and resistance training are known to increase brain and synaptic plasticity [369], support hippocampal function [239, 370, 371], and increase neurotrophic factors [372], thereby potentially having a protective effect on cognitive capacity [373]. Based on these findings, it can be considered that neuromuscular function may be an important and modifiable target for preserving cognitive capacity during the ageing process.

In cognitively healthy individuals, different types of exercise, whether RET, AET, or multimodal, can produce improvements in general cognition, with no significant differences between exercise types [374, 375]. In adults with MCI, RET has been demonstrated to elicit important positive effects on global cognition [376, 377], executive functions, memory [377], and attention [376, 377]. According to the results of the systematic review conducted by Huang et al. (2022) [377], exercise interventions may have positive effects on cognitive functions in individuals with MCI and dementia. This study also found that multi-component exercise programmes can be effective in improving both general cognitive function and executive functions in individuals with MCI, and that resistance training has beneficial effects on memory and attention

functions in dementia patients [378].

It must however be recognised that regular physical activity/exercise provides cognitive as well as physical and psychological benefits for older adults, participation in traditional physical exercise programs may not be possible for all older adults [5]. Physical limitations that older adults may have reduce the feasibility of traditional high-intensity exercise training and highlight the importance of alternative physical exercise training approaches that are of moderate or low intensity but can provide similar physiological effects. Moderate or low-intensity RET constitutes an important area of research in this context. For example, RET is well-established as an effective anabolic stimulus that (with sufficient nutrition) can elicit increases in muscle protein synthesis (MPS) and subsequently muscle mass and function [222, 379, 380, 381]. Whilst some studies do report adaptive blunting (i.e., attenuated or no hypertrophy in response to RET) [382, 383] in response to RET with advancing age, likely due to anabolic resistance which is a well-defined feature of ageing, the functional gains seen with RET appear to be largely unchanged across the adult life course, at least until the 8th decade of life. To exemplify this, Phillips *et al.,* performed a 20-week RET intervention in young, middle-aged and older adults. Whilst only the young and middle-aged individuals were able to achieve significant hypertrophy, with a negative relationship between age and hypertrophy, all age-groups made strikingly similar gains in whole-body strength (relative to baseline) such that the strength of the older individuals at the end of the intervention period was no longer different to the strength of the young group before RET [222].

It should be acknowledged that many older adults may not be physically able (i.e., due to joint limitations) and/or willing to perform RET at the intensity commonly prescribed for muscle hypertrophy and strength gains (~70% MVC) [384]. Despite this intensity being commonly postulated as a method to achieve muscle hypertrophy, work by Burd *et al.,* did show that equivalent increases in MPS could be achieved at a lower intensity (~30% MVC) [380]. This finding also translated into hypertrophic gains in subsequent exercise training intervention studies in both the upper [385, 386] and lower limbs [387], albeit with a significant limitation. The lower intensity RET is only as effective as the higher intensity when work-matched, meaning that far more repetitions need to be performed. Further, these studies were all based on young individuals. The need for a high repetition number to achieve matched work is likely problematic, especially for

older adults. Not only is "lack of time" (alongside, facilities access, transport and education/understanding) a stated reason for lack of exercise across all age-groups [238, 388], but a high repetition number may also exacerbate age-associated joint-related conditions [389, 390]. Beyond the common joint "aches and pains" in older age, a significant number of older adults will be waiting for elective orthopaedic surgery to replace a compromised joint (most often hips and knees, sometimes post-falling) [390], and as such may not be able to engage these joints in any RET, irrespective of intensity. On the other hand, for this age group, maintaining and increasing muscle strength should be a more important goal than muscle hypertrophy. This is because muscle strength is related not only to an increase in muscle volume but also to parameters such as motor unit activation, neuromuscular coordination and physical performance, which can support the daily independence of older adults.

Joint cysts and degenerative joint diseases in older adults are most often seen in the lower extremities (knee and hip), and therefore osteoarthritis and elective joint replacement surgery are most concentrated in this area. In this case, the applicability of traditional lower extremity resistance exercises is limited in older adults [44, 390]. In contrast, may be less affected by age-related degenerative conditions and therefore more suitable for exercise applications. While lower extremity resistance training has been extensively studied in older adults [391], studies investigating the effects of upper limb motor control and low-intensity resistance exercises are more limited. For all these reasons, focusing on upper limb exercises may provide an opportunity to offer a new approach aimed at reducing age-related muscle and cognitive losses. Therefore, a new upper limb exercise intervention that can be implemented by older adults and provide them with benefits may be necessary to reduce age-related muscle and cognitive function losses.

In order to address the multiple challenges associated with older adults performing traditional RET, this study aims to assess the impact of low-intensity, unilateral uMCT on both muscle and cognitive outcomes in older adults. MCT involves higher constant neural involvement than traditional RET, and when performed by younger individuals in their lower limbs has been shown to improve both functional parameters and those associated with neuromuscular connectivity [250]. Beyond this, MCT (also referred to as "force accuracy training- FAT" in the literature) has been shown to potentially

increase force control accuracy and reduce motor unit firing variability in young adults [250]. Walker et al. (2019) has found that older adults tend to have reduced maximum strength production and strength stability in low-intensity tasks compared to younger adults, but that this can be improved with appropriate training [392]. The findings of these studies are consistent with the results of a review study showing that motor control-based exercise programs may have positive effects on muscle strength control and motor task accuracy [393]. Therefore, MCT should be investigated more comprehensively in older adults who are likely to have cognitive, muscular, and neuromuscular functions below the optimal level at baseline.

This study investigated the effects of a 4-week unilateral uMCT training programme on cognitive and physical functions in healthy older adults, and the methodology is detailed in Chapter 3.

4.2 Method

4.2.1 Regulatory approval and participant eligibility

This study, approved by the Nottingham University Faculty of Medicine and Health Sciences Research Ethics Committee (FMHS 331-0723), included 20 healthy older adults (10 men, 10 women). A screening session was organised for older adults who volunteered to participate in the study, and BP and EKG records were taken to check their entire medical history and suitability for participation in the study.

4.2.2 Experimental Protocol

Participants who were suitable for the study were invited to the first (pre-training) assessment visit after screening. This assessment protocol was repeated post-training and after 4 weeks of detraining (follow-up). As the focus of this section, the MoCA, TMT and SCWT, which address cognitive functions, were used in each assessment session to evaluate different aspects of cognitive function. Additionally, a single fasted blood sample was taken at the start of each of these assessment visits via venepuncture (antecubital vein) to determine systemic (plasma) levels of IL-2 and BDNF. A schematic of the full study can be seen in Figure 3.1. All cognition test applications and blood analyses used were presented in detail in Chapter 3.

4.2.3 Upper motor control training

uMCT training was administered using a custom-made arm dynamometer that enabled isometric contractions of the elbow flexors and extensors. Each session was supervised by the researcher, lasted approximately 20 minutes, and was performed three times a week for four weeks. In each session, six to ten different force waveforms of varying amplitudes, corresponding to 10%, 25%, and 50% of MVC, were applied.

4.2.4 Statistical Analysis

GraphPad Prism (v10, San Diego, CA, USA) was used to perform analyses and generate graphs, and $p<0.05$ was considered statistically significant. Data for all cognition-related outcome measures did not show a normal distribution, and non-parametric statistical methods were applied.

The uMCT training application protocols and statistical analysis details are presented in Chapter 3.

4.3 Results

4.3.1 Participant characteristics

Participant characteristics are presented in Table 4.1.

Table 4. 1: *Participants characteristics (n =20)*

	Mean (SD)
Age (years)	73 (5.2)
Male/Female	10/10
Height (m)	1.63 (0.19)
Weight (kg)	77.3 (24.5)
BMI (kg/m^2)	26.84 (4.3)

4.3.2 MoCA

A significant effect of time was observed ($p < 0.01$), whereby pairwise comparisons revealed significant improvements in MoCA scores between pre-training (25.6 ± 1.90) and post-training (28.2 ± 1.18, $p < 0.01$) and between pre-training (25.6 ± 1.90) and follow-up (28.4 ± 1.19, $p < 0.01$). No significant difference was found between post-training and follow-up scores (p = NS), indicating that cognitive gains achieved through uMCT were maintained over the de-training phase (Figure 4.1).

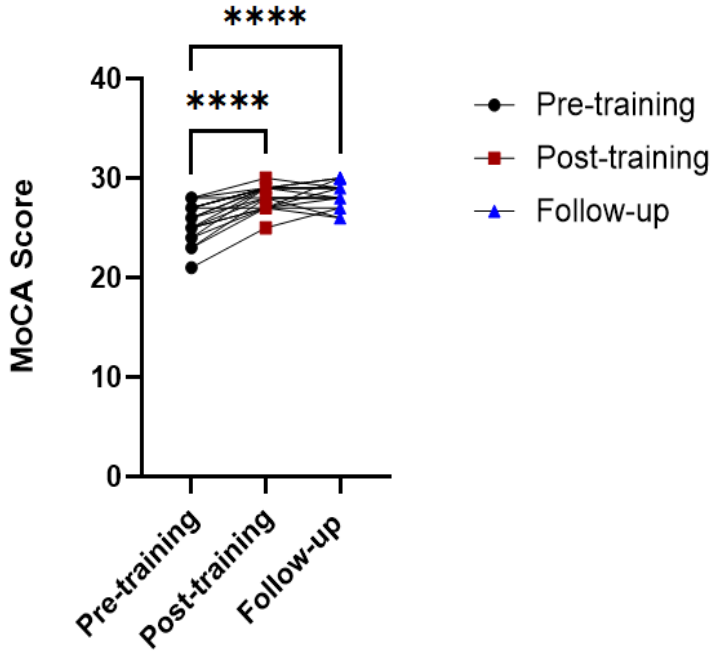


***Figure 4.1**: Montreal Cognitive Assessment (MoCA) before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Analysis via Friedman test with Dunn's post-hoc multiple comparisons. ****=p < 0.00001.*

4.3.3 TMT

There was a main effect of time for both TMT-A ($p < 0.01$) and TMT-B ($p < 0.05$). For TMT-A there was a significant improvement in TMT score from pre- to post-training (30.5 ± 8.7 vs. 24.9 ± 7.6, $p < 0.05$) and from pre-training to follow-up (30.5 ± 8.7 vs. 24.2 ± 6.2, $p < 0.01$). There was no significant difference between post-training and

follow-up scores (24.9 ± 7.6 vs. 24.2 ± 6.2, p = NS) (Figure 4.2A). The data pattern was similar for TMT-B; with a significant improvement in TMT score from pre- to post-training (66.0 ± 32.7 vs. 54.2 ± 25.8, p < 0.01) and from pre-training to follow-up (66.0 ± 32.7 vs. 52.8 ± 24.6, p < 0.01), with no difference between post-training and follow up (54.2 ± 25.8 vs. 52.8 ± 24.6, p = NS) (Figure 4.2B).

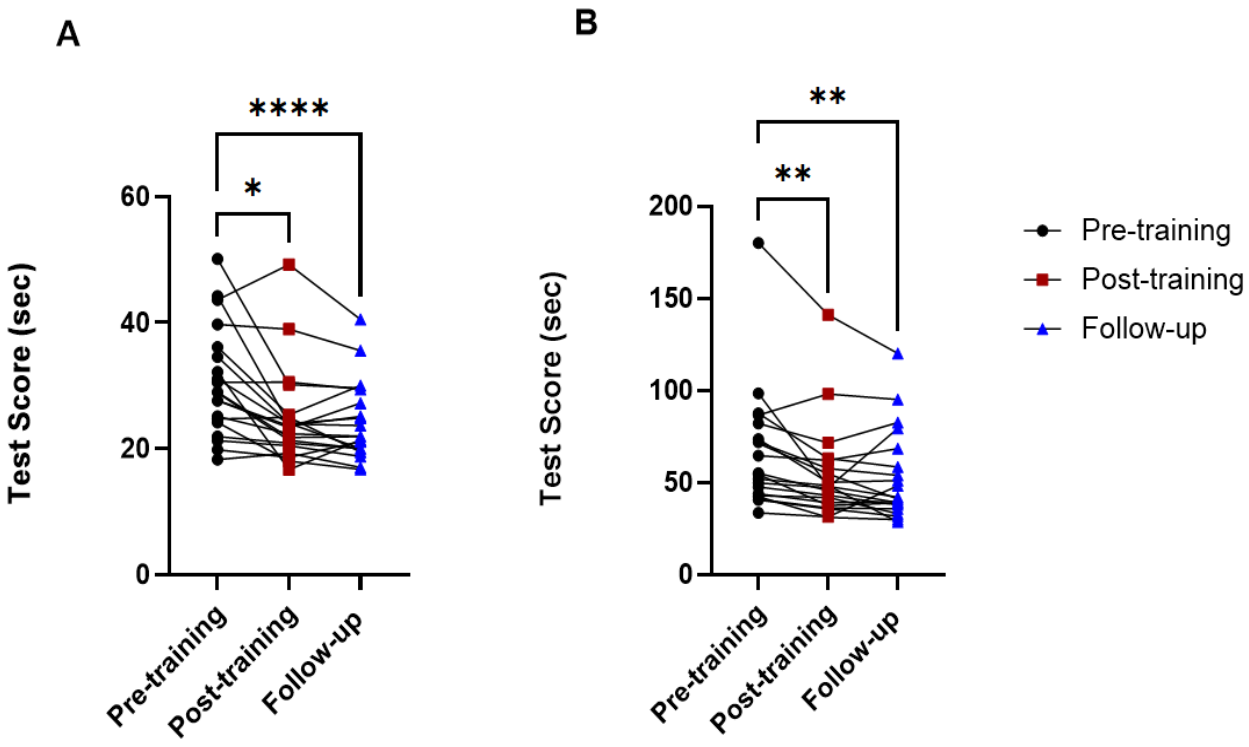


Figure 4.2:*A) Trail Making Test (TMT) Part A results and B) TMT Part B results before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Analysis via Friedman test with Dunn's post-hoc multiple comparisons. *=p < 0.05, **=p < 0.01, *** p < 0.001, ****=p < 0.00001.*

4.3.4 SCWT

4.3.4.1 SCWT Interference scores

The SCWT interference T-score analysis results indicated that uMCT training could provide significant and sustainable improvement in inhibition control. Higher scores on

the interference T-score reflect better executive function, and statistically significant increases were observed from pre-training (52.21 ± 4.66) to post-training (57.16 ± 6.74) and follow-up (57.37 ± 5.66) periods ($p < 0.01$ for both comparisons). No difference was found between post-training and follow-up (p = NS) (Figure 4.3A).

The interference raw score analysis yielded similar results and demonstrated a significant and sustained improvement in inhibitory control. The results showed a statistically significant difference between time points ($p < 0.01$), and post-hoc comparisons revealed significant improvements between pre-training (4.42 ± 7.55) and post-training (11.32 ± 10.26, $p < 0.05$) and follow-up (11.05 ± 6.96, $p < 0.05$), while no difference was found between post-training and follow-up (p = NS) (Figure 4.3B).

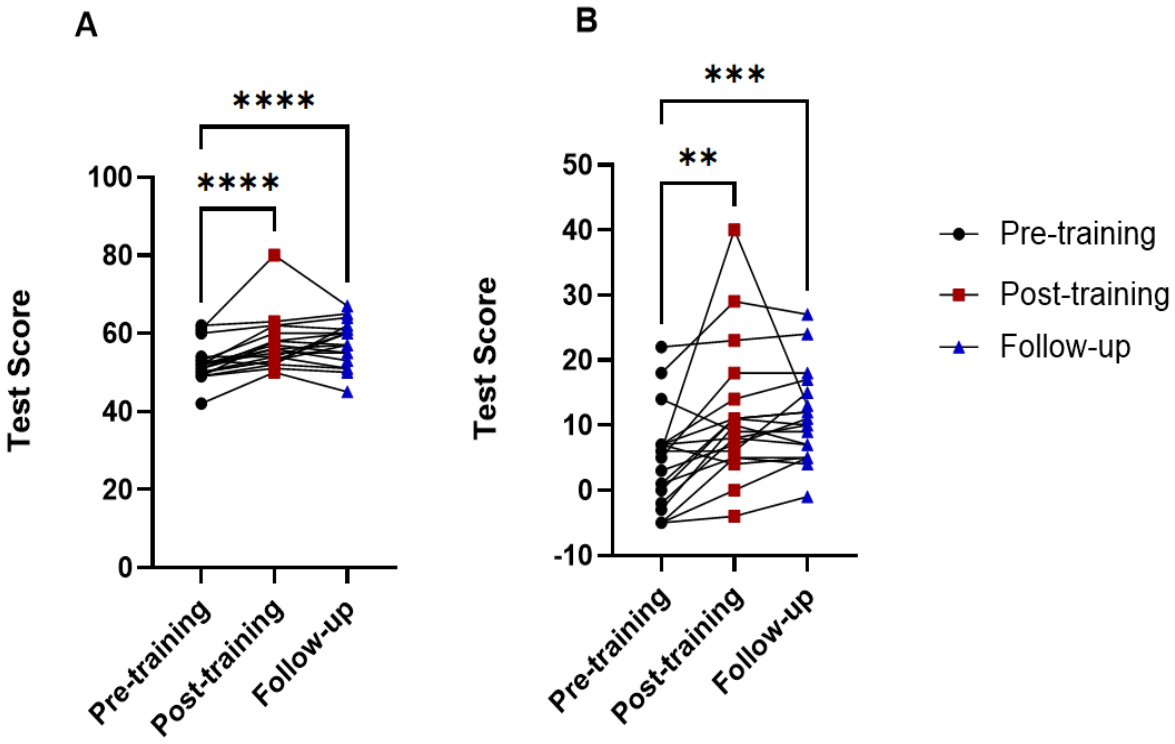


Figure 4.3:*A) Stroop Colour-Word Test (SCWT) Interference T-score and B) Stroop Colour-Word Test (SCWT) Interference Raw score before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Analysis via Friedman test with Dunn's post-hoc multiple comparisons. **=p < 0.01, ****=p < 0.00001.*

Abbreviations: SCWT (Stroop Colour-Word Test).

4.3.4.2 *Analysis of SCWT – Colour scores*

Both Colour T scores and Raw scores yielded similar results. Both scores improved significantly from pre-training (T score: 54.37 ± 10.01; Raw score: 65.89 ± 11.50) to post-training (T score: 58.68 ± 9.45; Raw score: 71.63 ± 12.04) (both $p < 0.01$) and from pre-training to follow-up (T score: 58.74 ± 10.31; Raw score: 72.11 ± 12.45) (both $p < 0.01$) while no significant difference was observed between post-intervention and follow-up scores (T score: 58.68 ± 9.45 vs. 58.74 ± 10.31, p = NS; Raw score: 71.63 ± 12.04 vs. 72.11 ± 12.45, p = NS), indicating that the improvement persisted over time (Figure 4.4). These findings demonstrate that uMCT training has a strong and lasting effect on cognitive processing speed.

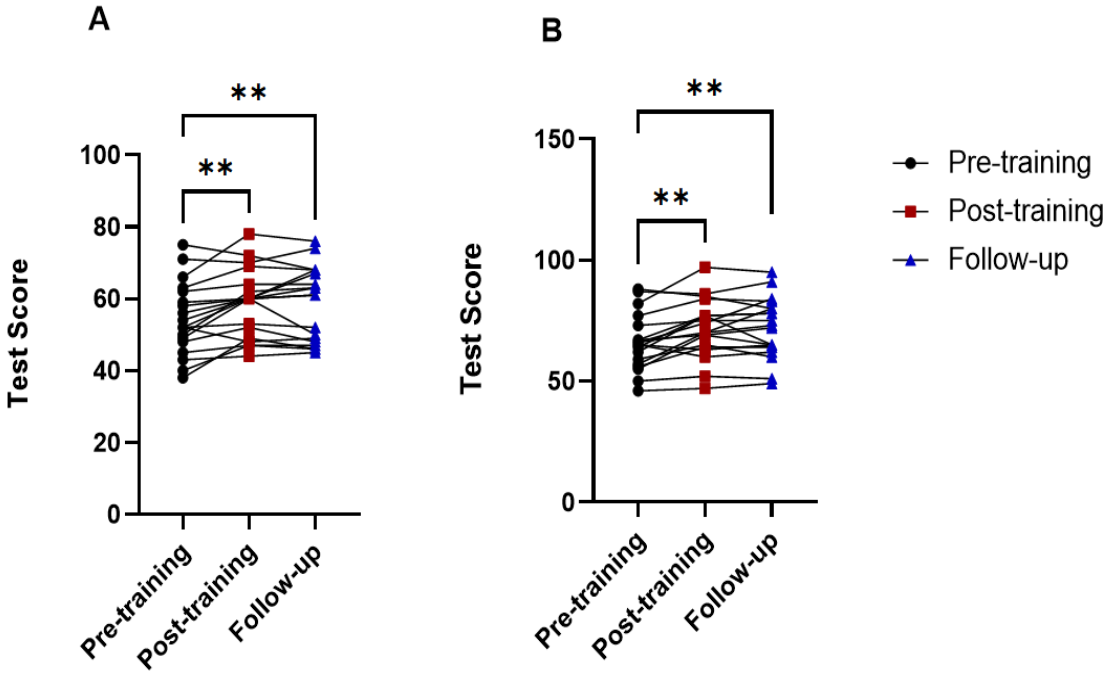


Figure 4.4:: *A) Stroop Colour-Word Test (SCWT) Colour T score and B) Stroop Colour-Word Test (SCWT) Colour Raw score before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Analysis via Friedman test with Dunn's post-hoc multiple comparisons. **=p<0.01.*

Abbreviations: SCWT (Stroop Colour-Word Test).

4.3.4.3 *Analysis of SCWT – Word scores*

The analyses revealed significant main effects of time for both the Word T Score, [Pre-training: 48.00 ± 9.03, Post-training: 53.58 ± 7.89, Follow-up: 53.16 ± 9.66; $p < 0.0001$) (Figure 4.5A), and the Word Raw Score, (Pre-training: 91.63 ± 11.99, Post-training: 99.47 ± 10.95, Follow-up: 99.11 ± 13.20; $p < 0.0001$) (Figure 4.5B) indicating large effect sizes. No significant difference was found between post-training and follow-up, indicating that the gains from uMCT training were maintained.

