Diagnostik och Intervention

Exercise for the Aging Brain - or are we just out biking?

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For Marilyn,
who - had she been given the opportunity to grow old -
wouldn't have bothered to age with grace;
rather with goofiness,
and busy hands
and dancing legs
and arms that never tired of carrying others.

Contents

Abstract

Background: Age-related cognitive and physiological decline can in part be mitigated by increasing older adults' physical exercise, but individuals respond differently, for example in cognitive domains such as working memory (WM). This thesis examines how high intensity exercise affects cognitive, neural, and physiological measures in older adults and explores how clinical findings can be translated into real world settings.

Methods: This thesis includes four papers, and is based on the Umeå HIT study, which compared supramaximal high intensity interval training (HIT) to moderate intensity training (MIT) for older adults. *Papers I-III* used data from the Umeå HIT randomized controlled trial (RCT), while *Paper IV* used data from the Umeå HIT Home Study. The Umeå HIT RCT assessed the effects of 12 weeks of twice-weekly supramaximal HIT (20 minutes total, including 10 x 6 second intervals) compared to MIT (40 minutes total, including 3 x 8-minute bouts) among non-exercising older adults (n = 68, 66-79 years old, 56% women). Exercise intensity was individualized and controlled. Specifically, *Paper I* assessed cognitive, physiological, well-being and adverse event outcomes, of supramaximal HIT vs MIT. *Paper II* assessed effects of supramaximal HIT vs MIT on a functional magnetic resonance imaging WM task and examined the relationship between improved leg strength and WM manipulation task-related blood oxygen level dependent (BOLD) response and performance in an MRI subsample. *Paper III* tested baseline- and change-factors related to WM improvement. *Paper IV*, based on the Umeå HIT Home study (n = 11, 69-74 years old, 55% women) explored how the original supramaximal HIT protocol could be adapted to home use through a co-creation study involving participants who had exercised in the supramaximal HIT-group of the RCT.

Results: *Paper I* found that irrespective of group, cardiorespiratory fitness and systolic and diastolic blood pressure were significantly improved, while global cognitive function was not affected. A significant group x time interaction was found in WM performance and isometric leg extensor strength in favor of supramaximal HIT. *Paper II* found that increased isometric leg extensor strength in the supramaximal HIT group was positively related to dorsolateral prefrontal cortex BOLD response, which in turn was related to increased WM performance. *Paper III* showed that the link between increased isometric leg extensor strength and improved WM also applied to a broader WM composite and the relationship was found in both exercise groups. It further showed that baseline white matter lesion load did not limit WM improvements following supramaximal HIT, unlike MIT. Upregulated brain derived neurotrophic factor was related to WM improvements, but differed by group, suggesting a stronger relationship in MIT. *Paper IV* identified alternative modalities to stationary bicycling and several adaptations to the supramaximal HIT protocol, including extending intervals to ten seconds, using an audio metronome to control intensity, and a mobile application for exercise delivery. Of the suggested modalities, chair stand intervals elicited similar acute physiological responses to supramaximal HIT on a stationary bicycle, intensity could be systematically modulated using a metronome, and the modality was considered safe.

<u>Conclusion:</u> This thesis found that supramaximal HIT elicits similar- to superior effects on physiological and cognitive outcomes compared to MIT, despite half the exercise time. Furthermore, leg strength improvements were related to increased BOLD response in a key WM area, which in turn was related to improved WM performance in supramaximal HIT. Leg strength gains were further related to broader WM improvements irrespective of exercise group, indicating that muscular adaptations may be an important target for future exercise-cognition studies. Unlike MIT, supramaximal HIT-related WM gains were not limited by baseline white matter lesion load, and future studies should test this hypothesis directly. Adapting HIT for home use, especially with chair stand intervals, appears promising for future implementation, potentially enabling both cardiorespiratory and muscular gains. Future research should test the feasibility and effects of home-based supramaximal chair stand, as a step toward future implementation to real-world settings for older adults.