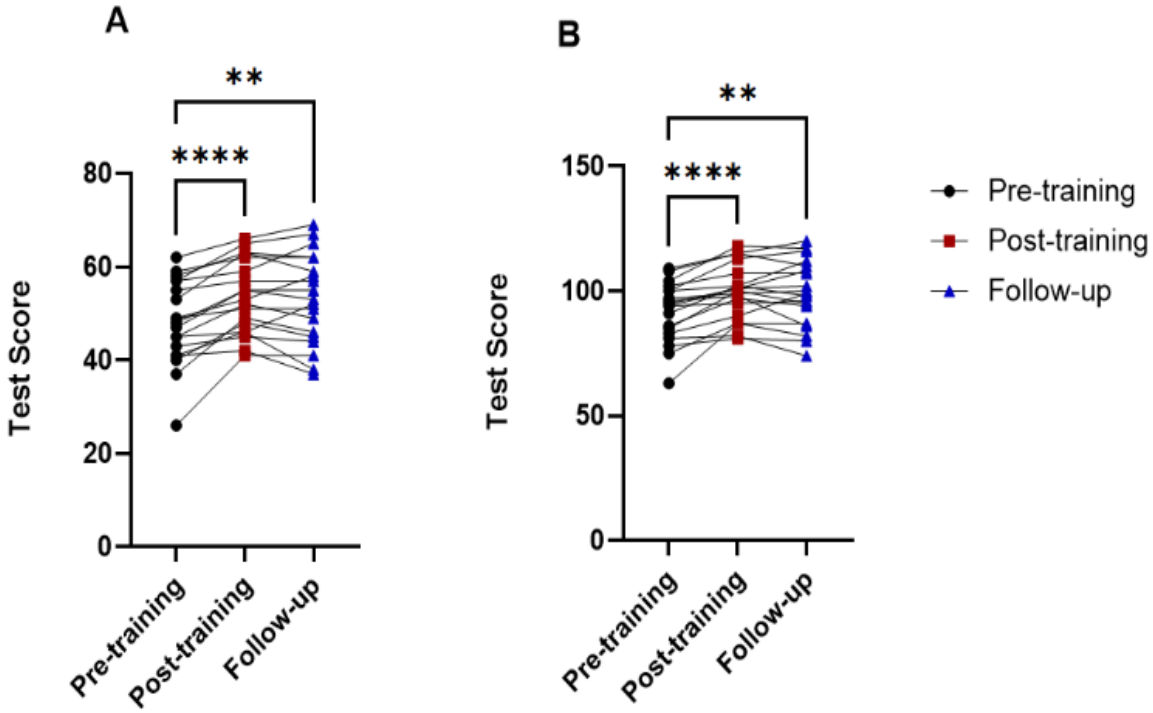


Figure 4.5: *A) Stroop Colour-Word Test (SCWT) Word T score and B) Stroop Colour-Word Test (SCWT) Word Raw score before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Analysis via Friedman test with Dunn's post-hoc multiple comparisons. **=p<0.01, ****=p<0.00001.*

Abbreviations: SCWT (Stroop Colour-Word Test).

4.3.4.4 *Analysis of SCWT Colour-Word scores*

A significant effect of time was found for both measures ($p<0.001$). Post-hoc Dunn tests revealed significant improvements between pre-training (Colour-Word Raw Score: 36.21 ± 7.29; Colour-Word T Score: 54.53 ± 7.49) and post-training (43.37 ± 10.55; 61.32 ± 10.26, $p<0.01$ and $p<0.001$, respectively). It was demonstrated that gains were maintained, as no significant difference was found between post-training (43.37 ± 10.55; 61.32 ± 10.26) and follow-up (43.05 ± 6.74; 61.00 ± 6.90, p=NS) (Figure 4.6A-B).

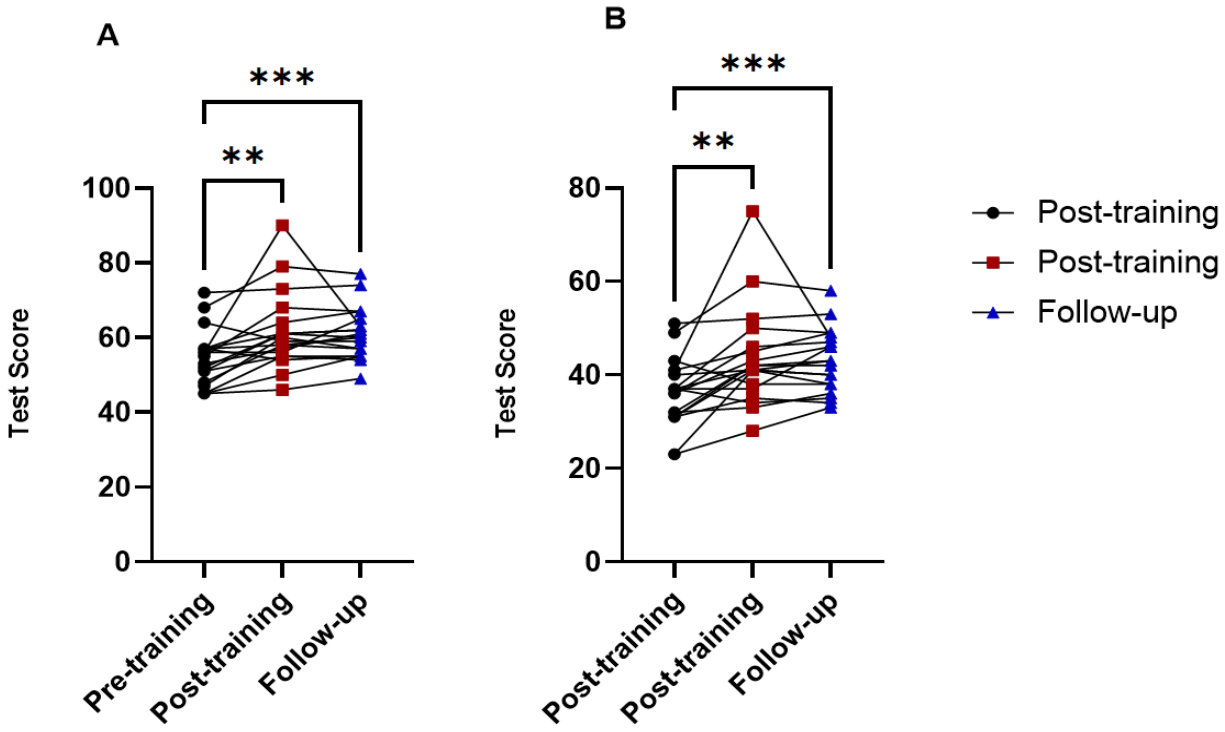


Figure 4.6: *A) Stroop Colour-Word Test (SCWT) Colour-Word T score and B) Stroop Colour-Word Test (SCWT) Colour-Word Raw score before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Analysis via Friedman test with Dunn's post-hoc multiple comparisons. **=p < 0.01, ***=p < 0.0001.*

Abbreviations: SCWT (Stroop Colour-Word Test).

4.3.5 IL-2 and BDNF

There was no significant difference between the time points for either IL-2 (Figure 4.7A) or BDNF (Figure 4.7B). Due to some samples falling below the minimum detectable concentration, IL-2 data is available for 18 participants, and 19 participants for BDNF. The raw data tables for IL-2 and BDNF and the ELISA test setup and application protocol are presented in detail in Appendix 9.4.

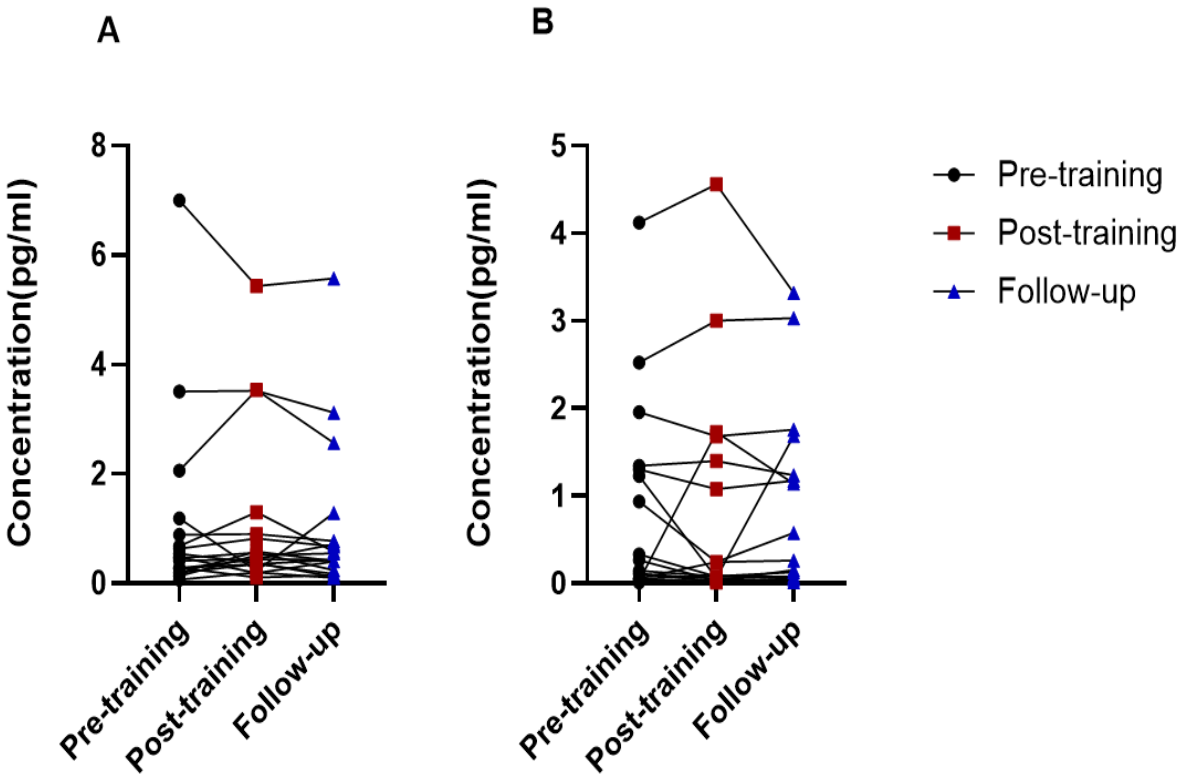


Figure 4.7:A) Interleukin-2 (IL-2) results and B) Brain-Derived Neurotrophic Factor (BDNF) results before (Pre-training) and after (Post-training).

4-weeks upper limb motor control training by (n=18; 10 male) older adults, and after 4-weeks de-training (Follow-up). Analysis via Friedman test with Dunn's post-hoc multiple comparisons.

Abbreviations: IL-2 (Interleukin-2), BDNF (Brain-Derived Neurotrophic Factor).

4.4 Discussion

This study examined the effect of low-intensity, unilateral uMCT on cognitive function in older adults. The results show that this form of training can elicit improvements in older adults, particularly in attention, executive function, inhibition control and processing speed. These results are consistent with other studies in the literature showing that both physical and motor-skill interventions can be effective at improving cognitive function [239, 370, 372]. This study adds to this evidence by showing that upper limb motor control training as an intervention may enhance aspects of cognitive function in otherwise healthy, community-dwelling older adults.

Physiologically, during the ageing process, significant cognitive losses may occur, particularly in processes for which the frontal lobe is responsible, such as executive functions, attention control, and working memory [7]. These losses are associated with reduced independence and quality of life in older adults [7, 394] and as such are also associated with increased health and social care costs [395, 396]. Therefore, interventions aimed at preserving or even enhancing cognitive function in the older population are clinically very important.

The existing literature provides a relative wealth of evidence that different exercise modalities, such as aerobic exercise training [281], resistance exercise training [240], and multimodal exercise training [337], may each have positive effects on cognitive function. Conversely, studies on isolated upper extremity exercise and those based on fine motor control are much more limited. The findings of this study, in terms of positive effects of uMCT on cognitive function in older adults are particularly important when the prevalence of lower limb joint (e.g., hip and knee) limitations in older adults [397], is considered, which may prohibit lower limb or whole-body exercise. Further, this intervention may have utility as surgical prehabilitation (including for lower limb operations) in older adults given both the upper-body nature of the intervention, and the short timeframe in which it was able to elicit benefit.

The results of the MoCA test in this study, which is a highly sensitive measure for screening global cognitive function, suggest that our low intensity uMCT intervention is effective at improving general cognitive function in disease-free older adults. In the literature, attention and executive functions, which are among the subcomponents of the MoCA test, are considered particularly decisive indicators in terms of cognitive development [298], it is reasonable to suggest that attention and executive functions

may have been strengthened via our intervention.

Both TMT-A and TMT-B were improved by unilateral uMCT, with TMT-A reflecting processing speed and TMT-B reflecting cognitive flexibility and executive function performance [339]. These improvements may be explained by the need to maintain focus and respond quickly during the uMCT intervention, as motor learning is reported to increase frontal and parietal cortex activation [398]. Compared to traditional RET or AET, uMCT requires a higher level of neural input. This is because uMCT can provide the integration of complex, goal-directed upper extremity movements, continuous visual-motor coordination, and attention-demanding motor control tasks. These elements can promote the simultaneous activation of motor and cognitive networks, developing neuroplastic adaptations through increased functional connectivity between the prefrontal, parietal, and cerebellar regions [399, 400].

The SCWT showed significant improvements in interference scores, colour recognition, and word reading speed in response to uMCT. Improvements in interference scores reflect improvements in ability to suppress extraneous stimuli, while improvements in colour and word scores indicate developments in processing speed and cognitive flexibility [346, 347]. Based on these results, uMCT appears to not only be effective at improving inhibition processes but also general attention and cognitive processing speed. Considering the daily life activities and quality of life of older adults, reducing distractions, faster decision-making, and increasing the capacity to perform multiple tasks are of clear importance [401]. For example, advanced attention control and executive functions can enable older adults to move safely and correctly in busy environments, such as crossing the street while watching traffic, or to perform daily tasks that require the simultaneous coordination of cognitive and motor actions (such as cooking or driving) [402]. Therefore, developments in attention control and executive functions can be considered factors that can directly contribute to independence and quality of life in later adulthood. It is known that exercise can have positive effects on different components of the SCWT [352, 403, 404]. What this study adds is that the uMCT intervention can elicit similar improvements with a short intervention time period, and that this improvement persists over a short period of detraining. This provides an alternative offering for those who, for a variety of reasons, may not be able to engage in traditional exercise training.

This study did not detect any statistically significant change in BDNF or IL-2 levels across our intervention period, contrasting with reports from previous studies which have shown that physical and motor activities can increase BDNF levels. BDNF is a neurotrophin that plays an effective role in functions such as synaptic transmission, learning, neuroplasticity and memory [405, 406]. As such, intervention studies showing increased BDNF levels suggest that these interventions support learning and memory processes in adults [407]. The lack of change in either BDNF or IL-2 levels in this study may be due to the limited sample size, although it should be noted that changes in these parameters have been seen in a similar sample size in previous studies in response to a physical intervention [407, 408]. Most prior intervention studies have employed a longer intervention period (e.g., [239]), and this may also be a factor explaining the absence of change observed herein. Further, as with most physiological alterations observed in response to exercise training [409], there will be some degree of interindividual variation, with "responders" and "non-responders" reported for both RET and AET [410, 411] . Specific to the biomarkers explored in this study, Tarassova et al., [412] demonstrated that post-exercise BDNF increases in response to exercise training may not be consistent across an intervention, particularly in older adults. Similarly, a separate study exploring the effect of exercise on immune markers including IL-2 showed that exercise interventions may not always produce a meaningful effect [413]. Furthermore, studies exist suggesting that motor skill-based exercises can enhance cognitive functions in adults through sensorimotor integration and prefrontal connections [414, 415]. However, these neuroplastic developments were not directly detected through the biomarkers (e.g., BDNF and IL-2) evaluated in this study.

One important and novel finding of this study is that achieved cognitive gains were maintained in the follow-up period (after 4-weeks post uMCT cessation). These results suggest that uMCT training may induce long-term, rather than short-term, neuroplastic changes, although the duration of this retention cannot be confirmed based on this study. One study in the literature suggests that lasting effects of exercise can be explained by the concept of "cognitive reserve", particularly in older adults [416] . Cognitive reserve is defined as the capacity to maintain cognitive performance by activating alternative neural networks or increasing the efficiency of existing networks in response to structural or functional losses in the brain that may occur with ageing [416, 417].

Therefore, exercise programmes based on motor skills are thought to increase neural efficiency and strengthen compensatory mechanisms that provide cognitive reserve, thereby supporting cognitive reserve and potentially offering protection against age-related cognitive decline. The 4-week follow-up period was chosen based on previous literature examining short-term retention of exercise-induced adaptations, although longer follow-up periods are needed to confirm sustained effects.

4.4.1 Study limitations

As with almost all human research studies, there are some limitations which must be considered. Firstly, the sample size is relatively small (n = 20) which may prevent the generalisability of the results. Secondly, only cognitive tests were used to test cognitive abilities in this study with the results not supported by neuroimaging. Neuroimaging methods such as functional magnetic resonance imaging (fMRI) or functional near-infrared spectroscopy (fNIRS) before and after the intervention would have allowed us to explore task-related activation and changes in functional connectivity, with previous exercise studies in older adults showing changes in the prefrontal cortex, hippocampus, and parietal regions [418, 419]. Future studies should aim to investigate the neural mechanisms underlying the observed cognitive improvements by incorporating neuroimaging modalities such as fMRI or fNIRS. This would allow for the assessment of changes in task-related brain activation and functional connectivity, particularly in regions associated with executive function and memory, alongside behavioural cognitive measures.

4.4.2 Conclusion

In conclusion, this study has showed that low intensity uMCT may have positive effects on the cognitive function of healthy older adults, and that these improvements are retained for one month after cessation of the intervention. Specifically, uMCT was able to elicit significant improvements in attention, executive function, and inhibition control; all within a short timeframe (4-weeks). These results suggest that uMCT could be a feasible and effective intervention method to improve the cognitive health of older adults, including those who may not be able to perform traditional higher intensity exercise, and/or whom need optimising prior to a known physiological and cognitive insult (e.g., surgery).

Chapter 5 Results for "The effect of low-intensity unilateral upper limb motor control training (uMCT) on physical function in healthy older adults: a pilot study"

5.1 Introduction

Ageing is a multifaceted biological process involving gradual alterations within structural, physiological, and neurological systems, and population ageing has become a widespread global phenomenon [89, 93, 420]. As mentioned in Chapter 1, it is known that, in addition to cognitive changes accompanying the ageing process, there are also physical changes, particularly in the musculoskeletal system including, but not limited to, neuromuscular structure and motor control. In Chapter 2, we examined the effect of preoperative physical exercise training on postoperative cognitive function through a systematic review and found that physical exercise may have a protective effect on cognition after surgery. However, as highlighted in the previous chapter, there is a clear lack of research specifically investigating the cognitive effects of targeted motor control training interventions, particularly low-intensity unilateral upper limb training, in older adults. To fill this gap, we conducted a pilot study to examine the effects of low-intensity, unilateral uMCT in healthy older adults on both cognitive (presented in Chapter 4) and physical function. This chapter will present the physical function outcomes. This study aimed to provide new evidence regarding the role of motor control training in the context of healthy ageing, considering the theoretical framework defined in previous sections and the knowledge gaps identified in the existing literature.

Various metabolic and physical adaptations accompany the ageing process, often contributing to chronic diseases, functional impairments, and reduced quality of life [421, 422]. It is well recognised that advancing age leads to a progressive reduction in muscle mass and strength, resulting in diminished force generation, impaired motor control, and a decline in overall physical functioning [78, 84, 423- 425]. It has been estimated that approximately 30% of muscular strength is lost between the ages of 50 and 70 [57, 426, 427]. In addition to strength loss, impairments in balance, coordination, and manual dexterity are also commonly observed in older adults. Collectively, these declines in physical capacity may compromise independence, increase the risk of falls, and ultimately lead to a lower quality of life [428, 429].

Physical function is defined as a multidimensional concept comprising many components, such as strength, balance, endurance, speed, and manual dexterity [430-432]. A reduction in any one of these components can affect the others, thereby manifesting as a general decline in functional capacity. Loss of muscle strength due to ageing may lead to slower gait speed and postural instability, whereas diminished manual dexterity may cause difficulties in daily tasks such as dressing and feeding among older adults [433- 435]. Beyond the individual level, age-related reductions in physical function have broader societal and economic implications. Functional decline in older adults can increase the risk of falls, and this increase can have negative health consequences. Falls in older adults are associated with prolonged hospitalisation, increased dependence on long-term care, and, consequently, higher healthcare expenditure [436, 437]. Therefore, interventions aimed at preventing or mitigating age-related deterioration in physical function are essential for promoting healthy ageing and reducing the public health burden of an ageing population.

Motor control is defined as the regulation of skeletal muscle activation by the central nervous system to produce accurate, purposeful, and coordinated movement. It is well established that ageing can lead to a decline in neuromuscular function. Age-related alterations in motor control, such as reductions in MU number, slower nerve conduction velocity, and shifts in muscle fibre type, are discussed in detail in Chapter 1 [78, 89, 424, 438]. In brief, neuromuscular changes accompanying ageing can result in reduced movement precision, longer reaction times, and impaired synchronisation of muscle activation. Consequently, these changes may cause diminished motor control and postural stability [93, 256, 439].

Traditional exercise modalities such high-intensity resistance or aerobic exercise may not be appropriate for all older adults, as orthopaedic limitations and/or cardiovascular conditions are common in this population [237]. For example, the high-intensity (~70% MVC) resistance exercise recommended for strength gains and muscle hypertrophy may not be physically suitable for every older adult, and older adults may not be enthusiastic about participating in this type of exercise [384]. Although some studies have shown that lower-intensity exercise can elicit comparable increases in MPS, such protocols require a higher number of repetitions to match overall work [380]. Considering that older adults frequently experience joint problems, performing a high number of repetitions may be challenging [390], and also time consuming. Moreover,

the majority of studies exploring the impact of resistance exercise training intensity have been conducted in younger adults, such that the effects on older populations remain uncertain.

Motor control-based training has been shown to optimise the timing of muscle activation, support motor unit remodelling, reduce excessive co-contraction, and contribute to maintaining motor unit function [70, 86, 212, 249]. Based on this evidence, motor control strategies may help preserve functional capacity and delay age-related motor impairments. In the present study, uMCT was selected to investigate its effects on physical function in older adults, given that joint pathologies (e.g., joint pathologies cysts and degenerative joint diseases) are more commonly observed in the lower limbs (knee and hip) [55, 93, 390].

This study aimed to examine the effects of a 4-week unilateral uMCT intervention on cognitive and physical function in older adults. The findings related to cognition are detailed in Chapter 4, while the present chapter focuses on physical function assessed through strength tests (MVC and handgrip), functional assessments (MCON outcomes, SPPB, Balance Test, TUG, and 9-Hole Peg Test), and the cross-education effect on motor control (i.e., can unilateral training of an upper limb alter lower limb and or contralateral upper limb function).

5.2 Method

5.2.1 Regulatory approval and participant eligibility

This study, approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences at the University of Nottingham (FMHS 331-0723), involved 20 healthy older adults (10 men, 10 women). Participants were invited to a screening session to check their eligibility for the study. During this session, their medical history, BP and ECG records were taken.

5.2.2 Experimental Protocol

In this study, which included pre-training, post-training, and after 4 weeks (follow-up) assessments, muscle strength and motor control were measured for both arms and both legs for functional evaluation. Additionally, hand strength was measured using a

handgrip. Hand dexterity (9-hole peg test), balance, SPPBT and TUG test were applied to assess physical function. All assessment sessions and details of the exercise intervention applied are shown schematically in Figure 3.1. All cognition test applications and blood analyses used were presented in detail in Chapter 3.

5.2.3 Upper motor control training

A specially designed arm rig for unilateral (dominant side) uMCT exercises was used to implement a training programme involving isometric elbow flexion and extension, conducted three times per week over a four-week period (see Section 3.3.5 for full protocol details). Participants were asked to follow a yellow ball throughout six to ten different force tracking waveforms with amplitudes of ±2%, ±4%, or ±8% at 10%, 25%, or 50% of the elbow flexion and extension MVC values recorded during the pre-training session.

5.2.4 Statistical Analysis

GraphPad Prism (v10, San Diego, CA, USA) was used for statistical analysis with significance set at $p<0.05$. All graphs were created using GraphPad Prism. Dexterity, MVC, and handgrip strength data were normally distributed, and changes across the time-points were analysed using a two-way ANOVA with Šidák post-hoc multiple comparisons. Balance and SPPB data did not show a normal distribution, and as such non-parametric statistical methods were used. In contrast, TUG data were normally distributed, and changes across the time-points were analysed using a one-way analysis of variance (one-way ANOVA).

The uMCT training application protocols and statistical analysis details are presented in Chapter 3.

5.3 Results

5.3.1 Participant characteristics

Participant characteristics are presented in Table 5.1.

Table 5. 1: *Participants characteristics (n = 20).*

	Mean (SD)
Age (years)	73.0 (5.2)
Male/Female	10/10
Height (m)	1.63 (0.19)
Weight (kg)	77.3 (24.5)
BMI (kg/m^2)	26.8 (4.3)

5.3.2 Muscle Strength

5.3.2.1 Biceps (BIC)

Two-way repeated measures ANOVA demonstrated a significant effect of time on BIC strength ($F (1.73, 65.79) = 22.43$, $p < 0.01$), but the main effect of arm (trained vs. untrained) was not significant (p = NS) and the arm × time interaction was also not significant (p = NS). According to descriptive statistics, BIC MVC values in the trained arm were 174.1 ± 79.7 N in the pre-training period, 201.6 ± 98.1 N in the post -training period, and 201.0 ± 91.7 N in the follow-up period; in the untrained arm, they were 162.2 ± 77.8 N, 195.9 ± 88.4 N, and 197.2 ± 96.5 N, respectively.

Šidák post-hoc analyses demonstrated significant increases in both the trained and untrained arms in the post-training and follow-up periods compared to pre-training (all $p < 0.05$) and no difference between post-training and follow-up (p=NS) (Figure 5.1).

These findings demonstrate a significant increase in BIC muscle strength over time, with similar patterns observed in both the trained and untrained arms.

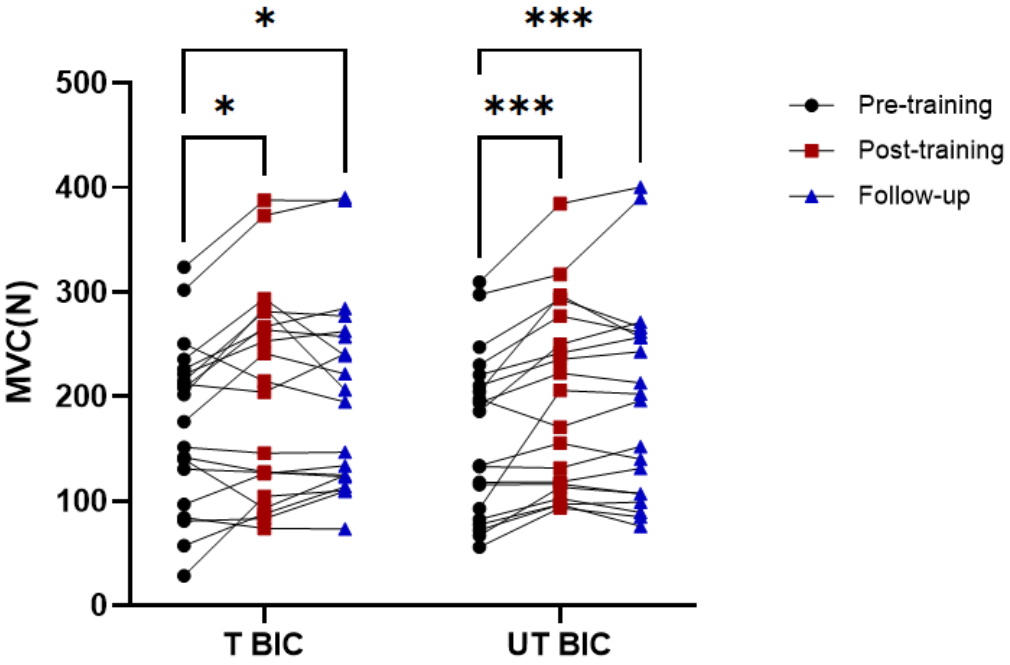


Figure 5.1*:T BIC and UT BIC MVC result before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Data were normally distributed and analyzed using repeated measures two-way ANOVA with Šidák post-hoc multiple comparisons. * = p < 0.05, *** = p < 0.001.*

Abbreviations: T BIC (trained biceps), UT BIC (untrained biceps), MVC (maximal voluntary contraction).

5.3.2.2 5.3.2.2 Triceps (TRI)

Two-way repeated measures ANOVA demonstrated a significant effect of time on TRI strength (F (1.381, 52.46) = 21.27, p < 0.01), but the main effect of arm (trained vs. untrained) was not significant (p = NS) and the arm × time interaction was also not significant (p = NS). According to descriptive statistics, TRI MVC values in the trained arm were 91.95 ± 48.82 N in the pre-training period, 143.6 ± 96.21 N in the post-training period, and 138.0 ± 79.65 N in the follow-up period; in the untrained arm, they were 93.08 ± 56.33 N, 137.3 ± 101.6 N, and 129.4 ± 85.61 N, respectively.

Šidák post-hoc analyses demonstrated significant increases in both the trained TRI and untrained TRI muscles in the post-training and follow-up periods compared to pre-training (all p < 0.05) and no difference between post-training and follow-up (p=NS).

Strength gains achieved with uMCT appear largely preserved during the detraining period in both arms (Figure 5.2).

These findings suggest that, similar to the BIC muscle, uMCT leads to an increase in triceps muscle strength not only in the trained arm but also in the untrained arm, and that this may be related to a cross-education effect.

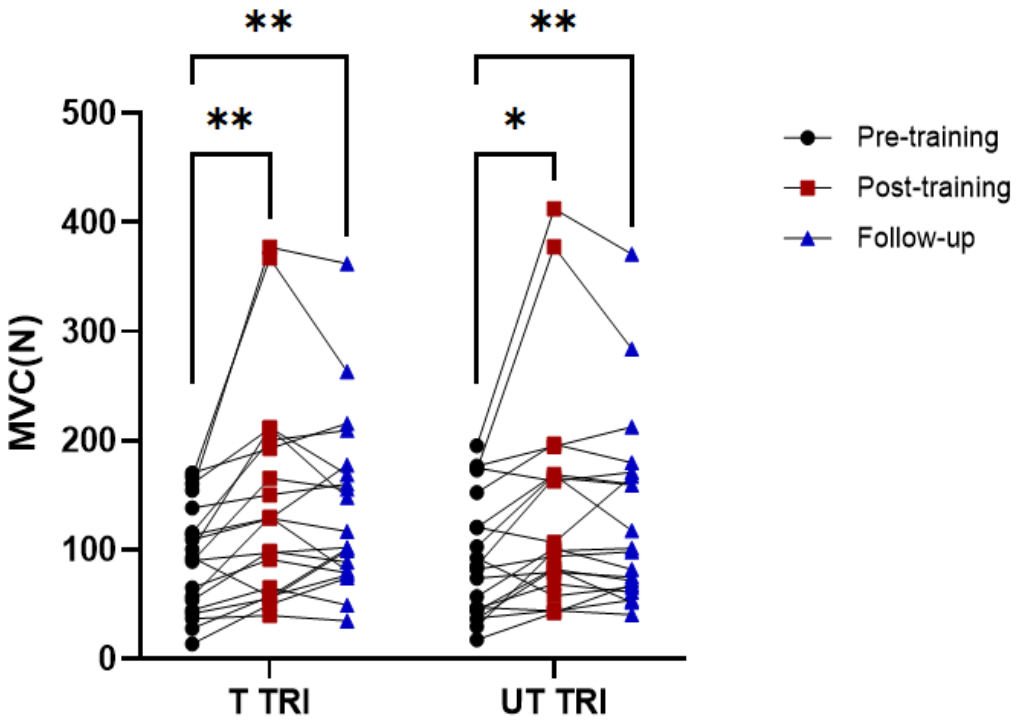


Figure 5.2*:T TRI and UT TRI MVC result before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Data were normally distributed and analyzed using repeated measures two-way ANOVA with Šidák post-hoc multiple comparisons. * = p < 0.05, **=p<0.01, *** = p < 0.001.*

Abbreviations: T TRI (trained triceps), UT TRI (untrained triceps), MVC (maximal voluntary contraction).

5.3.2.3 5.3.2.3 Tibialis Anterior (TA)

Two-way repeated measures ANOVA demonstrated a significant effect of time on TA MVC ($p < 0.05$), but the main effect of leg (trained vs. untrained) was not significant

(p = NS) and the leg × time interaction was also not significant (p = NS). According to descriptive statistics, TA MVC values in the trained-side leg were 41.12 ± 19.60 N in the pre-training period, 47.44 ± 28.90 N in the post-training period, and 54.79 ± 28.29 N in the follow-up period; in the untrained-side leg, they were 40.32 ± 19.01 N, 45.51 ± 26.25 N, and 52.63 ± 42.37 N, respectively.

Šidák post-hoc analyse demonstrated significant increases in both the trained-side TA muscle in the post-training and follow-up periods compared to pre-training (all $p < 0.05$) and no difference between post-training and follow-up (p = NS). Although an upward trend was observed for the untrained side TA, the changes over time were not statistically significant (p = NS) (Figure 5.3).

These findings indicate that, despite the trained side being only the dominant arm, the increase in MVC in the TA muscle of the dominant side can be explained by the cross-education effect.

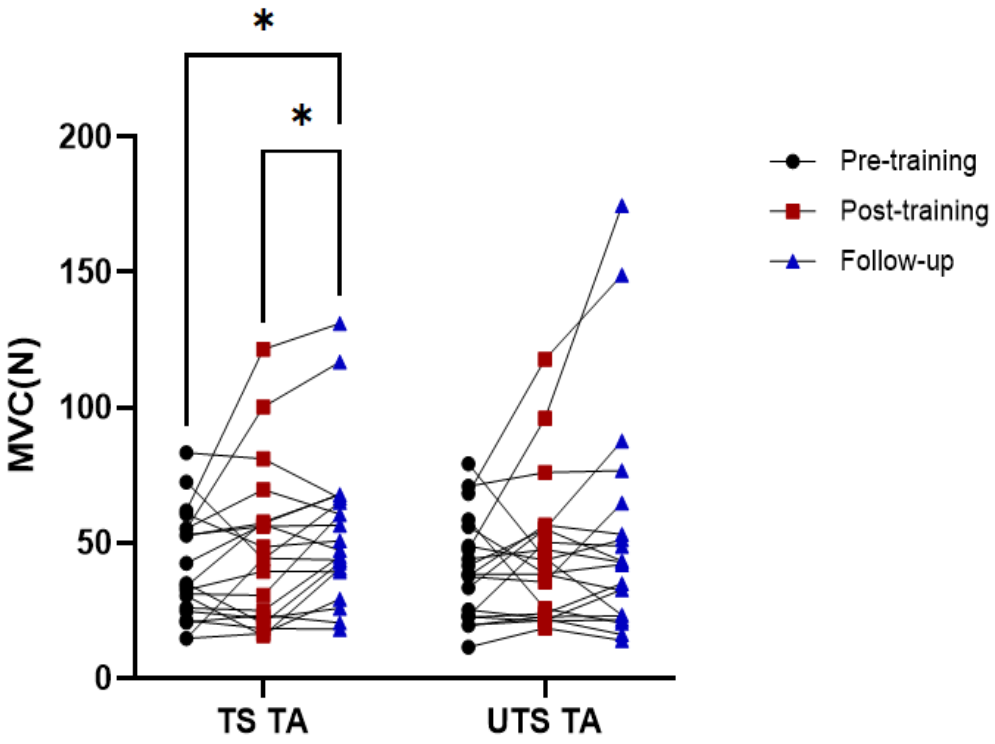


Figure 5.3:*TS TA and UTS TA MVC results before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Data were normally distributed and analyzed using repeated measures two-way ANOVA with Šidák post-hoc multiple comparisons. * = $p < 0.05$.*

Abbreviations: TS TA (trained-side tibialis anterior), UTS TA (untrained-side tibialis anterior), MVC (maximal voluntary contraction).

5.3.3 Handgrip strength

Two-way repeated measures ANOVA demonstrated a significant effect of time on handgrip strength ($F(2,76) = 3.89$, $p < 0.05$), but the main effect of arm (trained vs. untrained) was not significant (p = NS) and the arm × time interaction was also not significant (p = NS). According to the Šidák post-hoc comparison, the post-training measurement was significantly higher on the trained side compared to the pre-training measurement (pre: 28.77 ± 8.61 kg; post: 30.60 ± 8.60 kg; $p < 0.05$). However, the values in the follow-up period did not show a statistically significant difference compared to the post-training levels ($p > 0.05$). In the untrained group, no statistically significant change was detected at any time point (all $p > 0.05$).

Based on these findings, the 4-week unilateral uMCT resulted in a significant increase in handgrip strength on the trained side only, but this gain was only partially maintained during follow-up period (Figure 5.4).

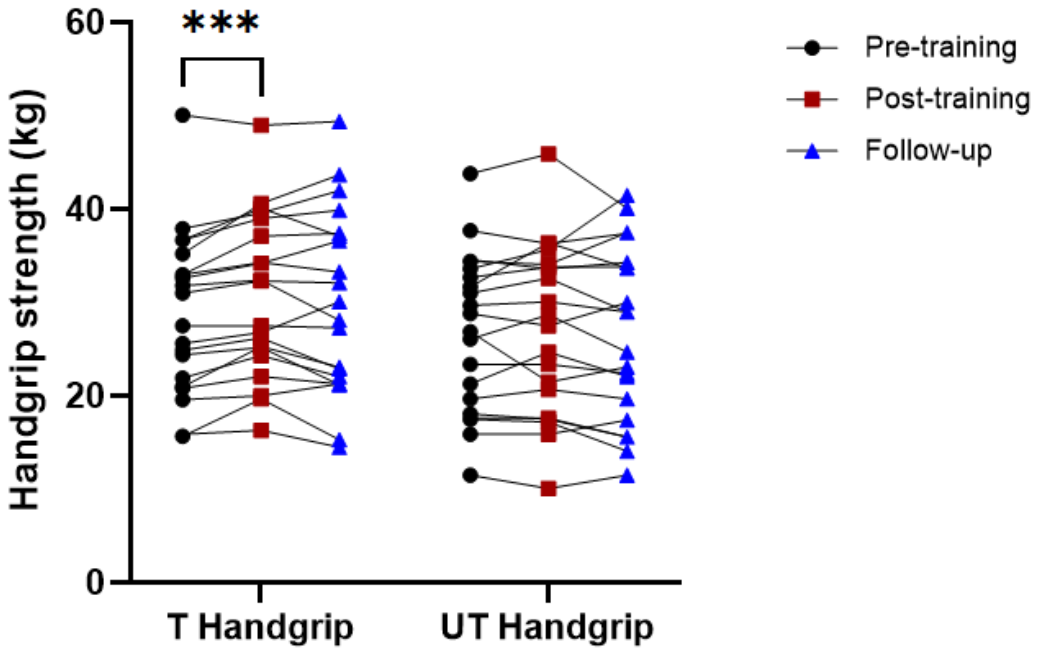


Figure 5.4:*T handgrip and UT Handgrip strength results before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Data were normally distributed and analyzed using repeated measures two-way ANOVA with Šidák post-hoc multiple comparisons. **** = $p < 0.0001$.*

Abbreviations: T Handgrip (trained handgrip), UT Handgrip (untrained handgrip).

5.3.4 MCON

There was a significant main effect of time, with the CC increasing from pre- to post-training (β = 0.099, 95% CI [0.026, 0.173] p = 0.008) and remaining elevated at follow-up (β = 0.082, 95% CI [0.009, 0.156] p = 0.029). A main effect of muscle was also observed: CC was lower in arm extension compared with the arm flexion (β = −0.132, 95% CI [−0.206, −0.059] p < 0.001) and markedly lower with dorsiflexion (β = −0.210, 95% CI [−0.283, −0.136] p < 0.001).

The main effect of training side (ipsilateral vs. contralateral) was not significant (β = −0.058, p < 0.05), indicating no bilateral differences (Figure 5.5).

No significant two-way interactions (Muscle x Time) were detected between time and

training side (all p > 0.15) or time and muscle (all p > 0.28), indicating that improvements over time were consistent across muscles and sides. Similarly, the three-way interaction (Time × TrainedSide × Muscle) was not statistically significant (all p > 0.06) (Figure 5.5).

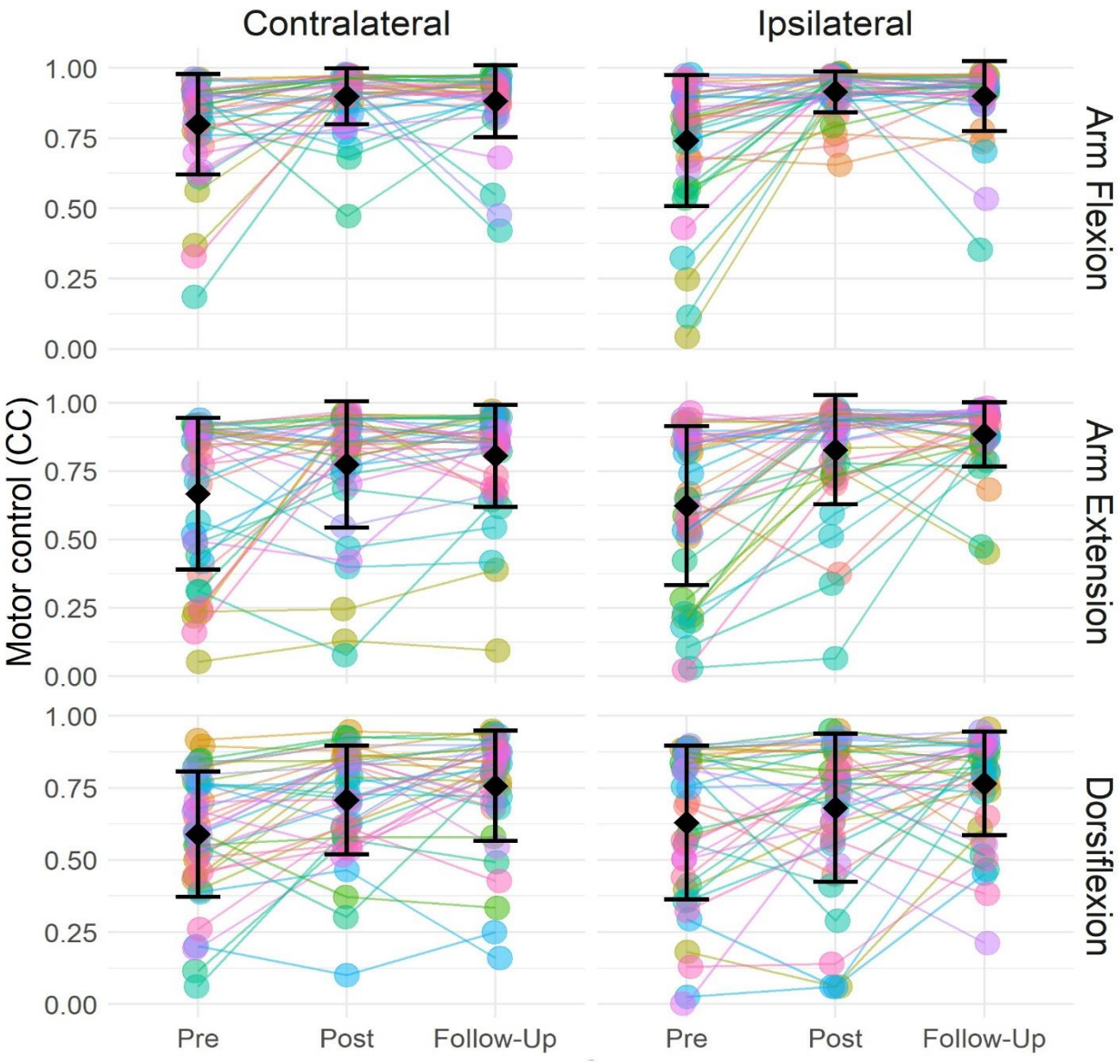


Figure 5.5:*Cross correlation analyses of target and achieved force across time, stratified by movement.*

Both trials at each timepoint are shown, with coloured dots representing subject means, linked across timepoints. Black diamond and error bars indicate mean and SD.

5.3.5 SPPB

A significant effect of time was observed for SPPB scores ($p < 0.01$). According to Dunn's multiple comparisons test, significant differences were found between pre-training and post-training ($p < 0.05$) and between pre-training and follow-up ($p < 0.05$), with no significant difference between post-training and follow-up. Median (interquartile range, IQR) scores were 11.0 (10.0–12.0) at pre-training, 11.5 (11.0–12.0) at post-training, and 11.0 (11.0–12.0) at follow-up. Although median values were similar at pre-training and follow-up, differences in score distributions resulted in statistical significance. It does appear that 4-weeks unilateral uMCT can lead to a significant improvement in overall physical performance (Figure 5.6).