Sammanfattning på Svenska

Fysisk träning har visat goda effekter på både kroppen och hjärnan hos äldre personer. Det finns samtidigt en stor variation i hur olika personer svarar på träning, speciellt när det gäller hjärnan, där vissa personer förbättrar kognitiva funktioner samt olika mått på hjärnans struktur och funktion medan andra inte gör det. För att bättre förskriva träning som kan ge goda effekter på hjärnan för äldre personer krävs en ökad förståelse för vilken slags träning som fungerar, vilka faktorer som är relaterade till ett positivt träningssvar samt möjligheten att utföra evidensbaserad träning i fler miljöer än kontrollerade träningsstudier. Denna avhandling jämför effekter av supramaximal högintensiv träning (HIT) och medelintensiv träning (MIT) för äldre personer (+ 65 år), avseende fysiologiska och neurokognitiva effekter. Avhandlingen undersöker även faktorer som kan vara relaterade till ett positivt träningssvar i den kognitiva funktionen arbetsminne. Avslutningsvis anpassas det supramaximala HIT-protokollet för att genomföras i hemmiljön.

I denna avhandling ingår fyra delarbeten. *Delarbete I-III* baseras på en randomiserad kontrollerad studie (RCT) som heter Umeå HIT RCT (68 deltagare) och *delarbete IV* baseras på en samskapande studie som heter Umeå HIT Hem (11 deltagare). Umeå HIT RCT undersökte effekter av tre månaders supramaximal HIT (10 x 6 sekunders intervaller, 20 minuter träning per pass) jämfört med MIT (3 x 8-minuters intervaller, 40 minuter träning per pass). Träningen genomfördes två gånger i veckan på stationära cyklar på ett gym, och träningsintensiteten i båda grupperna var individanpassad. *Delarbete I* undersökte träningseffekter på fysiologiska och kognitiva mått samt hälsorelaterad livskvalité. *Delarbete II* baserades på ett urval med 43 deltagarna som gjort ett arbetsminnestest vid en magnetkameraundersökning och undersökte effekter av träning på hjärnans respons vid arbetsminne. Vidare undersöktes hur träningens påverkan på syreupptagningsförmåga och benstyrka relaterade till förändring i hjärnans respons samt arbetsminnesprestation. Arbetsminnesprestation undersöktes vidare i *delarbete III*, och då i relation till vitsubstansförändringar och syreupptagningsförmåga vid baslinjen, samt hur förändringar på syreupptagningsförmåga, benstyrka och blodmarkörer relaterade till förändrad arbetsminnesprestation. I *delarbete IV* användes data från Umeå HIT Hem studien, där syftet var att anpassa det ursprungliga supramaximala HIT-protokollet till att fungera i hemmiljön hos äldre personer. Detta gjordes i en samskapande studie tillsammans med en grupp äldre personer, och skedde i två faser. Fas ett syftade till att identifiera alternativa träningssätt och anpassningar till protokollet, och fas två syftade till att jämföra akuta fysiologiska effekter mellan alternativa träningssätt och det ursprungliga protokollet på cykel.

Resultaten visade att både supramaximal HIT och MIT förbättrade syreupptagningsförmåga och blodtryck till liknande grad. Det fanns en skillnad mellan grupperna gällande benstyrka och arbetsminnes-prestation, där supramaximal HIT gav bättre resultat. Förändringar i benstyrka i supramaximala HIT-gruppen var relaterade till en ökad respons i dorsolaterala prefrontala kortex vid arbetsminnestestet, och en ökning i respons detta hjärnområde var i sin tur relaterad till förbättrad prestation på arbetsminnestestet som genomfördes vid hjärn-avbildningen. Vitsubstansförändringar vid baslinjen påverkade inte förbättringen i arbetsminnesprestation i supramaximala HIT-gruppen, utan de förbättrade sitt arbetsminne trots allvarliga lesioner vid baslinjen, medan MIT försämrades vid allvarliga lesioner. Syreupptagningsförmåga vid baslinjen var positivt relaterat till senare träningssvar i arbetsminne, där de med högre syreupptagningsförmåga vid baslinjen såg större förbättringar i arbetsminne. Förbättrad benstyrka var kopplat till förbättrat arbetsminnesprestation oavsett träningsgrupp medan förbättrad syreupptagningsförmåga inte var det. I den samskapande studien identifierades flertalet alternativa träningssätt, anpassningar till träningsprotokollet samt lösningar på hur intensitet kunde kontrolleras och individanpassas. Efter testning i träningslaboratorium framstod metronomstyrda intervaller med uppresningar från stol ge liknande akuta fysiologiska effekter som det ursprungliga supramaximala HIT-protokollet på stationär cykel, samtidigt som det bedömdes vara en säker träningsform.