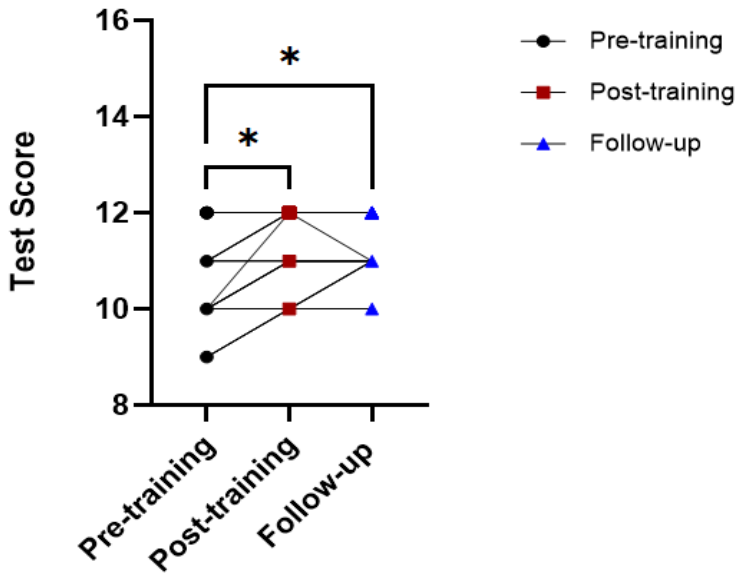


***Figure 5.6**:SPPB results before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Analysis via Friedman test with Dunn's post-hoc multiple comparisons. *=p<0.05.*

Abbreviations: SPPB (Short Physical Performance Battery).

5.3.6 TUG

There was no main effect of time for the TUG data ($p > 0.05$). Mean TUG scores were 9.12 ± 2.01 s at pre-training, 9.33 ± 1.24 s in the post-training assessment, and 9.30 ±

1.28 s in the follow-up test (Figure 5.7). These findings indicate that 4-weeks of unilateral uMCT did not result in a significant change in functional mobility as measured by the TUG test.

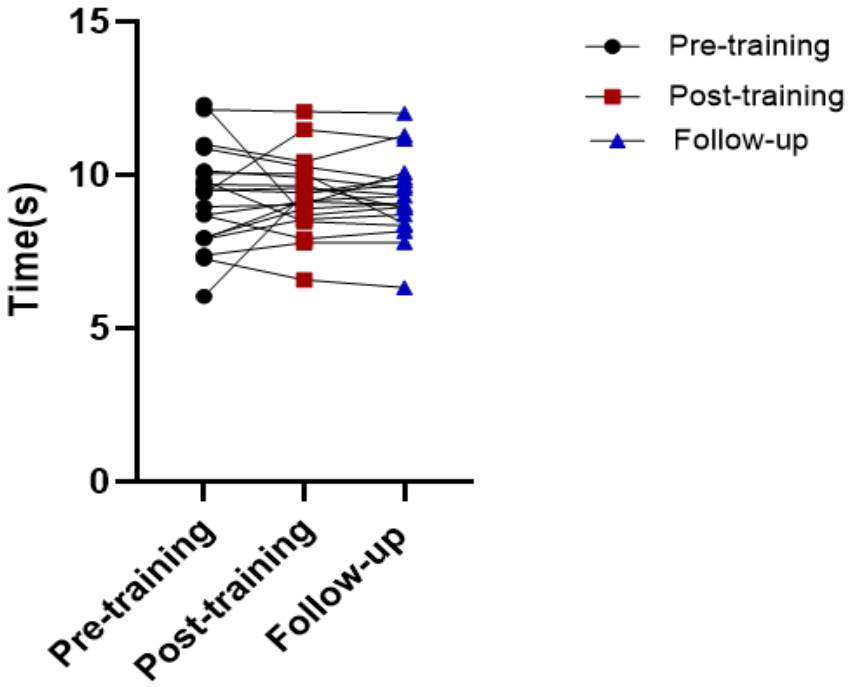


Figure 5.7:*TUG results before (Pre-training) and after (Post-training).*

4-weeks upper limb motor control training by (*n=20; 10 male) older adults, and after 4-weeks de-training* (*Follow-up).*

Data were normally distributed and analyzed using repeated measures one-way ANOVA with Tukey post-hoc multiple comparisons.

Abbreviations: SPPB (Short Physical Performance Battery).

5.3.7 Balance

Balance performance was assessed under three conditions: double-leg stance, single-leg stance on the trained side, and single-leg stance on the untrained side. Each condition was performed with both eyes open and eyes closed. No statistically significant differences were observed in either Distance Travelled (DT) or Ellipse Area (EA) parameters across most conditions. However, in the trained-side single-leg

stance with eyes open, a significant effect of time was observed. For DT, significant differences were found between pre-training (1706 mm, IQR: 1147–2486) and post-training (1097 mm, IQR: 902–1862; $p < 0.01$), and between pre-training and follow-up (897 mm, IQR: 681–1198; $p < 0.01$) (Figure 5.8A), with lower values indicating improved balance. For EA, a significant difference was observed between pre-training (249 mm², IQR: 100.5–857.5) and follow-up (91 mm², IQR: 62.5–239; $p < 0.05$) (Figure 5.8B). These findings suggest improved balance performance in the trained-side single-leg stance with eyes open.

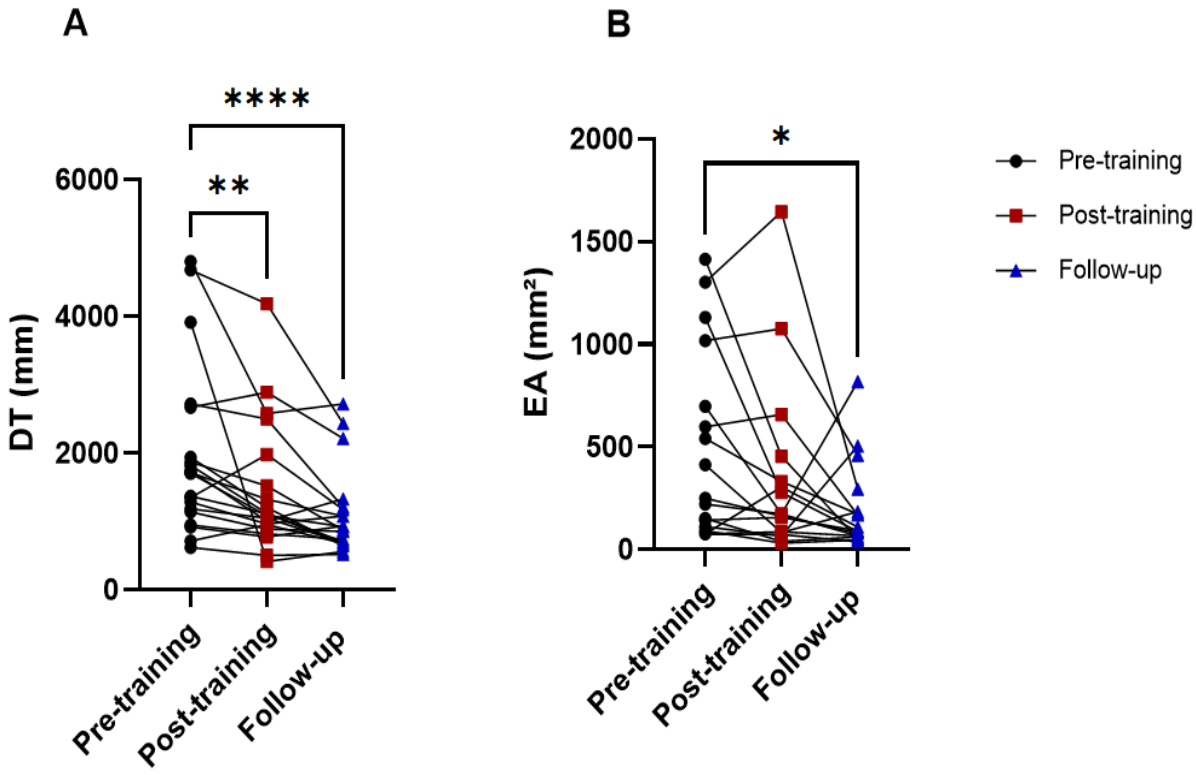


Figure 5.8*:A) TS leg- eyes open- DT and B) TS leg-eyes open- EA results before (Pre-training) and after (Post-training).*

*4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Analysis via Friedman test with Dunn's post-hoc multiple comparisons. *=p<0.05, **=p<0.01, ****=p<0.00001.*

Abbreviations: TS (trained-side), DT (Distance Travelled), EA (Ellipse Area).

5.3.8 Dexterity (9-Hole Peg Test)

Two-way repeated measures ANOVA demonstrated a significant effect of time on 9-hole peg test performance ($F(1.93, 73.38) = 6.21$, $p < 0.05$), but the main effect of arm (trained vs. untrained) was not significant (p = NS) and the arm × time interaction was also not significant (p = NS).

Šídák post-hoc comparisons revealed a significant improvement between pre-training and post-training measurements only in the trained arm (pre-training 23.51 ± 0.71 s, post-training 22.24 ± 0.63 s; $p < 0.05$). However, this improvement was not maintained during the follow-up period (23.05 ± 0.96 s). For the untrained arm, no significant difference was found between the untrained arm 9-hole peg test results and the test duration based on the time factor (p = NS). The mean test times for the untrained arm were 24.01 ± 3.48 seconds pre-training, 22.69 ± 3.44 seconds post-training, and 23.73 ± 3.56 seconds at follow-up (Figure 5.9).

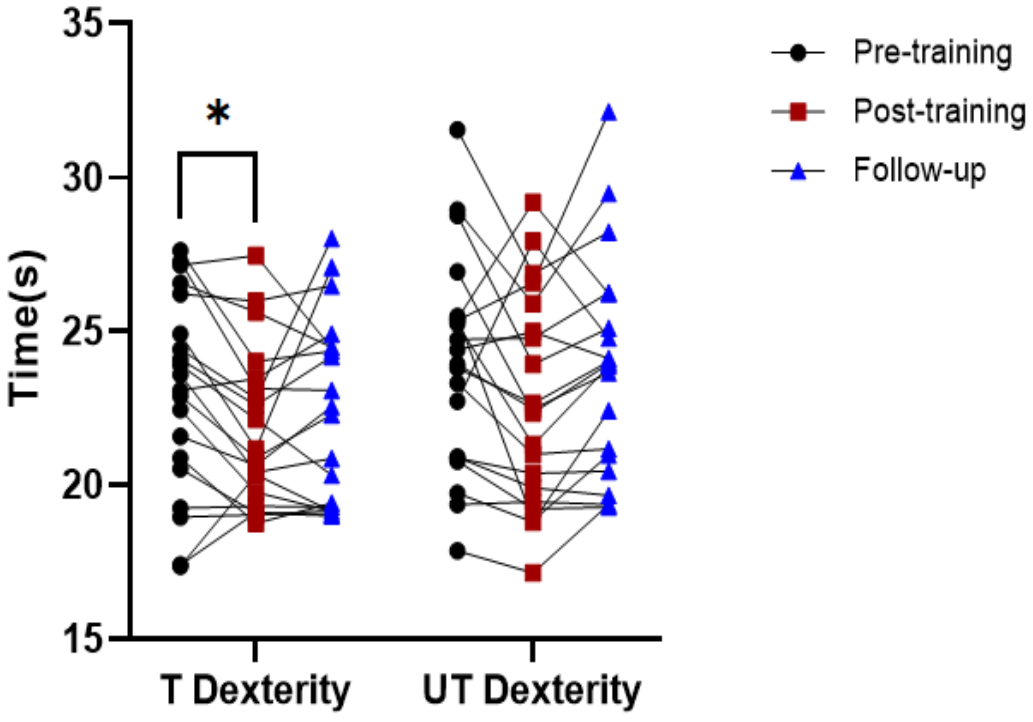


Figure 5.9: *T Dexterity and UT Dexterity results before (Pre-training) and after (Post-training). 4-weeks upper limb motor control training by (n=20; 10 male) older adults, and after 4-weeks de-training (Follow-up). Data were normally distributed and analyzed using repeated measures two-way ANOVA with Šidák post-hoc multiple comparisons. * = $p < 0.05$.*

Abbreviations: T Dexterity (trained dexterity), UT Dexterity (untrained dexterity).

5.4 Discussion

Physical performance is an objective, measurable whole-body function related to movement, encompassing central and peripheral nervous system functions, including muscle strength and balance [440]. This chapter demonstrates the effect of 4-weeks low intensity unilateral uMCT on physical performance in healthy older adults. The results demonstrate an increase in strength in both the trained and untrained BIC and TRI muscles, an increase in strength in the trained-side leg TA, an increase in handgrip strength on the trained side and an increase in motor control on both sides. Further, this intervention elicited an increase in SPPB performance, some balance parameters, and dexterity by the trained limb. Based on the results of this study, low-intensity unilateral uMCT training can be considered a safe, effective, and feasible approach for improving aspects of muscle strength and functional capacity in healthy older adults. Furthermore, some of these improvements were maintained during the follow-up period, suggesting a carry-over effect and the potential for longer-term adaptations beyond the active training phase.

The ageing process is a natural physiological phenomenon characterised by a gradual decline in muscle mass, strength, and neuromuscular control [39, 45, 52]. These changes are associated with muscle fibre turnover, a reduction in the number of MUs, and decreased nerve conduction velocity [74]. With ageing, MU size typically increases while their number decreases, a process that can impair overall muscle function and fine motor control [86, 441]. Exercise interventions in older adults can promote MU remodelling through neurotrophins release, helping to maintain muscle strength, although enlarged MUs may reduce movement precision [212, 442, 443]. The findings of the present study align with this concept, demonstrating that low-intensity unilateral uMCT can induce improvements in motor control and dexterity in older adults, suggesting potential neuromuscular adaptations.

Age-related neuromuscular adaptations, including fibre atrophy, collateral reinnervation, and altered fibre-type grouping, may further influence force control [212, 443]. In addition, NMJ instability and irregular motor unit firing contribute to the deterioration of neuromuscular function observed with ageing [93]. These

physiological declines lead to reductions in strength, balance, coordination, and functional performance in older adults [89, 93, 444]. Moreover, changes in muscle fibre quality can diminish explosive force production and exacerbate functional decline [445, 446]. Considering these factors, low-intensity, neuromuscular-focused interventions such as unilateral uMCT may play a valuable role in mitigating age-related physiological deterioration.

The results of this study, which examined the effect of unilateral uMCT on muscle strength and performance, are consistent with previous research [250] indicating studies that low-intensity resistance or motor control-based exercises may have beneficial effects on muscle strength and functional performance. In this study, bilateral BIC and TRI MVC scores increased significantly. Furthermore, handgrip strength showed a statistically significant increase in the trained side. There are studies in the literature showing that low-intensity (30–50% 1RM) exercise training may contribute to improving motor unit synchronisation by strengthening neuromuscular communication [447, 448]. This type of training has been reported to improve parameters such as motor unit recruitment, firing frequency, and intramuscular coordination by strengthening neuromuscular communication [448, 449]. The results of low-intensity unilateral uMCT training have also demonstrated strength gains, which are thought to be largely due to neuromuscular adaptations. This is because muscle hypertrophy mechanism is limited in older adults and that early strength gains are based on neural adaptations and improvements in motor control mechanisms [444, 450]. These neural adaptations may improve MVC levels by increasing the efficiency of muscle activation [450, 451]. These adaptations, including improved motor unit synchronisation, may contribute to enhanced functional performance in older adults [452]. Taken together, these findings suggest that motor control-based exercises may improve muscle strength and support functional performance through enhanced neuromuscular coordination.

This study demonstrated a statistically significant change in handgrip strength on the trained side, which aligns with findings suggesting that strength gains in the directly exercised muscle may be related to neural activation, motor unit recruitment, and specific muscular adaptation processes [451]. Similarly, Munn and colleagues (2005) [453] demonstrated that unilateral resistance exercise causes a significant increase in strength primarily in the trained limb, with limited or statistically insignificant changes in the contralateral limb. As grip production requires proximal upper limb stabilisation

and coordinated elbow control, improvements in biceps and triceps motor performance may also have contributed to the increase observed in trained-side handgrip strength. The significant improvement observed only on the trained side may therefore reflect local neuromuscular adaptations associated with repeated unilateral motor control practice. Although some studies have reported that high-intensity unilateral resistance training can increase strength on both trained and untrained sides [454], the present study found no significant change in handgrip strength on the untrained side. This difference is likely due to the nature of the exercise, which emphasised low-intensity motor control and coordination rather than maximal force production. Furthermore, reduced neuromuscular plasticity and diminished motor unit synchronisation commonly seen in older adults may also have limited the transfer of force to the untrained side [89, 93] .

In this study, other functional performance was assessed using SPPB, TUG, balance, and dexterity outcomes, and it was demonstrated that 4 weeks of unilateral uMCT may be effective on some functional parameters in older adults. However, no statistically significant differences were found in some functional performances, which is consistent with studies showing that physiological changes such as muscle strength loss, decreased proprioceptive responses, and slowed neuromuscular transmission in older adults may limit the responses to exercise [93, 444].

According to SPPB results, a significant improvement in participants' scores was achieved after uMCT, and furthermore, this improvement was maintained during the detraining period. This result suggests that motor control-based exercise may be an application that can increase the functional independence of older adults in activities of daily living by improving lower limb function. A study investigating the effect of low-load motor control exercises and high-load exercises on muscle strength and function found that after 12 weeks of exercise, low-load motor control exercises may lead to statistically significant improvements in muscle strength and control, as well as movement quality [455]. Based on this finding, it can be concluded that short-term exercises targeting lower limb muscle strength and functional performance can have positive effects in older adults. It is argued that these effects may be related to increased neuromuscular coordination, improved motor unit synchronisation, improved proprioception, and accelerated muscle strength production [451].

Studies examining the effect of motor control training on balance in the literature are

quite limited. In a study conducted by Tsekoura et al. (2021) [456] in older adults, they examined the effect of a programme consisting of home-based motor control and balance exercises on postural control and functional performance and reported positive developments. Furthermore, the researchers emphasised that motor control plays an important role, particularly in the reorganisation of balance strategies and the coordination of lower limb muscles. Based on these results, it can be argued that motor control-focused exercises, such as one-legged balance with eyes open, applied through uMCT, can improve balance performance through sensorimotor system adaptations.

However, no significant change in the TUG test was observed in the uMCT study based on the time factor. Although uMCT improves balance and skeletal muscle function, it may have a limited effect on overall performance parameters such as functional mobility due to its low metabolic and cardiovascular load. This limitation may explain why no significant change in the TUG test score was observed. In a study examining the effect of short-term exercise interventions on functional mobility, no significant improvement was observed in the balance, walking speed, and sit-to-stand performance of older adults after 4 weeks of strength training [457]. In contrast, a study demonstrated that a 12-week combined exercise intervention led to significant improvements in TUG performance among older adults [458], suggesting that the relatively short duration and motor control focus of the present uMCT intervention may account for the absence of a similar effect on TUG outcomes.

According to dexterity results, uMCT had a significant effect only on the trained arm, with no change observed on the untrained arm. Based on these results, it can be said that unilateral exercises may have limited cross-education effects on fine motor skills. Although studies exist showing that unilateral exercises can increase strength in the contralateral extremities [454, 459, 460, 461] through cross-education with neural adaptations, neurological transfer may be more limited in dexterity tasks because fine motor skills require more complex and precise coordination [260, 462]. The 9-hole peg test is a test that requires a high level of visual-motor integration, finger muscle control, and timing sensitivity [357, 463], and the development of dexterity on the contralateral arm with cross-education after 4 weeks of unilateral uMCT has been limited.

Motor control (CC) results, which indicate the level of coordination between the target and the force produced, were also evaluated in this study, and a significant increase was found. Furthermore, this increase was maintained during the follow-up period,

suggesting that 4 weeks of uMCT may induce lasting neuromuscular adaptations. These results are consistent with studies in the literature indicating that early-stage neural adaptations may play a fundamental role in motor performance development [464, 465]. Increased cortical excitability in the motor cortex, motor unit synchronisation, and effective connectivity between motor networks, achieved through motor control exercise, may be effective factors in improving motor control [464].

In this study, despite the application of unilateral uMCT, mixed linear model analyses indicated that the interaction between time and the trained side was not significant. This finding revealed that the increase in motor control occurred not only on the trained side but also on the contralateral side at a similar level, indicating that unilateral applications can trigger bilateral neural adaptations. Studies in the literature have demonstrated that the gains observed in the contralateral extremity following unilateral exercise can be explained by the 'cross-education' mechanism, which occurs largely via the primary motor cortex, supplementary motor area, and corpus callosum [261, 453, 466]. However, in this study, despite the training being applied unilaterally, the linear mixed effects analysis did not reveal a significant interaction between time and the training side. This reflects that CC development was similar for both the trained and untrained sides, suggesting that the pronounced lateralised effects frequently seen in strength gains may be more limited in motor control parameters.

On the other hand, differences observed between muscle groups (e.g., lower CC values in dorsiflexion (TA)) reflect that proprioceptive feedback, motor planning, and muscle activation strategies may vary depending on the type of movement and task complexity. Neuromuscular changes during ageing, such as motor unit loss, slowing of reinnervation processes, and decreases in nerve conduction velocity, may limit the capacity for adaptation, particularly in fine motor tasks [86, 441] . Therefore, the transfer of gains to the contralateral side may be partially limited by task specificity. Based on these findings, we can say that four weeks of unilateral uMCT may affect plasticity, particularly at the central nervous system level, and strengthens bilateral CC organisation; however, longer-term protocols involving different intensities and task variety may make contralateral transfer more pronounced.

5.4.1 Study limitations

This study has some limitations. Firstly, the relatively small sample size is one such limitation and may have limited the statistical power. This limitation may have made it difficult to interpret some results (e.g., TUG and balance measurements) that were close to the significance level but not statistically significant. Furthermore, again due to the small sample size, it may have increased the effect of variability among participants, potentially masking the true intervention effects, particularly in non-parametric analyses. Therefore, the generalisability of the results of this study, conducted with a small sample group, to the wider population is limited, and these results need to be confirmed by future studies with larger sample groups.

The second limitation of this pilot study is the relatively short duration of the intervention, which may have limited the functional performance outcomes to neuromuscular adaptation and limited the cross-education effect. Longer-term interventions are required to achieve optimal development in motor learning, neuromuscular adaptation, and especially cross-education effects. Based on the results of this study, our short-term intervention demonstrated early adaptations at the neuromuscular level, but it was concluded that longer-term applications are needed for gains in functional and balance aspects.

The final limitation is the sensitivity and specificity limitations of some of the outcome measures used in the study. For the TUG and balance assessments, commonly used clinical measures were selected; however, these may lack sufficient sensitivity to detect small but clinically meaningful changes in participants with high functional levels. Based on this, more sensitive and task-specific measurement tools could be used in future studies to overcome this limitation.

5.4.2 Conclusion

In conclusion, low-intensity unilateral uMCT has been demonstrated to have positive effects on muscle strength, motor control, and functional performance in older adults. In particular, the increase in bilateral upper limb muscle strength and motor control suggests that these exercises may support neuromuscular adaptation. Furthermore, the observed improvements in lower limb functional performance (SPPB) suggest that motor control-based exercises may be beneficial for physical independence in activities

of daily living. Importantly, some of these improvements, particularly in cognitive and functional measures, were maintained during the follow-up period, suggesting a degree of retention after the intervention. Furthermore, the failure to obtain statistically significant results in TUG and balance parameters indicates that the exercise training in this study was short-term (4 weeks) and that the effects of short-term applications on functional capacity may be limited. Overall, based on the findings of this study, low intensity uMCT is considered a safe, feasible, and potentially effective intervention method for older adults with physical impairments.

Chapter 6 Forming a consensus among different groups of clinical staff involved in the perioperative care of older adults on the potential for prehabilitation to improve postoperative cognition: a modified Delphi study

6.1 Introduction

Cognitive complications that may arise after major surgery in older adults may negatively affect the patient and increase use of healthcare services [141, 159, 467]. POD and POCD are among the most common cognitive complications that can occur after surgery and are clinically adverse conditions [148, 275, 468]. These two complications are explained in detail in the introduction (Chapter 1). Strategies aimed at preventing postoperative cognitive complications are limited, and there is still uncertainty regarding the effectiveness of existing strategies [149, 202, 469, 470]. This situation makes it essential to investigate preoperative interventions that could serve as protective measures.

POD and POCD are well known to have adverse effects on functional independence and quality of life, particularly in older individuals [140, 179, 471]. To reduce these risks, preoperative exercise-based prehabilitation strategies and cognitive training interventions [472, 473] are available. However, when looking at these interventions, the results are quite heterogeneous, and there are differences in terms of exercise type, duration, and intensity. In our study, which investigates the effect of preoperative physical exercise on postoperative cognition, presented in detail in Chapter 2, limitations in sample sizes and the non-standardisation of cognitive assessment tools used have reduced the strength and generalisability of the evidence obtained [139]. For these reasons, these approaches have not yet become part of standard preoperative clinical care.

“Prehabilitation” is defined as a multidimensional approach that includes exercise, nutritional support, and psychosocial support for patients before surgery, with the aim of increasing their functional capacity [474]. Prehabilitation has become part of standard care prior to major surgery, as it has been shown to have positive effects on patients’ cardiorespiratory capacity, muscle strength, mobilisation, and length of hospital stay [475, 476]. Strategies to maintain and enhance cognitive reserve could be

integrated into prehabilitation programmes, but at present the most ideal intervention, timing, and doses are unclear. In addition, the clinical understanding and practice of healthcare professionals providing perioperative care to older adults in this area is lacking.

Based on strong evidence of the positive effects of exercise on improving cognitive functions and preserving cognitive reserve in the general population, it is reasonable to consider exercise-based interventions implemented in the preoperative period as a protective measure against potential surgery-related cognitive impairments.

Away from the peri-operative setting, there is a wealth of literature demonstrating the positive impact of exercise training on multiple aspects of cognitive function [279- 282] in both young [284] and older adults [285], with further evidence supporting the role of exercise training to reduce the risk of cognitive decline in later years [286, 287]. Within this, exercise is used as an umbrella term to describe various types of structured physical activity (e.g., aerobic, resistance and balance-based exercise training such as Tai-Chi), with different potential mechanisms underpinning cognitive improvement ascribed to each [282]. These mechanisms include improving brain plasticity [288, 289], increasing the level of growth factors involved in BDNF and IGF-1, regulation of inflammatory cytokines [290, 291], increasing cerebral blood flow [292], and reducing oxidative stress [293]. However, despite this existent evidence base, to date there has been no synthesis of the available evidence regarding the effect of preoperative exercise training on postoperative cognition.

Within the scope of this thesis, a systematic review study [139] was conducted on the relationship between preoperative exercise interventions and postoperative cognition in the literature, which is presented in detail in Chapter 2. Only three studies were found in this review, and none of them had an age limit. Furthermore, three different studies used different exercise modalities and assessment tools. Given the limitations and heterogeneity extending from preoperative rehabilitation to the effect on postoperative cognition, the systematic collection of expert opinions is of great importance.

The Delphi method is one of the most frequently used methods for establishing consensus on clinical issues, but it has also been criticized by some researchers as potentially creating a basis for ‘eminence-based’ rather than ‘evidence-based’ approaches in areas where evidence is limited [477, 478]. One limitation in experts

reaching consensus is 'collective ignorance,' which can lead to agreements that represent the group but lack a solid scientific foundation. When experts hold differing views, deep disagreements may arise and may not always be resolved. Therefore, consensus cannot replace the best available evidence but should be seen as its complement [479]. Given the limited and heterogeneous evidence base, the Delphi method was chosen for this study, as it was used to systematically gather multidisciplinary expert opinions to determine future research priorities rather than to replace empirical evidence.

The aim of this Delphi Study was to determine the contributions of prehabilitation in terms of cognitive outcomes and to provide guidance for future research and clinical practice involving patients. A modified three-round Delphi method was employed, involving clinicians from specialties such as anaesthesiology, surgery, geriatrics, and physiotherapy working in the older adult surgery team.

6.2 Methods

This study was reviewed and approved by the Nottingham University Faculty of Medicine Research Ethics Committee (FMHS 265-0724). All participants provided written consent in English via the survey platform (Microsoft Forms) after confirming their understanding of the study requirements.

6.2.1 The Delphi process

There are different methods for reaching consensus in clinical research. One of these methods is the Nominal Group Technique (NGT), in which all participants gather face-to-face in the same environment to generate ideas. This method is based on prioritising the ideas generated and is considered a quick and practical method. However, the requirement for all participants to be face-to-face limits the venue and the number of participants, and furthermore, it is a method that may be disadvantageous due to the risk of dominant individuals within the group steering the process [480]. Consensus methods such as consensus conferences or traditional expert panels, which are generally based on a single session of discussion on the topic, also exist. Consensus conferences and traditional expert panels are commonly used methods for establishing consensus,

but they have some significant limitations. The selection of panel members is often unsystematic and may reduce the reliability of the panel's representativeness [477, 481]. Expert panels are costly and therefore more difficult to repeat [481]. Although these methods facilitate the exchange of views among experts, their disadvantage is that, because they involve only a single session, they do not allow for the systematic refinement of opinions, and there is a possibility that the loudest voices may dominate these discussions [482].

The Delphi method was selected due to the limited and heterogeneous evidence base regarding the cognitive effects of prehabilitation. While the systematic review conducted within the scope of this thesis synthesised the existing evidence and investigated potential mechanical effects in studies with healthy volunteers, the Delphi study contributed to the integration of multidisciplinary clinical expertise to contextualise these findings and identify areas of consensus and uncertainty. These complementary approaches helped triangulate the evidence to inform future research priorities and clinical decision-making.

The Delphi method is a consensus method that allows for the systematic collection of experts' opinions over multiple rounds and provides participants with the opportunity to review their opinions repeatedly through feedback provided in each round. This iterative process strengthens the validity of the final consensus. A main advantage of this consensus method is that it allows individuals from different disciplines to express their opinions anonymously and, by organising multiple rounds, provides the opportunity to revise their responses based on the results of the previous round [483] . This reduces the influence of dominant individuals in group discussions and minimises preconceptions arising from group dynamics [483]. Moreover, participants can be involved in the process through online or written surveys, which allows for the collection of opinions from many participants in geographically diverse regions [483] . Thus, Delphi studies are not limited by time or place. In this study, the Delphi method was chosen instead of other consensus techniques or a single-round survey to achieve a systematic and refined agreement on the topic. During the Delphi process, questions related to a predetermined subject were sent to experts through successive rounds, with subsequent rounds planned according to the feedback received, aiming to progressively increase the level of consensus [478].

It is well recognised that, in clinical issues where evidence is limited, the Delphi method offers a valuable approach to developing consensus and informing decision-making [483]. Furthermore, the Delphi method is a widely accepted method used in healthcare to reach consensus on a clinical issue and to produce a conclusion related to the issue. It is a flexible approach that collects expert opinions from different fields on clinical issues and produces a consensus [484, 485].

The process of the Delphi study is to repeatedly transmit accepted or revised/rejected statements based on round responses for predetermined statements until consensus is reached [486]. The use of expert-based assessment assumes that the opinions of a group of experts with different perspectives will provide more valid findings than those obtained from a single expert [485, 487].

In the Delphi method, it is more appropriate to adapt the method to the research objectives rather than re-designing the research objectives to fit the method [488]. In a traditional Delphi study, the first round usually includes open-ended questions, and the aim is to determine the focus of the study. However, prior to this study, existing literature was reviewed to identify gaps in this area, and the first round of questions was determined based on the focus of the study. In the traditional Delphi method, free text responses are usually collected only in the first round, whereas in this study, participants were provided with a free text box to express their opinions throughout all three rounds. This method enabled all participants to express their opinions at every stage of the study, thereby aiming to proceed in a more inclusive and dynamic manner.

The Delphi process is an iterative process that uses repeated rounds to reach an acceptable level of consensus among experts on a given topic. After each round:

- The statements agreed upon by the experts were extracted from subsequent rounds of analysis.
- While some participants agreed on the statements they proposed changes to the wording. Statements that achieved over 80% agreement were revised where necessary in the free-text comments.
- New statements were developed based on open-ended comments.
- Some statements have been combined or reorganised under separate headings based on participants' suggestions.

Since there is no universally accepted threshold for defining consensus in the Delphi process, in line with previous studies [489, 490], consensus was accepted when there was 80% or more agreement among panel members on ‘inclusion’ or ‘exclusion’. The study was conducted in three rounds. The first round was conducted in February 2025, and the second round was conducted in March 2025. The third and final round was completed in May 2025.

6.2.2 Expert panel selection

An expert panel is defined as a group of individuals with experience or knowledge on a specific topic, whose purpose is to strengthen the reliability of consensus [491]. The criteria for panel participation were as follows: geriatricians, physiotherapists, anaesthetists, and others (nurses, dieticians, occupational therapists, advanced clinical practitioners) working as clinical staff in the UK with experience in pre- or post-operative care of geriatric patients. The geriatric surgeon and other medical staff from the geriatric surgery team were invited but did not attend. The detailed composition of the expert panel can also be found in the results. Participants in the first round of the Delphi study were contacted via the university's clinical staff email lists and the university's official newsletters/social media platforms. Emails were sent to participants individually to ensure anonymity.

A purposive sampling strategy was developed to recruit healthcare professionals from different fields involved in surgical care pathways for older adults. This strategy included the most appropriate participants in the study and ensured that all relevant stakeholders contributed to the consensus process. Data were collected online using surveys created using Microsoft Forms. The online survey provided participants with the opportunity to participate in the study at a time and location convenient for them within the specified timeframe. All collected data were downloaded to a password-protected Microsoft Excel file. The online surveys protected participant anonymity and protected them from some of the biases that might occur in in-person interviews. There were three weeks to complete the survey sent for each round, and participants were asked to complete it at their convenience. No additional consent or approval was required.

Participants who were contacted via email or social media clicked on the link sent to

them and read the information page. This page provided all the relevant information that would be included in a traditional participant consent form. If they did not agree to participate in the study, they could end the session and close their browsers. Participants who agreed to participate in the study were directed to the survey page by clicking the "Next" button. Participants who did not consent could close the survey at this stage and were not informed of any further information. Participation in the study was entirely voluntary, and the participant may withdraw from the study without giving any reason. However, participants were informed in advance that this data could not be deleted and would only be used after clicking the "Submit" button. Data from participants who did not complete all rounds of the study was used in the final analysis, based on the research team's assessment. In this study, there was only one reason for participants' exclusion: failure to respond to the email sent for the next round in time. Exclusions were entirely due to their failure to complete the form despite the reminder emails; no other exclusion criteria were applied.

For the second round of the Delphi process, the survey link was sent via email using the contact information provided in the first round. Participants who did not wish to participate could end the survey by closing their browsers. This process was continued until the three Delphi rounds were completed. Participants were given three weeks to complete each round of the survey, and a reminder email was sent each week. Participants who did not complete any round within the given time frame and did not contact the researchers were excluded from subsequent rounds of the process.

6.2.3 Methods of Data Analysis

The collected data were stored in an appropriately named folder on the University's secure OneDrive. These data were then exported to Microsoft Excel and Graph Pad was used to facilitate data analysis. In this study, responses were collected using a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree), and the collected data were analysed and presented using descriptive statistics. The consensus criterion was determined to be at least 80% of participants selecting the ‘agree’ or ‘strongly agree’ option, in line with criteria commonly accepted in the literature. The percentage distribution of the data were calculated using GraphPad Prism (10.5.0) software.

6.2.3.1 Delphi rounds

Participants in 3 rounds included medical staff working in the UK. The first round consisted of 41 statements in 8 sections (Understanding POD, Understanding POCD, Understanding Resilience to Surgery in terms of POD and POCD, The Impact of Pre-Operative Cognition, The Impact of Surgical Prehabilitation on Physiological Function, The Composition of Surgical Prehabilitation, The Impact of Surgical Prehabilitation on Cognitive Function, Prehabilitation Programs). Using a Likert scale, experts selected the extent to which they agreed with a statement or how important a statement was. The scale included the options "strongly agree," "agree," "neither agree nor disagree," "disagree," and "strongly disagree."

Anonymised results were downloaded from Microsoft Forms and reviewed. Items that received more than 80% of responses of 'strongly agree' and 'agree' were considered to have reached consensus, while all other items were revised after analysis of the open-text responses and recirculated. The open-ended responses were not analysed using a formal process, but they were discussed with the working group, and the statements were revised accordingly for the next round. The survey link with revised statements was sent to the previous round of respondents.

6.3 Results

6.3.1 Summary of rounds

Participants in 3 rounds included medical staff working in the UK (round 1, n = 47; round 2, n = 32; round 3, n = 24). A flowchart showing how statements moved through the consensus process is shown in Figure 6.1.

Table 6.1 summarizes the responses for each round. This summary includes the purpose of the round, the number of statements included the number of statements on which consensus was reached, the number of statements revised for the next round, and the number of statements removed or rejected in the relevant round.

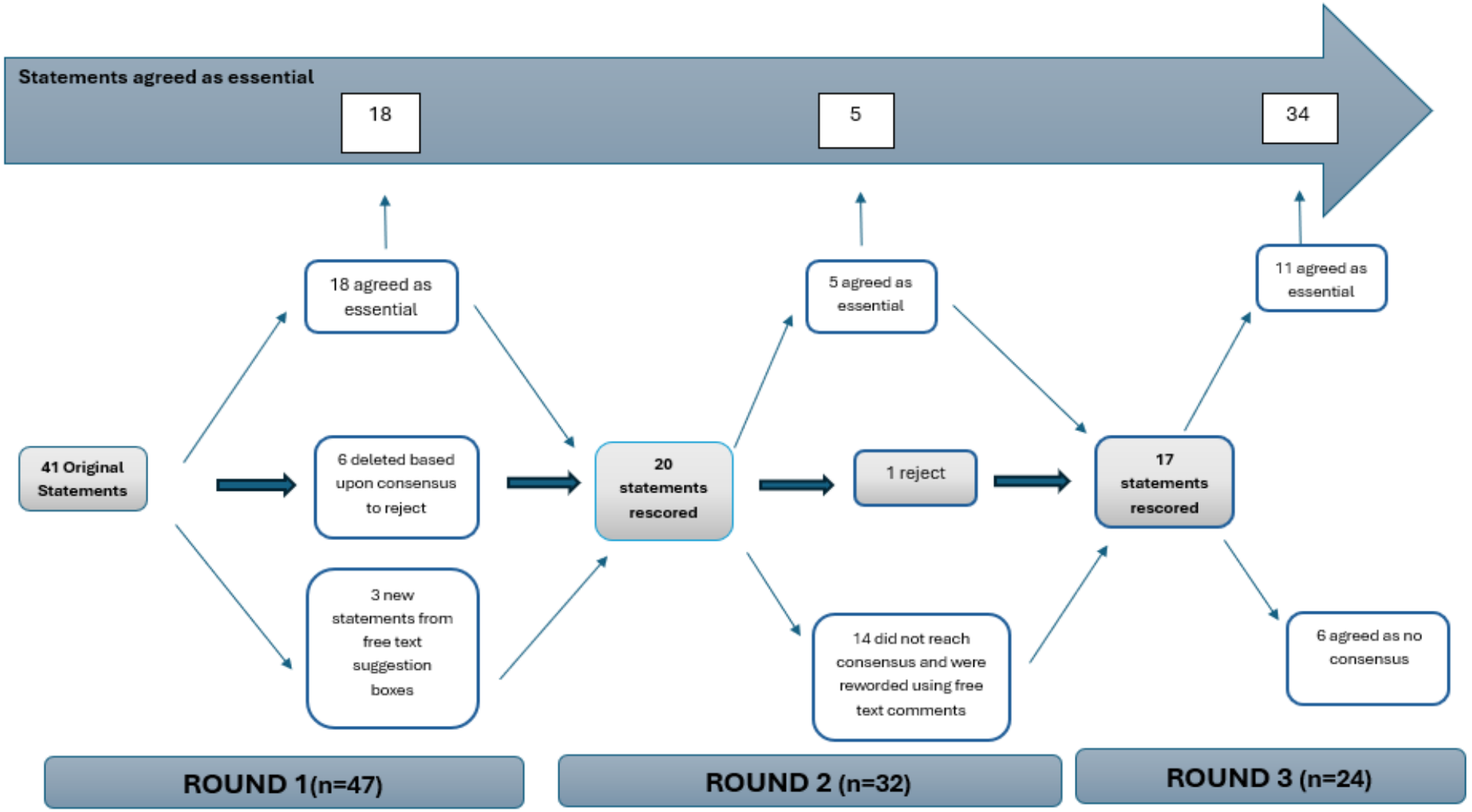


Figure 6.1: *Flowchart of Delphi statements through rounds 1–3.*

In the first round, 18 statements were accepted, 23 of which were reviewed by the research group using qualitative free-text responses and edited for the second round. In the second round, 20 statements were submitted, 5 statements were accepted, and 1 statement was rejected. Based on the free-text responses in the second round, 14 statements were edited, and 3 new statements were added. In the third round, 11 statements were accepted out of 17, and 6 statements were recorded as no consensus.

Table 6. 1: *Summary of responses for each round.*

	Number of Statements	**Round aim**	**Statements that reached consensus (<80%)**	**Statements modified for the next round**	**Statements removed or rejected or no consensus**
Round 1	41	Exploratory	18	23	0
Round 2	20	Clarifying	5	14	1
Round 3	17	Clarifying and confirmatory	11	0	6

6.3.2 Response rate

In the first round, 47 responses were obtained, while in the second round this number dropped to 32, indicating a 32% loss. In the third round, 24 responses were obtained, showing an additional 25% loss compared to the second round. Over three rounds, the expert panel consisted of 19–23% anaesthetists (round 1, n = 11; 2nd round, n = 6; 2nd round, n = 5), 26-31% geriatricians (1st round, n = 12, 2nd round, n = 10, 3rd round, n = 7), 21-26% physiotherapists (1st round, n = 12; 2nd round, n = 7; 3rd round, n = 5), 26-29% other medical staff (1st round, n = 12; 2nd round, n = 9; 3rd round, n = 7). The participation rates for each round of participants are presented in Table 6.2.

Table 6. 2: *The rate of participants for all rounds.*

Professions	Round 1 (n=47)	Round 2 (n=32)	Round 3 (n=24)
Advance Clinical Practitioners (ACP)	13% (n=6)	16% (n=5)	17%(n=4)
Anaesthetist	23% (n=11)	19% (n=6)	21%(n=5)
Dietitian	2% (n=1)	-	-
General Practice (GP)	2% (n=1)	3% (n=1)	-
Geriatrician	26% (n=12)	31% (n=10)	29%(n=7)
Nurse	4% (n=2)	6% (n=2)	8%(n=2)
Physiotherapist	26% (n=12)	21% (n=7)	20%(n=5)
Occupational Therapist (OT)	4% (n=2)	3% (n=1)	4%(n=1)

6.3.3 Summary of results

In the first round, 18 statements were accepted by consensus, mainly addressing the definitions of POD, POCD, and the identification of certain risk factors. No statements were rejected at this stage, and those without consensus were carried forward to the second round. In the second round, responses from 32 participants resulted in the acceptance of 5 additional statements and the rejection of 1, mostly related to preoperative exercise approaches, bringing the total number of accepted statements to 23. In the third round, with 24 participants, 11 more statements were accepted by consensus, while 6 did not reach consensus and were reported as 'no consensus,' particularly concerning the cognitive or fine motor components of preoperative exercise programmes. In summary, consensus was reached on 34 statements, which are presented in Table 6.3.

These statements can be categorised into eight domains: i) Understanding POD (n = 2), ii) Understanding Post-operative Cognitive Dysfunction (POCD) (n = 3), iii) Understanding Resilience to Surgery in terms of POD and POCD (n = 9), iv) The

Impact of Pre-Operative Cognition (n = 7), v) The Impact of Surgical Prehabilitation on Physiological Function (n = 8), vi) The Composition of Surgical Prehabilitation (n=5), vii) The Impact of Surgical Prehabilitation on Cognitive Function (n = 1). A full breakdown of responses, including the percentage of agreement and when consensus was reached, is presented across Tables 6.3–6.11. These tables summarise the final Delphi outcomes for statements accepted by consensus, rejected, or retained as no consensus.

According to the results obtained after three rounds:

- 34 statements (82.9%) were accepted by consensus.
- 1 statement (2.4%) was rejected.
- 6 statements (14.6%) did not reach consensus and remained as ‘no consensus’.

In general, the findings of the study demonstrate that there is significant consensus on the definitions, risk factors, and preventative strategies for postoperative cognitive impairment (POD and POCD). A high level of consensus was reached regarding the components of preoperative exercise programmes aimed at improving physiological functions. However, it has been observed that differences of opinion persist among experts regarding exercise components targeting cognitive and fine motor skills.