Sammanfattningsvis gav supramaximal HIT liknande eller till och med bättre resultat på fysiologiska och kognitiva utfall, trots halva träningstiden jämfört med MIT. Flera faktorer identifierades som intressanta fynd relaterade till förbättrat arbetsminne, och framtida studier bör undersöka kopplingar mellan förbättrad benstyrka och kognitiva funktioner samt undersöka hur supramaximal HIT kan förbättra kognitiva funktioner trots allvarliga vitsubstansförändringar. Avslutningsvis bör det anpassade träningsprotokollet för supramaximal HIT med uppresningar från stol utvecklas till en mobil applikation och dess genomförbarhet och effekter bör testas i framtida studier. Detta för att i framtiden möjliggöra för att supramaximal HIT kan vara tillgänglig för en bredare grupp personer.

Abbreviations

Δ	Change
AOS	Automated Operation Span
BcA	Bias-Corrected and Accelerated
BDNF	Brain-Derived Neurotrophic Factor
BDS	Backward Digit Span
BOLD	Blood Oxygen Level Dependent
CI	Confidence Interval
CR10	Category Ratio 10
CRF	Cardiorespiratory Fitness
DLPFC	Dorsolateral Prefrontal Cortex
FLAIR	Fluid-Attenuated Inversion Recovery
FS	Feeling Scale
fMRI	Functional Magnetic Resonance Imaging
HIT	High Intensity interval Training
HR	Heart Rate
IGF-1	Insulin-like Growth Factor 1
LMM	Linear Mixed-effects Model
MAP	Maximum Aerobic Power
MD	Mean Difference in change
MIT	Moderate Intensity Training
MMSE-SR	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MPO^6	Mean Power Output for 6 seconds
MRI	Magnetic Resonance Imaging
PFC	Prefrontal Cortex
RPE	Ratings of Perceived Exertion
SD	Standard Deviation
SE	Standard Error
SF-36	Swedish Short Form (36) Health Survey
TPO	Target Power Output
VEGF	Vascular Endothelial Growth Factor
VO_2max	Maximal rate of Oxygen Consumption
VO_2peak	Peak rate of Oxygen Consumption
WM	Working Memory

Original papers

This thesis includes the following four papers, which will be referred to by their Roman numerals (I-IV). *Paper I* is reproduced under the CC BY-NC 4.0 License, and *Paper II* is reproduced under CC BY 4.0 license.

I. Simonsson, E., **Levik Sandström, S**., Hedlund, M., Holmberg, H., Johansson, B., Lindelöf, N., Boraxbekk, C. J., & Rosendahl, E. (2023). Effects of controlled supramaximal high-intensity interval training on cardiorespiratory fitness and global cognitive function in older adults: The Umeå HIT study – A randomized controlled trial. *The Journals of Gerontology: Series A, 78*(9), 1581–1590.

II. **Sandström, S.,** Simonsson, E., Hedlund, M., Rosendahl, E., & Boraxbekk, C. J. (2025). Working memory improvements following supramaximal HIT predicted by increased prefrontal activation and leg strength gains. *Cerebral Cortex, 35*(10).

III. **Sandström S,** Josefsson M, Hedlund M, Rosendahl R, Boraxbekk CJ. Who responds and why? Factors related to exercise-induced working memory gains. (Manuscript)

IV. **Sandström S**, Frankel J, Lindelöf N, Hedlund M, Frykholm E, Fridberg H, Rosendahl E, Boraxbekk CJ, Sandlund M. High Intensity Interval Training for Older Adults – From the Laboratory Towards a Home Setting: a Co-Creation Study. (Manuscript under review)

Additional publication not included in the thesis:

Frykholm, E., Simonsson, E**., Levik Sandström, S**., Hedlund, M., Holmberg, H., Johansson, B., Lindelöf, N., Boraxbekk, C.-J., & Rosendahl, E. (2024). Applicability of a supramaximal high-intensity interval training program for older adults previously not engaged in regular exercise: Analyses of secondary outcomes from the Umeå HIT Study. *Psychology of Sport and Exercise, 73*, 102647.