Table 6. 3: *Accepted statements across the three rounds.*

Domain	Statement
Understanding Post-operative Delirium (POD)	• POD may have permanent effects • POD may occur at any time during the first few days after surgery, including both within and after the first 24 hours • Exercise prehabilitation may reduce the risk of developing POD in older surgical patients
Understanding Post-operative Cognitive Dysfunction (POCD)	• POCD is confusion and memory problems that occur after surgery • POCD may have permanent effects • Persistent (prolonged) POD may increase the risk of developing POCD.
Understanding Resilience to Surgery in terms of POD and POCD	• Previous or current mental health diagnosis may increase the risk of developing POD and POCD • Having chronic pain may increase the risk of developing POD and POCD • Lack of social networks may increase the risk of developing POD and/or POCD • Lower socioeconomic status may increase the risk of developing POD and/or POCD • Living alone may increase the risk of developing POD and/or POCD • Lower educational status may increase the risk of developing POD in older surgical patients • Lower educational status may increase the risk of developing POCD in older surgical patients • Living in a care home (residential- or nursing-home) may increase the risk of developing POD • Living in a care home (residential- or nursing-home) may increase the risk of developing POCD
The Impact of Pre-Operative Cognition	• Good cognition in the pre-operative period… - Reduces the possibility of developing postoperative delirium (POD) - Reduces the possibility of developing postoperative cognitive dysfunction (POCD) - Reduces post-operative time to mobilisation • Facilitates better tolerance of the cognitive demands of surgery • Facilitates quicker return to participation in normal daily activities after surgery

	• Facilitates better tolerance of the risk of complications after surgery
The Impact of Surgical Prehabilitation on Physiological Function	• Exercise training should be part of standard preoperative care • Preoperative exercise programs can improve muscle function • Preoperative exercise programs can improve cardiorespiratory function • Preoperative exercise programs should ideally begin at least two weeks before surgery • Starting preoperative exercise programs one month or earlier before surgery may provide most benefit • Preoperative exercise programs should aim to include at least two sessions per week • Preoperative exercise programs should include sessions that are 20 mins or more in duration • Preoperative exercise sessions should be tailored to individual requirements
The Composition of Surgical Prehabilitation	• Preoperative exercise programs should be designed to increase muscle strength • Preoperative exercise programs should be designed to improve balance and flexibility • Preoperative exercise programs should be designed to improve cardiorespiratory fitness • Preoperative exercise programs should be personalised to each patient • Preoperative exercise programs can be either group-based or individual, depending on the situation
The Impact of Surgical Prehabilitation on Cognitive Function	
Prehabilitation Programs	• Preoperative 'exercise' programs should include gross neuromuscular components (i.e., force control and balance)

The statements presented to participants and all changes made during the three rounds of this study are summarised in Table 6.4-11.

Table 6. 4: *Percentage agreement for statements that achieved consensus (>80%) following Round 1 (N=18).*

Statements	Strongly Agree+ Agree	Neither	Strongly Disagree+ Disagree	IQR	CONSENSUS
POD may have permanent effects	90%	8%	2%	1	AGREE
POCD is confusion and memory problems that occur after surgery	87%	13%	0%	0	AGREE
POCD may have permanent effects	83%	17%	0%	1	AGREE
Previous or current mental health diagnosis may increase the risk of developing POD and POCD	81%	17%	2%	1	AGREE
Having chronic pain may increase the risk of developing POD and POCD	83%	13%	4%	0	AGREE
Good cognition in the pre-operative period reduces the possibility of developing postoperative delirium (POD)	88%	6%	6%	0	AGREE
Good cognition in the pre-operative period reduces the possibility of developing postoperative cognitive dysfunction (POCD)	88%	8%	4%	0	AGREE
Good cognition in the pre-operative period reduces post-operative time to mobilisation	81%	17%	2%	0	AGREE
Good cognition in the pre-operative period facilitates better tolerance of the cognitive demands of surgery	87%	13%	0%	0	AGREE

Good cognition in the pre-operative period facilitates quicker return to participation in normal daily activities after surgery	89%	11%	0%	0	AGREE
Exercise training should be part of standard preoperative care	85%	13%	2%	1	AGREE
Preoperative exercise programs can improve muscle function	94%	6%	0%	1	AGREE
Preoperative exercise programs can improve cardiorespiratory function	94%	6%	0%	1	AGREE
Preoperative exercise programs should be designed to increase muscle strength	85%	15%	0%	1	AGREE
Preoperative exercise programs should be designed to improve balance and flexibility	87%	13%	0%	1	AGREE
Preoperative exercise programs should be designed to improve cardiorespiratory fitness	92%	8%	0%	1	AGREE
Preoperative exercise programs should be personalised to each patient	87%	11%	2%	1	AGREE
Preoperative 'exercise' programs should include gross neuromuscular components (i.e., force control and balance)	81%	19%	0%	0	AGREE

Table 6. 5: *Percentage agreement for statements that did not achieve consensus (>80%) following Round 1 (N=23).*

Statements	Agree	Neither	Disagree	Reaction	CONSENSUS
POD is a confusion that occurs immediately after surgery	40%	32%	28%	Separate 2 questions	NO CONSENSUS
POD goes away on its own after surgery	7%	53%	40%	Reword	NO CONSENSUS
Preoperative exercise training may reduce the risk of POD	49%	47%	4%	Reword	NO CONSENSUS
POCD will go away on its own after surgery	4%	58%	38%	Reword	NO CONSENSUS
Preoperative exercise training may reduce the risk of POCD	45%	53%	2%	Reword	NO CONSENSUS
If POD is persistent, it could eventually become POCD	72%	28%	0%	Reword	NO CONSENSUS
Level of education may be associated with the risk of developing POD and POCD	49%	43%	8.%	Reword	NO CONSENSUS
Social networks may be associated with the risk of developing POD and POCD	67%	22%	11%	Reword	NO CONSENSUS
Socioeconomic status may be associated with the risk of developing POD and POCD	64%	34%	2%	Reword	NO CONSENSUS

Living status (alone/with family or care home) may be associated with the risk of developing POD and POCD	79%	21%	0%	Separate 2 questions	NO CONSENSUS
Good cognition in the pre-operative period reduces postoperative length of stay in hospital	75%	23%	2%	Delete (Ask again under a general heading)	NO CONSENSUS
Good cognition in the pre-operative period facilitates better tolerance of the physiological demands of surgery	66%	28%	6%	Delete (Ask again under a general heading)	NO CONSENSUS
Good cognition in the pre-operative period facilitates better tolerance of the stress of surgery	70%	26%	4%	Delete (Ask again under a general heading)	NO CONSENSUS
Good cognition in the pre-operative period reduces the likelihood of higher-level care (i.e., high dependency/intensive care treatment) after surgery	64%	28%	8%	Delete (Ask again under a general heading)	NO CONSENSUS
Preoperative exercise programs should start at least 1 month before	77%	21%	2%	Reword	NO

surgery					CONSENSUS
Preoperative exercise programs should include a minimum of 3 sessions each week	62%	38%	0%	Reword	NO CONSENSUS
Each session of preoperative exercise programs should last at least 20 minutes	64%	32%	4%	Reword	NO CONSENSUS
Preoperative exercise programs should be group-based	36%	62%	2%	Reword	NO CONSENSUS
Preoperative exercise programs can improve cognition	51%	47%	2%	Reword	NO CONSENSUS
Preoperative exercise programs can reduce the risk of POCD	53%	45%	2%	Reword	NO CONSENSUS
Preoperative exercise programs can reduce the risk of POD	53%	45%	2%	Reword	NO CONSENSUS
Preoperative 'exercise' programs should include fine neuromuscular components (i.e., dexterity)	43%	53%	4%	Reword	NO CONSENSUS
Preoperative 'exercise' programs should include cognitive components (i.e., memory)	62%	34%	4%	Reword	NO CONSENSUS

Table 6. 6: *New statements introduced following Round1.*

Statements
Good cognition in the pre-operative period facilitates better tolerance of the risk of complications after surgery
POD is a state of confusion that occurs within the first 24 hours after surgery
POD is a state of confusion that occurs after the first 24 hours following surgery
Living alone may increase the risk of developing POD and/or POCD
Living in a residential facility (care- or nursing-home) may increase the risk of developing POD and/or POCD

Table 6. 7: *Percentage agreement for statements that achieved consensus (>80%) following Round 2 (N=5).*

Statements	Agree	Neither	Disagree	IQR	CONSENSUS
Lack of social networks may increase the risk of developing POD and/or POCD	84%	16%	0%	0	AGREE
Lower socioeconomic status may increase the risk of developing POD and/or POCD	81%	19%	0%	0	AGREE
Living alone may increase the risk of developing POD and/or POCD	81%	19%	0%	0	AGREE
Good cognition in the pre-operative period facilitates better tolerance of the risk of complications after surgery	81%	19%	0%	0	AGREE

Preoperative exercise programs can be either group-based or individual, depending on the situation	85%	12%	3%	0.75	AGREE

Table 6. 8: *Percentage agreement for statements that did not achieve consensus (>80%) following Round 2 (N=14).*

Statements	Agree	Neither	Disagree	Reaction	CONSENSUS
POD is a state of confusion that occurs within the first 24 hours after surgery	74%	13%	13%	Reword	NO CONSENSUS
POD is a state of confusion that occurs after the first 24 hours following surgery	78%	13%	9%	Reword	NO CONSENSUS
Exercise prehabilitation may reduce the risk of POD	53%	44%	3%	Reword	NO CONSENSUS
POCD always resolves without intervention	4%%	21%	75%	Reword	NO CONSENSUS
Exercise prehabilitation may reduce the risk of POCD	56%	41%	3%	Reword	NO CONSENSUS
If POD persists it may become POCD	78%	16%	6%	Reword	NO CONSENSUS
Lower educational status may increase the risk of developing POD	69%	28%	3%	Reword	NO

and POCD					CONSENSUS
Living in a residential facility (care- or nursing-home) may increase the risk of developing POD and/or POCD	75%	25%	0%	Reword	NO CONSENSUS
Preoperative exercise programs should begin at least two weeks before surgery, but ideally one month before surgery	75%	22%	3%	Reword	NO CONSENSUS
Preoperative exercise programme should include a minimum of two sessions each week	63%	34%	3%	Reword	NO CONSENSUS
Preoperative exercise sessions should be tailored to individual requirements and last at least 20 minutes	72%	25%	3%	Reword	NO CONSENSUS
Preoperative exercise programs may improve cognition	50%	43%	7%	Reword	NO CONSENSUS
Preoperative exercise components should optionally include fine neuromuscular components (i.e., dexterity)	47%	47%	6%	Reword	NO CONSENSUS
Preoperative exercise components should optionally include cognitive components (i.e., memory)	63%	31%	6%	Reword	NO CONSENSUS

Table 6. 9: *Percentage agreement for statements rejected by consensus (>80%) after Round 2 (N=1).*

Statements	Agree	Neither	Disagree	IQR	CONSENSUS
POD always resolves without intervention	6%	13%	81%	0.75	REJECT

Table 6. 10: *Percentage agreement for statements that achieved consensus (>80%) following Round 3 (N=11).*

Statements	Agree	Neither	Disagree	IQR	CONSENSUS
POD may occur at any time during the first few days after surgery, including both within and after the first 24 hours	96%	4%	0%	1	AGREE
Persistent (prolonged) POD may increase the risk of developing POCD.	92%	8%	0%	1	AGREE
Lower educational status may increase the risk of developing POD in older surgical patients	88%	12%	0%	0	AGREE
Lower educational status may increase the risk of developing POCD in older surgical patients	83%	17%	0%	0	AGREE
Living in a care home (residential- or nursing-home) may increase the risk of developing POD	96%	4%	0%	1	AGREE
Living in a care home (residential- or nursing-home) may increase the	92%	8%	0%	1	AGREE

risk of developing POCD					
Preoperative exercise programs should ideally begin at least two weeks before surgery	83%	17%	0%	1	AGREE
Starting preoperative exercise programs one month or earlier before surgery may provide most benefit	88%	12%	0%	1	AGREE
Preoperative exercise programs should aim to include at least two sessions per week	83%	17%	0%	1	AGREE
Preoperative exercise programs should include sessions that are 20 mins or more in duration	88%	12%	0%	1	AGREE
Preoperative exercise sessions should be tailored to individual requirements	88%	12%	0%	1	AGREE

Table 6. 11: *Percentage agreement for statements that did not achieve consensus (>80%) following Round 3 (N=6).*

Statements	Agree	Neither	Disagree	CONSENSUS
Exercise prehabilitation may reduce the risk of developing POD in older surgical patients	67%	33%	0%	NO CONSENSUS
POCD usually resolves without any specific intervention	13%	42%	45%	NO

				CONSENSUS
Exercise prehabilitation may reduce the risk of developing POCD in older surgical patients	67%	33%	0%	NO CONSENSUS
Preoperative exercise programs may help to improve postoperative cognitive function	75%	25%	0%	NO CONSENSUS
Pre-operative exercise training should include aspects focussed on small movement (i.e., dexterity)	54%	38%	8%	NO CONSENSUS
Pre-operative exercise training should also include aspects focussed on cognition (i.e., memory)	63%	33%	4%	NO CONSENSUS

6.4 Discussion

The present study employed a modified Delphi method to achieve consensus on preoperative exercise training in older adults with the aim of protecting or improving postoperative cognition. Forty-one statements related to preoperative exercise and postoperative cognitive problems were grouped under eight headings (Understanding POD, Understanding POCD, Understanding Resilience to Surgery in terms of POD and POCD, The Impact of Pre-operative Cognition, The Impact of Surgical Prehabilitation on Physiological Function, The Composition of Surgical Prehabilitation, The Impact of Surgical Prehabilitation on Cognitive Function, Prehabilitation Programs) and were presented to participants. After three rounds, consensus was reached on thirty-four statements, one statement was rejected, and no consensus was reached on six statements. These results appear consistent with trends in the literature regarding the reduction of conceptual uncertainties in the areas of POD and POCD, the effects of prehabilitation in clinical settings, and the importance of preoperative cognitive preparation for older adults. Although there are studies examining the effects of preoperative rehabilitation on postoperative cognitive function in adults [295- 297], no specific studies have focused on older adults.

This Delphi study has identified areas where experts from different disciplines have reached consensus on the role of preoperative exercise in preserving or improving cognitive and physical function in older adults undergoing surgery. However, empirical evidence demonstrating the effects of preoperative exercise approaches is limited, indicating the need for further research in this area.

This study concluded that the experts included had a high level of consensus, particularly regarding the definition, risk factors, causes, and process of POD and POCD. Participants emphasized that POD may be a condition that can occur not only in the first 24 hours after surgery but also after the first 24 hours post-surgery and may have permanent effects in some patients. These findings from the study are consistent with the literature, as there are studies reporting that POD is not merely a temporary cognitive impairment but can also form the basis for long-term cognitive impairments [141, 148, 275, 468]. Similarly, the experts participating in our study agreed that POCD is a condition characterized by decreased attention, memory, and executive function, which is consistent with the description of postoperative cognitive changes in the study

by Evered et al. (2018) [159]. These results suggest that experts from different fields have adopted the current terminological framework and share similar views with the theoretical approaches in the literature.

In the first round, statements regarding the potential protective effects of preoperative interventions on physical functions such as muscle strength and balance were among the accepted statements. Furthermore, participants agreed that preoperative exercise programmes should consist of training that includes gross motor activities aimed at increasing muscle strength, improving balance and flexibility, and enhancing cardiorespiratory performance. Consistent with the findings of this study, the literature provides evidence that prehabilitation can preserve and enhance physiological capacity [475, 476].

Participants reached a consensus that, in addition to individual risk factors such as preoperative mental health and chronic pain, the presence of environmental risk factors such as educational level, socioeconomic status, living alone or in a care home could be significant in causing POD and POCD. This is consistent with existing empirical evidence showing the association of these environmental factors with cognitive impairment [150, 168]. These factors are thought to be related to 'cognitive reserve'. Cognitive reserve is a neuropsychological protective mechanism whereby an individual increases their brain's resilience through lifelong education, social interaction, and all forms of mental stimulation [34, 416, 492, 493]. Low levels of education and limited mental stimulation can lead to a decrease in cognitive reserve capacity and predispose individuals to postoperative cognitive impairments [140, 494]. Furthermore, older adults with low education level or low socioeconomic level show social vulnerability, and this vulnerability has been found to be related to cognition, which is parallel to our study result [495].

Social isolation and loneliness have been shown to be a risk factor for cognitive decline and dementia [496]. Price et al. (2008) [494] and Evered et al. (2018) [189] stated that low cognitive reserve may be a factor that increases the risk of developing POCD after surgery in older adults, and that education level and mental activity history may also be protective factors. Therefore, the consensus among experts in this study regarding social environment, education, and living conditions as risk factors for cognitive decline directly aligns with existing literature. Based on these results, it can be said that

there is consensus that cognitive reserve is not only a neurobiological condition but can also be influenced by social and environmental factors, and that these factors may also be triggers for postoperative cognitive impairment. Based on this consensus, clinical practice should be guided by the effect of preoperative cognitive preparation and social support on postoperative cognition.

Furthermore, in the second round, evidence regarding the cognitive benefits of prehabilitation is more limited. In our study, the statement *"POD always resolves without intervention"* was rejected, indicating the necessity of developing interventions for the prevention and/or management of POD. The presence of this rejected statement is methodologically significant, as it not only represents a contrary opinion but also provides valuable insights into the need for targeted clinical interventions in this field.

There is consensus among participating experts that exercise interventions performed in the preoperative period may have positive effects on postoperative complications. The results of this study are consistent with the literature suggesting that prehabilitation can increase muscle strength, cardiovascular capacity, and overall functional endurance [473, 474, 475]. Experts also agreed on prehabilitation parameters such as exercise programs starting at least 2 weeks before surgery and consisting of at least two sessions per week. In this case, prehabilitation can be seen as a structured clinical practice model. However, there is no consensus on whether preoperative exercise training may have a protective effect on cognitive functions. Indeed, the literature presents limited and heterogeneous results regarding the effect of preoperative exercise training on postoperative cognitive function. Our systematic review [139] conducted within the scope of this thesis revealed a limited number of studies and heterogeneity. In this context, there is a need for robust randomized controlled trials on the effect of preoperative physical exercise on postoperative cognition.

Most of the six statements on which consensus could not be reached concerned the effect of prehabilitation on postoperative cognition and the modality of prehabilitation. Although they agreed on the effect of preoperative exercise on postoperative physical function and on the need to focus on gross motor activities, they could not reach a consensus on the effect of including cognitive exercises and fine motor activities in preoperative rehabilitation on the postoperative period. The literature contains studies suggesting that preoperative cognitive training may be beneficial for cognitive

parameters such as cognition, memory, and executive functions in the postoperative period [138, 497, 498]. Humeidan et al. (2021) [138] showed in their study that 10 days of cognitive training before surgery may reduce the risk of POD. Similarly, there is a study demonstrating that preoperative cognitive exercise in adults may have an improving effect on executive function and processing speed [499, 500].

However, systematic reviews and narrative synthesis in the literature has pointed out that there are limitations in generalizing the results due to the variability in sample characteristics, duration of application, and cognitive parameters tested [202]. Similarly, Ishizawa et al. (2025) [501] in their narrative review highlighted that evidence regarding the effect of preoperative cognitive optimisation on postoperative cognitive functions in older surgical patients is still limited. This review also suggested that preoperative cognitive training may reduce postoperative delirium, while highlighting that there are only a limited number of clinical studies suggesting a positive effect of preoperative cognitive training on postoperative cognitive function. Furthermore, it has demonstrated that there is heterogeneity in terms of the dose, duration, and type of platform of cognitive training and that more studies are needed [501]. In addition, it has drawn attention to the need for studies in preoperative patients with pre-existing cognitive impairment or dementia, in addition to studies conducted in cognitively healthy adults in the preoperative period.

In fact, these controversial results reflect the current uncertainty in the literature, as the experts participating in the Delphi study did not reach a consensus on cognitive prehabilitation. Looking at current empirical studies, while there is strong support for the positive effects of physical exercise on postoperative physical functions, the evidence suggests that level the effects of cognitive exercise on postoperative cognitive parameters is still unclear. This result clearly demonstrates the need for well-designed randomized controlled trials to investigate the effect of prehabilitation training, which includes different parameters such as cognitive and fine motor skills, on postoperative cognition.

6.4.1 Strengths and Limitations

This study has some limitations. no formal sample size calculation was conducted for the Delphi process, which may limit the robustness and representativeness of the

consensus achieved. Additionally, due to the nature of the Delphi method, the results are based solely on the opinions of experts working in the UK; therefore, the generalisability of the findings may be limited. Furthermore, there were participant losses between rounds, which may have affected the representativeness of the responses. Another limitation regarding the panel composition is the absence of geriatric surgeons in the study. As surgeons are among the key decision-makers in perioperative processes, the non-participation of this group in the study is a limitation that may restrict the clinical acceptance of the consensus reached. Despite these limitations, the strengths of the study are noteworthy. The inclusion of experts from different clinical fields in the participant panel ensured that the consensus reached reflected a broader perspective. Moreover, the systematic and structured three-round process enabled experts to re-evaluate their opinions, thereby enhancing the reliability of the results. In all these respects, the study makes an original contribution by presenting expert opinions on the potential effects of preoperative exercise programmes on the cognitive functions of older adults.

6.4.2 Conclusion

In conclusion, this study highlights a gap in the literature regarding the role of preoperative exercise training in postoperative cognitive function in older adults and systematically presents the views of experts working in this field and from different clinical disciplines. The 34 statements accepted in three categories provide researchers and clinicians with a framework that can guide the prevention of complications in older surgical patients. Statements on which consensus could not be reached highlight areas requiring further research. These statements form a roadmap for future studies and ensure that the findings of this study serve as an expert-based guide that can inform clinical practice.

Chapter 7 General Discussion

7.1 Summary

The work presented in this doctoral thesis aimed to investigate the effects of preoperative physical exercise on postoperative cognitive and physical outcomes in older adults, and to evaluate its potential as a preoperative intervention. This thesis investigates the effect of uMCT on postoperative cognition and physical function in healthy older adults, to investigate its potential as a preoperative intervention. Further, this thesis also presents work aiming to achieve consensus among medical staff from different disciplines regarding the effects of preoperative physical exercise on postoperative cognitive function. This work was divided into three discrete but interconnecting chapters, which were a literature review (Chapter 2), a healthy volunteer study (Chapter 3, 4 and 5) and a Delphi study (Chapter 6). This chapter will summarize how the findings of each chapter integrate to answer the original broad research question which was the basis of this thesis.

An extensive review of the literature was made and detailed in Chapter 1 in order to understand what was already known on the subject area. Although many studies have examined the effects of preoperative exercise training on postoperative physical function in older adults, there is vast heterogeneity across these studies with regards to participant characteristics, the exercise modalities applied, and the measures of physical function each of which make it difficult to draw conclusions based on the results of these studies. Further, there are far less studies looking at cognitive outcomes. Therefore, a systematic review in Chapter 2 that examined the effect of preoperative exercise training on postoperative cognitive function in older adults. This exercise was valuable in highlighting only in the literature in this area, with only 3 studies eligible for inclusion. Based on the findings of this review, it is suggested that preoperative physical activity may contribute to reducing the risk of postoperative cognitive decline. However, the strength of this evidence is limited due to methodological heterogeneity, insufficient representation of older adults, and small sample sizes.

The three studies included in the systematic review demonstrate that preoperative exercise interventions may potentially benefit cognitive and/or physical outcomes; however, methodological limitations significantly undermine the strength of these findings. For example, in the study by Kim et al. (2021) [295], the sample size is small,

the intervention period is short, and generalisability is limited as it focuses solely on a population that has undergone knee arthroplasty. The second study, a randomised pilot study conducted by Rengel et al. (2020) [296], examined the effect of combined cognitive and physical prehabilitation on surgical outcomes. The pilot study design, small sample size, and short-term follow-up findings reduced the reliability of this study. Similarly, the final study by Trubnikova et al. (2021) [297] examined the effect of short-term physical prehabilitation on neurophysiological indicators. This study was conducted at a single centre with a limited number of participants. Although the age criterion in this study was 40-70, the number of older adults was limited, and the representation of older adults was insufficient. For all these reasons, although the existing literature points to potential benefits of preoperative exercise in the postoperative period, methodological heterogeneity, limited sample size, and inadequate representation of older adults in the studies limit the strength of the evidence and highlight the need for better-designed research in this area.

Considering the shortcomings of the studies included in the systematic review, it was concluded that more rigorously designed experimental studies targeting cognitive function are necessary, and as such a pilot study, detailed in Chapters 3, 4, and 5, was planned and conducted. This pilot study, which examines the effects of 4 weeks low-intensity unilateral uMCT on both cognitive and physical function on community-dwelling older adults, was planned to address methodological diversity and sample limitations in the research literature and also to pave the way for larger suitably powered studies exploring this intervention in the pre-operative space. Furthermore, this pilot study also includes assessments during a detraining period, providing important additional information regarding the maintenance of cognitive and physical gains. Overall, a suite of cognitive tests concluded that short-term uMCT could be effective on cognitive function and that these gains are able to be maintained during an equally short period of detraining. The application of our uMCT protocol in healthy older adults, independent of the preoperative period, is a critical step in demonstrating the physiological applicability, potential scientific effects, and sustainability of the protocol. Furthermore, this work suggests that it is feasible to conduct such an intervention on community-dwelling older adults over a period of 4-weeks. This intervention could conceivably be tested in older adults awaiting surgery and/or in older adults living with frailty or cognitive impairment where improvements in the assessed

outcomes may be even more meaningful.

Chapter 5 examined the physical function outcomes of the study outlined above. It was demonstrated that 4-weeks uMCT could improve the upper-body strength of older adults. Further, aspects of balance, motor control and whole-body physical function were also improved by this intervention, leading to the suggestion that uMCT may be a safe, feasible and effective method for improving the functional capacity of older adults, and supporting the notion that it warrants exploration as surgical prehabilitation and/or in those with functional compromise.

The findings of this study are consistent with studies in the literature reporting that low-intensity exercise programmes can have positive effects on muscle mass (502,503). While strength increases were observed on the exercised side, an increase in MVC was observed on the contralateral side for BIC and TRI due to a cross-training effect. The expected strength increase was limited due to the cross-training effect attributed to age-related decrease in neuroplasticity. The positive effect of uMCT on the SPPB score suggests that it may increase functional independence in older adults, while no effects on the TUG test are attributed to limitations of low metabolic load and short exercise duration. The statistically significant effect on manual dexterity only on the exercised side, and the absence of the expected cross-training effect, may be explained by age-related decrease in neuroplasticity. However, explaining this situation solely with age-related neuroplasticity is insufficient, and factors such as training duration and intensity, biological and functional differences among participants, and the sensitivity of the assessment measurement methods may also play a role in the effect of cross-training. This suggests that neurological transfer may be limited to fine motor skills. In conclusion, it was concluded that 4 weeks of uMCT may be effective on muscle strength and plasticity in the neuromuscular system, but longer duration or different intensity protocols may be necessary for the cross-training effect to occur.

Chapter 6 presented results of a Delphi study, which was conducted to systematically collect the views of medical staff on whether preoperative exercise programmes in older adults have a protective effect on postoperative cognition and to reach consensus on this issue. This was done by applying a modified Delphi method. As a result of this study, consensus was reached on 34 of the 41 statements grouped under eight headings, one was rejected, and no consensus was reached on six. In this study, which included

healthcare staff involved in the surgical pathway for older adults, a high degree of consensus was achieved on the definition, causes, and risk factors of POD and POCD; consensus was reached on the statements that low educational level, social isolation, and low cognitive reserve may be factors that could increase the risk of cognitive impairment. Furthermore, statements regarding the potential of preoperative exercises to increase muscle strength, cardiovascular capacity, and functional endurance were accepted; however, no consensus was reached regarding the protective effect of these exercises on cognitive functions.

The lack of consensus on this issue highlights the inadequacy of the existing evidence, and that more comprehensive, appropriately powered randomised controlled trials are needed. However, it is not correct to attribute the differences of opinion on this subject solely to the inadequacy of the existing evidence. Many factors, such as the educational background of the experts involved in the study, their clinical priorities, and their awareness of postoperative cognitive health, may contribute to this situation. Based on these study results, the next question to be asked is how we can increase healthcare professionals' awareness of and interest in postoperative cognitive function. While this Delphi study is robust in providing a multidimensional perspective through the participation of specialists from different clinical disciplines involved in the surgical processes of older adults, its generalisability is limited due to its reliance solely on UK-based experts and participant attrition. In conclusion, this study highlights the knowledge gap regarding the effect of preoperative exercise on postoperative cognitive function in older adults and provides an important roadmap for future studies.

Overall, this research demonstrates that uMCT may be effective on both cognition and physical function in healthy older adults. Low intensity uMCT is a simple, feasible, and safe training method for older adults and may be an alternative option to classic exercise programmes, particularly in periods when older adults may be more vulnerable, such as the preoperative period.

7.2 Clinical Applications

Cognitive and physical function declines can be observed in the natural physiology of ageing [7, 234]. In addition, the increase in the older population has led to an increase in the need for surgical interventions, which has resulted in developments in surgical

techniques and anaesthesia practices [111, 112, 117]. Approximately half of adults over the age of 65 undergo at least one surgical procedure in their lifetime [113], and in addition to ageing, postoperative cognitive and physical complications may occur. An important and common postoperative cognitive complication is POCD, which may be under-recognised. POCD may affect the recovery, hospital stay, independence, and quality of life of older adults in the postoperative period [141, 143, 144]. Postoperative complications can lead to prolonged recovery times, loss of independence, and reduced quality of life in older adults. For this reason, preoperative exercise programmes aiming to enhance cognitive reserves and improve cognitive function may be clinically significant in terms of postoperative recovery.

Chapters 3, 4, and 5 detail how uMCT may have positive effects on both cognitive and physical function in healthy older adults. Improvements in MVC, handgrip strength, and motor control may be associated with a reduction in falls, increased independence in daily living activities due to increased muscle strength, and an improvement in quality of life in older adults [54, 73, 77]. Turning to cognitive improvement, postoperative cognitive impairment can persist in the long term, especially in older adults, and this prolonged condition may even be associated with serious cognitive impairments such as dementia [144]. With uMCT, both cognitive and physical gains can be achieved through neuroplasticity, thereby supporting postoperative recovery.

It should be noted that this study was designed as a pilot investigation with embedded feasibility components and was not intended to provide definitive evidence of effectiveness. Instead, the primary aim was to assess feasibility, including intervention delivery, participant adherence, and the appropriateness of the selected outcome measures.

On the other hand, uMCT is a training programme that can be easily integrated into prehabilitation programmes. The maintenance or improvement of cognitive function with a simple intervention could have wide- and far-reaching impact, especially if incorporated into pre-existing prehabilitation services [201, 476], where currently nutritional state and physical function are optimised, and cognitive health is less well catered for. A specially prepared rig and a screen are sufficient for the implementation of this exercise training. Furthermore, unilateral uMCT as a candidate intervention is a low-intensity exercise modality that can even be used for older adults who cannot use

one upper limb due to stroke or any other reason, and vulnerable older adults who are at high risk of exercising before surgery.

Based on the findings of the Delphi study detailed in Chapter 6, the awareness of the multidisciplinary surgical team (MDT) regarding the scope and potential effects of preoperative training and, in particular, motor control-based interventions should be developed for the clinical application of uMCT. The medical staff participating in the Delphi study agreed on the definition, effects, and ways in which POD and POCD affect patients, but they did not agree on the effects of exercise-based prehabilitation on these clinical problems. Therefore, before moving to clinical practice, an understanding based on the feasibility, mechanism of action, and possible positive outcomes of this intervention should be developed. Subsequently, the responsibilities of the MDT in transferring the intervention to the clinic, patient education, identification of suitable candidates, referral processes, or follow-up stages should be clearly defined, the division of tasks clarified, and the implementation processes planned accordingly.

Although statistically significant changes were observed in several outcomes, it remains unclear whether these changes exceed minimum clinically important difference (MCID) threshold, which represent the smallest change considered meaningful in a clinical context. Therefore, the clinical relevance of these findings should be interpreted with caution, particularly given the relatively high-functioning nature of the sample.

In addition, potential floor and ceiling effects of the outcome measures should be considered. In the present study, participants were relatively high-functioning older adults, and baseline scores for measures such as SPPB and TUG were already close to near-optimal levels. As a result, the sensitivity of these measures to detect further improvements may have been limited, potentially leading to an underestimation of the true intervention effects.

However, several methodological considerations should be taken into account when interpreting these findings. The use of multiple outcome measures increases the risk of Type I error due to multiple statistical comparisons. Furthermore, variability in the sensitivity and clinical relevance of the selected outcome measures may influence the detection of meaningful changes. Differences in outcome selection across studies may also limit direct comparability with the existing literature.

7.3 Limitations and Future Considerations

One of the main limitations of this work is that the sample sizes are relatively small. Although this limits the validity of any conclusions, it provides a solid foundation for future research. Conducting this study with an adequately powered sample size in the future could increase the validity of the results obtained. Furthermore, as this study was a pilot and exploratory study, a 4-week exercise programme was implemented; the relatively short duration of this exercise programme is another limitation of the study. If a study involving a longer exercise training is planned in the future, it is hoped that cognitive biomarkers [504, 505] and physical function tests.

Chapter 4 describes the cognitive assessment, the primary outcome of the study, using three separate cognitive tests (TMT, MoCA, and SCWT) and examining cognition-related biomarkers in blood samples; however, imaging methods yielding more objective results were not employed. There is a study showing changes at the cortical level in older adults with short-term exercise applications using the fMRI method [506], and therefore it can be said that another limitation of the study is the non-use of imaging methods. Although no statistical significance was achieved in cognitive biomarkers in the results of this study, statistical significance alone does not make a research result valuable; what is important is that the findings obtained are related to their actual clinical effect. Therefore, statistically non-significant results should not be considered entirely irrelevant; sample size, duration and intensity of the intervention, or the measurement tools used are important factors in evaluating the results. In this context, future studies that evaluate cognitive performance measures and biomarkers together, with larger sample sizes and longer intervention periods, will contribute to the literature by providing a more comprehensive assessment of real clinical value.

Again, although there was an improvement in balance parameters in Chapter 5, this was not statistically significant. This was in part due to due to the short duration of the study and the low sample size. Statistical significance in a single balance parameter alone does not lead to the conclusion that longer-term or larger-sample studies will reveal improvements in balance. However, future studies with longer intervention periods and larger sample sizes will be valuable in assessing whether stronger and more reliable effects exist in areas such as balance, mobility, and related quality of life, which are clinically important outcome measures in older adults.

Furthermore, while a cross-education effect was achieved in motor control and MVC, the cross-education effect could not be achieved in fine motor dexterity due to the short duration of the exercise. This situation is consistent with the findings in the literature that the cross-education effect may be delayed in fine motor activities [260, 462], and positive results may be achieved on dexterity in the future by planning a longer-term study. Fine motor skills are a critical parameter for the independence of older adults in their daily living activities, as basic activities such as eating, dressing, and personal care require fine motor control. In addition, poor fine motor skills are related not only to hand function but also to functional independence and self-care capacity [433]. Therefore, there is a need for studies that will examine in a more comprehensive manner the effect of improvements in fine motor skills in older adults on functional independence and quality of life for these individuals.

Another limitation of this study is the absence of a control group, which is due to the fact that this study was planned as a pilot study. However, the study results form the basis for future studies to be planned. In the future, randomised controlled trials comparing sham exercise or different exercise modalities should be planned to demonstrate more robustly the effect of low-intensity unilateral UMC on both cognition and physical function.

Finally, the study only included follow-up assessments four weeks after training, and there are no long-term follow-up data. The 4-week exercise programme implemented only investigated short-term effects; although the follow-up time point demonstrated that cognition, MVC, motor control, dexterity, and SPPB results were maintained, but it is unknown whether the long-term effects persisted. However, this design also offers a clinically significant advantage. It is well known that there is often a mandatory waiting period between the decision and the surgery, particularly in older adults scheduled for surgery. Considering the target group for which this study is planned to be implemented in the future, it provides real-life information on the potential benefits of short-term exercise training that can be implemented in the preoperative period. Future studies examining the persistence of these effects with longer follow-ups will provide valuable contributions to the literature.

This uMCT study was conducted on healthy older adults. Future research should investigate whether this intervention may be effective for older adults with multiple

long-term conditions, frailty, and strokes which may functionally and/or cognitively impair its implementation and necessitate a modified protocol. The group most likely to benefit and are also easily identifiable are older adults undergoing optimisation for surgery. The results of the completed study suggest that unilateral uMCT is a safe, easy-to-implement and feasible exercise for older adults. It is also considered a safe and applicable training method for older adults who cannot use their lower imbs and who are more vulnerable due to low intensity.

7.4 Conclusions

In conclusion, the objectives of this thesis were: i) to conduct a pilot study to investigate the effects of preoperative uMCT exercise training on postoperative cognition and physical function in older adults undergoing surgery; ii) to investigate the effects of uMCT on cognitive and physical function in healthy older adults independent of a surgical context, and iii) to establish a consensus among multidisciplinary medical staff regarding the effects of preoperative exercise training on postoperative cognitive and physical outcomes. This thesis study provides valuable preliminary findings on the feasibility of low-intensity motor control exercises in older individuals prior to surgery. It has been demonstrated that 4 weeks of uMCT may have positive effects on both cognition and physical function in healthy older adults. However, as the results obtained are pilot study data, more comprehensive, long-term, and biologically based research is needed to generalise these findings. Future studies in this direction will contribute to the development of safer and more effective strategies for older individuals preparing for surgery.

Due to the increasing older population and the rate of surgery among older adults, this study has the potential to make a valuable contribution to future interventions aimed at protecting against both age-related declines in muscle strength and cognition, as well as postoperative cognitive and physical function impairments. It therefore contributes to increasing healthy life expectancy, improving quality of life, and advancing future healthcare services.

Chapter 8 References

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Chapter 9 Appendices

9.1 Publications

Ekici HS, Collins J, Kafadar AH, Yildirim MC, Phillips BE, Gordon AL. The effect of pre-operative exercise training on post-operative cognitive function: a systematic review. Eur Geriatr Med. 2024 Oct;15(5):1259-1266.

Yildirim, Mehmet C., Ekici, Hatice S., Collins, Jemima, Piasecki, Jessica, Skelly, Rob, Gordon, Adam L. and Phillips, Bethan E. "Effectiveness of aerobic exercise interventions on balance, gait, functional mobility and quality of life in Parkinson's disease: an umbrella review" *Translational Exercise Biomedicine*, vol. 1, no. 3-4, 2024, pp. 195-211.

9.2 Conference presentations

- CRN East Midlands Regional Dementia Workshop (5th May 2023): *Systematic Review "The effect of preoperative exercise training on postoperative cognitive function"* (abstract submission and poster presentation).
- EuGMS Congress (20-22 September 2023): *Systematic Review "The effect of preoperative exercise training on postoperative cognitive function"* (abstract submission and poster presentation).
- Biomedical Basis of Elite Performance (BBEP) Meeting (19-20 December 2024): "*The effect of upper limb motor control training (uMCT) program on neuromuscular function in healthy older adults: A pilot study"* (abstract submission and poster presentation).
- British Geriatric Society (BGS) 2025 Autumn Meeting (12-14 November 2025): "*The Effects of Unilateral Upper Limb Motor Control Training on Cognitive Function in Older Adults"* (abstract submission and oral presentation).

9.3 Systematic Review Search Method (Chapter 2)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.33
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p.33
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.33-34
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p.33-34
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p.35
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p.35
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p.35-36
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p.36-39
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.36-39
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p.36-37
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p.36-37
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p.36
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p.40-41
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	p.40-41
Study characteristics	17	Cite each included study and present its characteristics.	p.37–39, 42
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p.42-43
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	p.43–44
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p.45–47
	23b	Discuss any limitations of the evidence included in the review.	p.48
	23c	Discuss any limitations of the review processes used.	p.48
	23d	Discuss implications of the results for practice, policy, and future research.	p.49–50
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p.35
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Figure 9.1 *PRISMA 2020 checklist.*

From: Page MJ, McKenzie JE, Bossuyt PM, et al. [2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. DOI: 10.1136/BMJ.n7.

Table 9. 3: *Ovid MEDLINE search (1946 to 2024)*

1	cognitive* impair*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	86136
2	cognitive dysfunction/	31842
3	cognitive dysfunction.mp.	46594
4	cognitive function.mp.	46145
5	1 or 2 or 3 or 4	137917
6	(surgery or surgical or operative).mp.	3469012
7	exp Surgical Procedures, Operative/	3461499
8	6 or 7	4938395
9	5 and 8	9038
10	pocd.mp.	1109
11	Postoperative Cognitive Complications/	390
12	10 or 11	1321
13	9 or 12	9370
14	exercise.mp.	408550
15	exp exercise/	236284
16	exp exercise therapy/	60810
17	14 or 15 or 16	473203
18	13 and 17	282

Table 9. 4: *Embase (1974 to 2024)*

1	cognitive* impair*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	137377
2	cognitive defect/	197166

3	cognitive dysfunction.mp.	27522
4	cognitive function.mp.	69969
5	1 or 2 or 3 or 4	300565
6	(surgery or surgical or operative).mp.	4608952
7	exp surgery/	5475603
8	6 or 7	6514210
9	5 and 8	31139
10	pocd.mp.	1492
11	postoperative cognitive dysfunction/	1706
12	10 or 11	2346
13	9 or 12	31509
14	exercise.mp.	573256
15	exp exercise/	401247
16	exp kinesiotherapy/	92926
17	14 or 15 or 16	622875
18	13 and 17	1359

Table 9. 5: *Ovid Emcare (1995 to 2024)*

1	cognitive* impair*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word]	46895
2	cognitive defect/	57698
3	cognitive dysfunction.mp.	6955
4	cognitive function.mp.	23737
5	1 or 2 or 3 or 4	96985
6	(surgery or surgical or operative).mp.	899063
7	exp surgery/	1164372
8	6 or 7	1387194
9	5 and 8	8648
10	pocd.mp.	495

11	postoperative cognitive dysfunction/	603
12	10 or 11	857
13	9 or 12	8771
14	exercise.mp.	217393
15	exp exercise/	171359
16	exp kinesiotherapy/	39618
17	14 or 15 or 16	238795
18	13 and 17	358

Table 9. 6: *EBSCOHost CINAHL (1981 to 2024)*

S1	TI (cognitive* n1 impair*) OR AB (cognitive* n1 impair*)	33039
S2	TI ((cognitive n1 dysfunction) OR (cognitive n1 function)) OR AB ((cognitive n1 dysfunction) OR (cognitive n1 function))	22966
S3	(MH "Cognition Disorders")	33426
S4	S1 OR S2 OR S3	67316
S5	TI (surgery or surgical or operative) OR AB [surgery or surgical or operative)	459454
S6	(MH "Surgery, Operative+")	749939
S7	S5 OR S6	961870
S8	S4 AND S7	3653
S9	TI (pocd) OR AB (pocd)	264
S10	S8 OR S9	3692
S11	TI (exercise) OR AB (exercise)	134092
S12	(MH "Exercise+")	128584
S13	(MH "Therapeutic Exercise+")	61851
S14	S11 OR S12 OR S13	223271
S15	S10 AND S14	136

Table 9. 7: *Cochrane Library (1996 to 2024)*

ID	Search Hits	
#1	(cognitive* near impair*):ti,ab,kw	13338
#2	(cognitive near dysfunction):ti,ab,kw	4724
#3	(cognitive near function):ti,ab,kw	13652
#4	MeSH descriptor: [Cognitive Dysfunction] this term only	2274
#5	#1 or #2 or #3 or #4	25390
#6	(surgery or surgical or operative): ti,ab,kw	286389
#7	MeSH descriptor: [Surgical Procedures, Operative] explode all trees	129624
#8	#6 or #7	332440
#9	#5 and #8	2403
#10	pocd:ti,ab,kw	415
#11	MeSH descriptor: [Postoperative Cognitive Complications] explode all trees	47
#12	#9 or #10 or #11	2489
#13	exercise:ti,ab,kw	113499
#14	MeSH descriptor: [Exercise] explode all trees	28693
#15	MeSH descriptor: [Exercise Therapy] explode all trees	16366
#16	#13 OR #14 OR #15	117521
#17	#12 AND #16	169

Table 9. 8: *PubMed (1955 to 2024)*

ID	Search Hits	
#1	(cognitive impairment) OR (cognitive function) OR (cognitive dysfunction)	152879
#2	("cognitive dysfunction"[MeSH Terms])	45717
#3	#1 or #2	163655
#4	(surgical OR surgery OR operative OR [surgical	4956897

	procedures, operative [MeSH Terms])	
#5	#3 or #4	10570
#6	POCD OR ("postoperative cognitive complications"[MeSH Terms])	1825
#7	#5 or #6	10570
#8	(exercise OR ["exercise"[MeSH Terms]) OR ["exercise therapy"[MeSH Terms]	514165
#9	#7 and #8	10904

9.4 ELISA assay (Chapter 3)

9.4.1 IL-2 ELISA Test

The Human IL-2 ELISA test was performed using the Invitrogen (ThermoFisher) brand (Human IL-2 High Sensitivity ELISA Kit- Catalog Number BMS221-2HS (96 tests), LOT:435871). The Human IL-2 High Sensitivity kit is a solid-phase sandwich Enzyme-Linked Immunosorbent Assay (ELISA) designed to detect and quantify the level of human IL-2 in cell culture supernatants, plasma, and serum.

9.4.1.1 Preparation of reagents

a) Prepare Washing Buffer (1x)

The entire volume (50 mL) of Washing Pad Concentrate (20x) was transferred to a clean 1,000 mL graduated cylinder, then brought to a final volume of 1,000 mL with distilled or deionised water. It was gently stirred to prevent foaming.

b) Prepare Assay Buffer (1x)

Assay Buffer Concentrate (20x) was transferred in its entirety (5 mL) to a clean 100 mL graduated cylinder, then brought to a final volume of 100 mL with distilled water. It was stirred slowly to prevent foaming.

c) Preparation of Biotin-Conjugate

Concentrated Biotin-Conjugate solution was diluted 1:100 with Sample Diluent, and Biotin-Conjugate was prepared 30 minutes prior to use.

d) Prepare Streptavidin-HRP

Dilute Streptavidin-HRP in a clean plastic tube with Assay Buffer (1x) at a ratio of 1:100 and prepare Streptavidin-HRP 30 minutes before use.

e) Prepare Human IL-2 Standard

Human IL-2 Standard was diluted using distilled water. 450 µL of distilled water was used to achieve a concentration of 2,400 pg/mL for the diluted standard. It was gently shaken to ensure complete and homogeneous dissolution. The standard solution was allowed to dilute for 10–30 minutes, then thoroughly mixed.

In a clean plastic test tube, immediately before use, the diluted standard was diluted with Sample Diluent at a ratio of 1:20. Mix gently by shaking (standard concentration = 120 pg/mL). To prepare Human IL-2 Standard dilutions in tubes, a serial dilution was performed. Seven tubes were labelled, one for each standard point: S1, S2, S3, S4, S5, S6, S7. A 1:2 serial dilution was prepared for the standard curve. 225 µL of Sample Diluent was added to each tube. 225 µL of diluted standard (concentration = 120 pg/mL) was added to the first tube labelled S1, then mixed (standard 1 concentration = 60 pg/mL). 225 µL of this dilution was added to the second tube labelled S2, then mixed thoroughly before the next transfer. The serial dilutions were repeated 5 more times to create the points of the standard curve, using the Sample Diluent as a blank. The entire dilution process is shown in the figure 2 below.

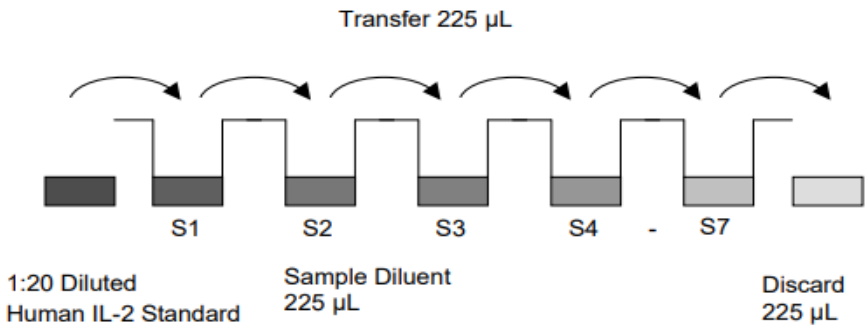


Figure 9.2 *Dilute standards – tubes*

9.4.1.2 *Preparation of controls*

High and Low controls were reconstituted by adding distilled water in the specified volumes (600 µL and 500 µL, respectively). The controls were allowed to reconstitute for 10–30 minutes. They were gently shaken to ensure complete and homogeneous

dissolution. Each reconstituted control was diluted 1:10 with Sample Diluent.

Amplification Reagent I and Amplification Reagent II were prepared immediately before use. Reagent I was diluted at a ratio of 1:100, and Reagent II was diluted at a ratio of 1:1000.

9.4.1.3 Perform the ELISA protocol

The number of microplate strips and the appropriate number of blank and standard plates were determined based on the sample size. The plate layout is shown in Figure 3. The microplate strips were washed twice with exactly 400 µL Washing Buffer (1x) for each well, and the washings were thoroughly aspirated between washes. The Washing Buffer was allowed to remain in the wells for 10–15 seconds prior to aspiration. The micro-well strips were used immediately after washing and were not allowed to dry.

	1	2	3	4	5	6	7	8	9	10	11	12
A	Blank1 Group 1	Blank1 Group 1	High Contr... Group 1 1:10	QC FOL0001 Group 1 1:2	03_PRE0001 Group 1 1:2	05_FOL0001 Group 1 1:2	08_POST000... Group 1 1:2	11_PRE0001 Group 1 1:2	13_FOL0001 Group 1 1:2	19_POST000... Group 1 1:2	23_PRE0001 Group 1 1:2	
B	Std0001 Group 1 60 pg/mL	Std0001 Group 1 60 pg/mL	Low Contro... Group 1 1:10	QC FOL0002 Group 1 1:2	03_POST000... Group 1 1:2	06_PRE0001 Group 1 1:2	08_FOL0001 Group 1 1:2	11_POST000... Group 1 1:2	14_PRE0001 Group 1 1:2	19_FOL0001 Group 1 1:2	23_POST000... Group 1 1:2	
C	Std0002 Group 1 30 pg/mL	Std0002 Group 1 30 pg/mL	High Contr... Group 1 1:10	01_PRE0001 Group 1 1:2	03_FOL0002 Group 1 1:2	06_POST000... Group 1 1:2	09_PRE0001 Group 1 1:2	11_FOL0001 Group 1 1:2	14_POST000... Group 1 1:2	20_PRE0001 Group 1 1:2	23_FOL0001 Group 1 1:2	
D	Std0003 Group 1 15 pg/mL	Std0003 Group 1 15 pg/mL	Low Contro... Group 1 1:10	01_POST000... Group 1 1:2	04_PRE0002 Group 1 1:2	06_FOL0001 Group 1 1:2	09_POST000... Group 1 1:2	12_PRE0001 Group 1 1:2	14_FOL0001 Group 1 1:2	20_POST000... Group 1 1:2	24_PRE0001 Group 1 1:2	
E	Std0004 Group 1 7.5 pg/mL	Std0004 Group 1 7.5 pg/mL	QC PRE0001 Group 1 1:2	01_FOL0001 Group 1 1:2	04_POST000... Group 1 1:2	07_PRE0001 Group 1 1:2	09_FOL0001 Group 1 1:2	12_POST000... Group 1 1:2	18_PRE0001 Group 1 1:2	20_FOL0001 Group 1 1:2	24_POST000... Group 1 1:2	
F	Std00031 Group 1 3.75 pg/mL	Std00031 Group 1 3.75 pg/mL	QC PRE0002 Group 1 1:2	02_PRE0001 Group 1 1:2	04_FOL0002 Group 1 1:2	07_POST000... Group 1 1:2	10_PRE0001 Group 1 1:2	12_FOL0001 Group 1 1:2	18_POST000... Group 1 1:2	21_PRE0001 Group 1 1:2	24_FOL0001 Group 1 1:2	
G	Std00021 Group 1 1.88 pg/mL	Std00021 Group 1 1.88 pg/mL	QC POST000... Group 1 1:2	02_POST000... Group 1 1:2	05_PRE0002 Group 1 1:2	07_FOL0001 Group 1 1:2	10_POST000... Group 1 1:2	13_PRE0001 Group 1 1:2	18_FOL0001 Group 1 1:2	21_POST000... Group 1 1:2		
H	Std00011 Group 1 0.94 pg/mL	Std00011 Group 1 0.94 pg/mL	QC POST000... Group 1 1:2	02_FOL0001 Group 1 1:2	05_POST000... Group 1 1:2	08_PRE0001 Group 1 1:2	10_FOL0001 Group 1 1:2	13_POST000... Group 1 1:2	19_PRE0001 Group 1 1:2	21_FOL0001 Group 1 1:2		

Figure 9.3 *IL-2 ELISA test plate layout.*

- Standard dilutions were transferred twice from each standard dilution (S1 – S7) 100 µL to standard wells according to Figure 9.3.

	1	2	3	4
A	Standard 1 60.00 pg/mL	Standard 1 60.00 pg/mL	Sample 1	Sample 1
B	Standard 2 30.00 pg/mL	Standard 2 30.00 pg/mL	Sample 2	Sample 2
C	Standard 3 15.00 pg/mL	Standard 3 15.00 pg/mL	Sample 3	Sample 3
D	Standard 4 7.50 pg/mL	Standard 4 7.50 pg/mL	Sample 4	Sample 4
E	Standard 5 3.75 pg/mL	Standard 5 3.75 pg/mL	Sample 5	Sample 5
F	Standard 6 1.88 pg/mL	Standard 6 1.88 pg/mL	Sample 6	Sample 6
G	Standard 7 0.94 pg/mL	Standard 7 0.94 pg/mL	Sample 7	Sample 7
H	Blank	Blank	Sample 8	Sample 8

Figure 9.4 *Arrangement of blanks, standards, and samples in the microwell strips*

- Based on the results of the pilot assay performed before the main assay, the sample was used by diluting it at a ratio of 1:2. 100 µL of Sample Diluent was added twice to the empty wells.

- 50 µL of Sample Diluent was added to the sample wells. 50 µL of each sample was added twice to the sample wells. 50 µL of Biotin Conjugate was added to all wells. A sticky film was applied, and the microplate was incubated at room temperature for 2 hours in a microplate shaker. The sticky film was removed, and the wells were emptied.

- The microplate strips were washed six times as previously described, then the next step was performed immediately. 100 µL of the prepared Streptavidin-HRP was added to all wells, including empty wells.

- It was covered with an adhesive film, then incubated in a microplate shaker at room temperature in the dark for exactly 1 hour. The adhesive film was

removed, then the wells were emptied. The microplate strips were washed six times as previously described.

- 100 µL of the prepared Amplification Reagent I was added to all wells, including the empty wells. It was covered with adhesive film, then incubated in a microplate shaker in the dark at room temperature for exactly 15 minutes. The adhesive film was removed, and the wells were emptied. The microplate strips were washed six times as previously described.

- 100 µL of the prepared Amplification Reagent II was added to all wells, including empty wells. Cover with adhesive film, then incubate in the microplate shaker at room temperature in the dark for exactly 30 minutes. Remove the adhesive film, then empty the wells. Wash the microplate strips 6 times as previously described.

- Add 100 µL of Substrate Solution to all wells. Incubate the microplate strips at room temperature in the dark for 10–20 minutes. Avoid direct exposure to intense light.
- To stop the enzyme reaction, 100 µL of Stop Solution was quickly added to each well and the results were read immediately. The absorbance of each microwell was read on a spectrophotometer using 450 nm as the primary wavelength. The absorbance of both the samples and standards was determined.

9.4.1.4 Standard Curve Generation

To quantify IL-2 concentrations in participants' plasma samples, a standard curve was created using serial dilutions of IL-2. Absorbance was measured at 450 nm with a 570 nm wavelength correction using a Varioscan LUX microplate reader. The fitted results curve, adjusted using a four-parameter logistic (4PL) model, showed excellent fit to the data with an R^2 value of 0.998, with the standard concentration range being 7.8 pg/mL to 500 pg/mL. All sample concentrations were calculated by interpolation from this curve based on optical density (OD) values. Duplicate measurements were performed for each sample. The sensitivity and reliability of the test were confirmed by obtaining

a coefficient of variation (CV%) of less than 10%, which is within the acceptable analytical range. The standard curve is below (Figure 9.4).

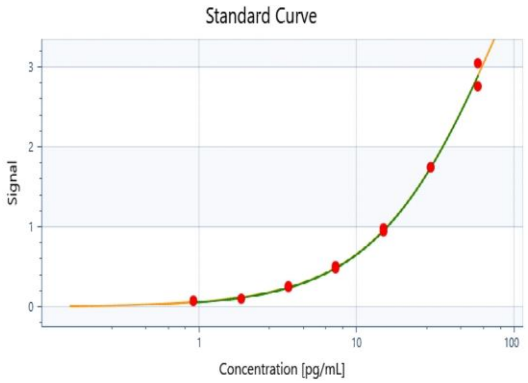


Figure 9.5 *Standard Curve for IL-2*

9.4.1.5 9.3.2 BDNF ELISA Test

The BDNF ELISA test was performed using the Invitrogen (ThermoFisher) brand (Human BDNF ELISA Kit Catalog Number EH42RB (96 tests), EH42RBX10 (10 x 96 tests)) kit. The Human BDNF ELISA Kit is a solid-phase sandwich Enzyme-Linked Immunosorbent Assay (ELISA) designed to detect and quantify the level of human BDNF in cell culture supernatants, plasma, and serum.

9.4.1.6 Preparation of reagents

a) 1X Wash Buffer Preparation

Allow the Wash Buffer Concentrate (20X) to reach room temperature and stir to redissolve any precipitated salts. Dilute 20 mL of Washing Buffer Concentrate with 380 mL of deionised or distilled water and label it as 1X Washing Buffer.

b) Preparation of diluent

Assay Diluent B was diluted 5-fold with deionised or distilled water prior to use.

c) Preparation of biotin conjugate

Centrifuge the biotin conjugate briefly before use. Add 100 µL of 1X Test Diluent B to the vial to prepare the biotin conjugate concentrate. Mix gently by pipetting up and down. The biotin conjugate concentrate was diluted 80-fold with 1X Test Diluent B and prepared for use in step 2 of the ELISA procedure.

9.4.1.7 Sample preparation

Samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes. Frozen samples were not allowed to be frozen and thawed more than once. They were completely thawed and thoroughly mixed (not vortexed) prior to analysis.

9.4.1.8 Sample dilution

Based on the pilot assay results before the main assay, the sample was used without diluting.

9.4.1.9 Dilution of standards (Figure 6)

- Plastic tubes were used to dilute the standards.
- The lyophilised standard vial was centrifuged briefly.
- 720 µL of Test Diluent A was added to the vial to prepare a 400 ng/mL standard. The powder was gently stirred until completely dissolved. Add 40 µL of BDNF standard from the vial to a tube containing 960 µL of Test Diluent A or 1X Test Diluent B to prepare a 16 ng/mL standard solution. Pipette 300 µL of Test Diluent A or 1X.
- Each tube was thoroughly mixed before the next transfer. Test Diluent A used as the zero standard (0 ng/mL).

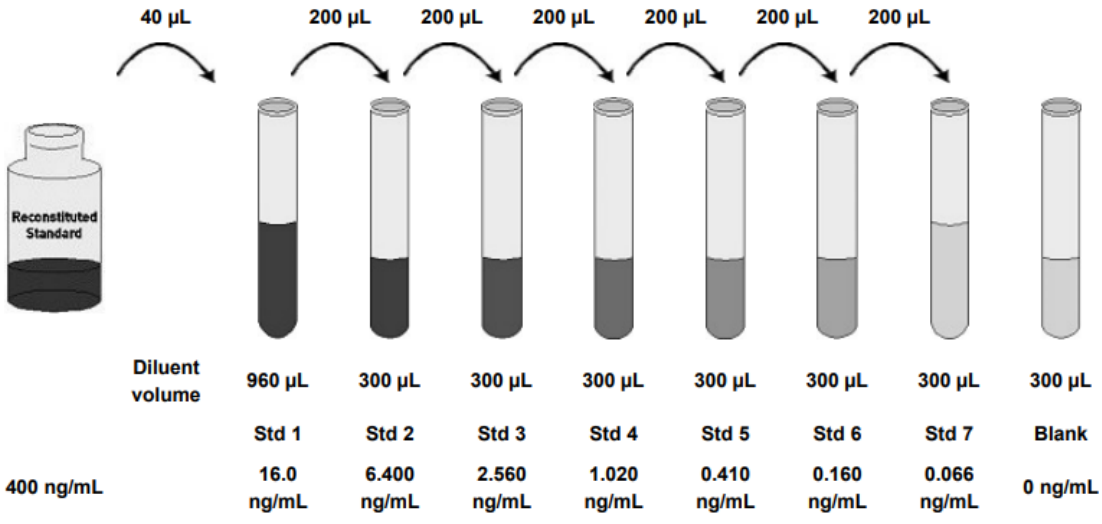


Figure 9.6 *Dilute standards*

Preparation of 1X Streptavidin-HRP solution

- Streptavidin-HRP was prepared 15 minutes prior to use.
- Since precipitation may occur during storage, the Streptavidin-HRP was briefly shaken and gently mixed by moving the pipette up and down.
- The Streptavidin-HRP was diluted 200-fold with 1X Test Diluent B.

Perform ELISA

All reagents were allowed to reach room temperature before use. All liquid reagents were mixed before use. A pilot experiment was conducted prior to the test, and a standard curve was created. The ELISA protocol was performed using the diagram below.



1- Bind antigen



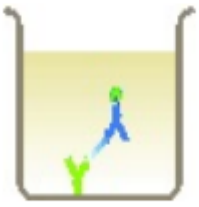
a. For the standard curve, 100 µL of standard was added to the appropriate wells.

For the samples, 100 µL of diluted sample was added to the wells.

b. The wells were closed and incubated at room temperature for 2.5 hours with gentle shaking.

c. The solution was discarded and washed four times with 1X Washing Buffer. Each well was washed by filling it with Washing Buffer (300 µL) using a multi-channel pipette. After the final wash, the plate was turned upside down and dried with a clean paper towel.

2-Add biotin conjugate

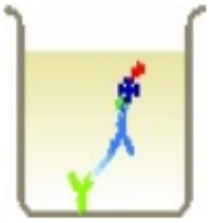


a. 100 µL of the prepared biotin conjugate was added to each well.

b. It was incubated at room temperature for 1 hour with gentle shaking.

c. The solution was discarded, and the washing procedure was repeated according to the previous protocol.

3- Add Streptavidin-HRP



a. 100 µL of prepared Streptavidin-HRP solution was added to each well.

b. Incubation was carried out at room temperature for 45 minutes with gentle shaking.

c. The solution was discarded, and the washing procedure was repeated according to the previous protocol.

4- Add TMB substrate



a. 100 µL of TMB Substrate was added to each well. The substrate began to turn blue.

b. Incubated for 30 minutes at room temperature in the dark with gentle shaking.

5- Add stop solution



50 µL of Stop Solution was added to each well. The plate was gently tapped on the side to mix. The solution in the well turned from blue to yellow.

1. *Read the plate and generate the standard curve*

The absorbance at 450 nm was read (SkanIt Software for Microplate Readers RE, ver 7.1.0.44). The plate was read within 30 minutes after the Stopping Solution was added.

For the measurement of BDNF concentrations in plasma samples, a five-parameter logistic (5PL) standard curve was used, created from serial dilutions of the BDNF standard in the Invitrogen BDNF ELISA kit. The test was read at 450 nm, and blank values were subtracted prior to analysis. A value of 0.999 R^2 was obtained for this standard curve, demonstrating excellent fit to the data. The standard concentration ranged from 0.066 ng/mL to 16 ng/mL. All sample concentrations were calculated by interpolation from this curve based on optical density (OD) values. For duplicate measurements, the coefficient of variation (CV%) was found to be <15%, which is within acceptable limits, thereby confirming the sensitivity of the test.

The standard curve formula and plate layout are shown below (Figure 7-8).

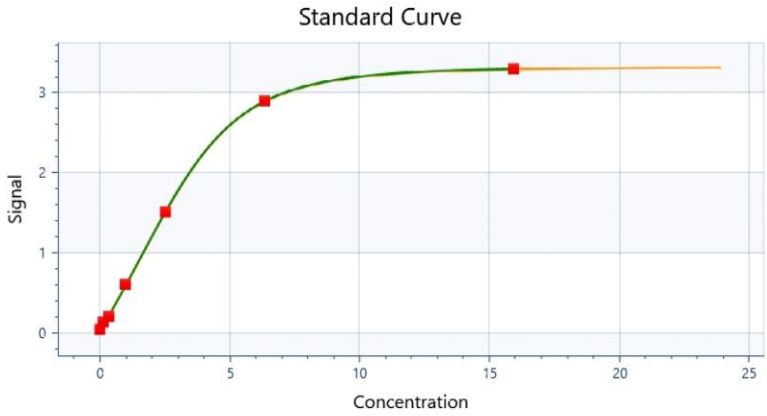


Figure 9.7 *Standard curve for BDNF*

	1	2	3	4	5	6	7	8	9	10	11	12
A	Std0001 Group 1 16 ng/mL	Std0001 Group 1 16 ng/mL	QC PRE0001 Group 1 1:1	02_FOL0001 Group 1 1:1	05_POST000... Group 1 1:1	08_PRE0001 Group 1 1:1	10_FOL0001 Group 1 1:1	13_POST000... Group 1 1:1	19_PRE0001 Group 1 1:1	21_FOL0001 Group 1 1:1		
B	Std0002 Group 1 6.4 ng/ml	Std0002 Group 1 6.4 ng/ml	QC POST000... Group 1 1:1	03_PRE0001 Group 1 1:1	05_FOL0001 Group 1 1:1	08_POST000... Group 1 1:1	11_PRE0001 Group 1 1:1	13_FOL0001 Group 1 1:1	19_POST000... Group 1 1:1	23_PRE0001 Group 1 1:1		
C	Std0003 Group 1 2.56 ng/ml	Std0003 Group 1 2.56 ng/ml	QC FOL0001 Group 1 1:1	03_POST000... Group 1 1:1	06_PRE0001 Group 1 1:1	08_FOL0001 Group 1 1:1	11_POST000... Group 1 1:1	14_PRE0001 Group 1 1:1	19_FOL0001 Group 1 1:1	23_POST000... Group 1 1:1		
D	Std0004 Group 1 1.02 ng/ml	Std0004 Group 1 1.02 ng/ml	01_PRE0001 Group 1 1:1	03_FOL0002 Group 1 1:1	06_POST000... Group 1 1:1	09_PRE0001 Group 1 1:1	11_FOL0001 Group 1 1:1	14_POST000... Group 1 1:1	20_PRE0001 Group 1 1:1	23_FOL0001 Group 1 1:1		
E	Std0005 Group 1 0.41 ng/mL	Std0005 Group 1 0.41 ng/mL	01_POST000... Group 1 1:1	04_PRE0002 Group 1 1:1	06_FOL0001 Group 1 1:1	09_POST000... Group 1 1:1	12_PRE0001 Group 1 1:1	14_FOL0001 Group 1 1:1	20_POST000... Group 1 1:1	24_PRE0001 Group 1 1:1		
F	Std0006 Group 1 0.16 ng/ml	Std0006 Group 1 0.16 ng/ml	01_FOL0001 Group 1 1:1	04_POST000... Group 1 1:1	07_PRE0001 Group 1 1:1	09_FOL0001 Group 1 1:1	12_POST000... Group 1 1:1	18_PRE0001 Group 1 1:1	20_FOL0001 Group 1 1:1	24_POST000... Group 1 1:1		
G	Std0007 Group 1 0.066 ng/m	Std0007 Group 1 0.066 ng/m	02_PRE0001 Group 1 1:1	04_FOL0002 Group 1 1:1	07_POST000... Group 1 1:1	10_PRE0001 Group 1 1:1	12_FOL0001 Group 1 1:1	18_POST000... Group 1 1:1	21_PRE0001 Group 1 1:1	24_FOL0001 Group 1 1:1		
H	Blank1 Group 1	Blank1 Group 1	02_POST000... Group 1 1:1	05_PRE0002 Group 1 1:1	07_FOL0001 Group 1 1:1	10_POST000... Group 1 1:1	13_PRE0001 Group 1 1:1	18_FOL0001 Group 1 1:1	21_POST000... Group 1 1:1			

Figure 9.8 *BDNF test plate layout*