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I’ve been told this is the most important section of my thesis, and the one that most people will read. So here goes…

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Introduction

Today, more people live longer than throughout human history, and while this is a fantastic feat of modern science, challenges in increasing years of healthy living remain. As we reach the last third of our life, many processes in our bodies change, interacting with each other, and affecting us from the innermost workings of our brain to the tip of our toes. We experience different aging trajectories, as determined by a combination of genetics, environmental exposures, and lifestyle factors. We differ with regards to how well cognitive, neural, and bodily functions work when we enter older age, in this thesis defined as over 65 years old, as well as our trajectories of change, with some declining early and quickly while others maintain many functions until late in life. In turn, this decline has consequences on our level of independence, quality of life, and years of healthy living.

This thesis delves into how one type of lifestyle factor, namely physical exercise, influences cognitive functions, patterns of neural activity, and physiological adaptations among older adults. Ultimately, the goal of studying exercise-effects aims to prolong years of healthy aging. While such long-term conclusions are beyond the scope of this thesis, assessing exercise-induced cognitive and physiological effects, as well as examining factors related to individual differences in exercise response, helps us gain insight into who benefits from exercise and perhaps, why. This thesis spans the fields of cognitive neuroscience and exercise physiology. It aims to investigate where cognitive functions, their underlying neural architecture, and physiological adaptations to exercise meet. A primary focus is on the cognitive domain working memory (WM), a higher-order cognitive function that we use constantly throughout the day, and which declines as we age. This thesis tries to untangle how exercise affects the brain and cognitive functions among older adults, while also exploring strategies to increase the availability of evidence-based exercise forms.

Neurocognitive aging

As we reach the final third of our life, even brains unafflicted by neuropathology begin to undergo marked changes, the clearest everyday example of which is a decline in many higher order cognitive functions such as WM, episodic memory, executive functions, and processing speed (Nyberg et al., 2020). Within one person, these functions tend to decline together speaking to a general fluid intelligence factor, and the shared variance between cognitive domains increases with advancing age (Tucker-Drob et al., 2019). Furthermore, research has also shown relatively high within-person stability across a lifespan, with cognitive functions early in life being highly related to level of cognitive function later (Rönnlund et al., 2015).

While group-level decline and within-person stability may be one trend, another is an increase in aging-related between-person variability, or, in other words, an increase in differences between individuals in cognitive ability (Gorbach, 2017; Nyberg et al., 2020). Longitudinal evidence has identified subgroups exhibiting different patterns of decline, for example people who maintain stable cognitive functions, those who decline, and people with age-typical average change (Josefsson et al., 2012). Other identified subgroups include successful agers, who started with high levels of cognitive functions that were maintained over time, decline agers who started with high levels of cognitive functions that then declined over time, and low stable agers who had normal to poor cognitive functions that remained stable over time (Lin et al., 2017).

Changes to brain structure and function underly age-related decline in cognitive function. Gray matter tends to decrease and is associated with global cognitive decline (Smith et al., 2023), while atrophy to specific areas is related to decline in the cognitive functions dependent upon them, such as atrophy to the hippocampus being related to a decline in episodic memory (Gorbach, 2017), i.e., our ability to recall past events (Tulving, 2002). Longitudinal research shows aging-related increases in white matter lesions that accelerate after 60 years of age, and which are associated with cognitive decline (Luo et al., 2023). White matter lesions are found in up to 90% of subjects over 65 years of age, however severity levels vary (Schmidt et al., 2011), and longitudinal evidence suggests that higher baseline white matter lesions are related to subsequent faster cognitive decline (Li et al., 2023).

Meanwhile, changes to brain structure provide somewhat limited knowledge about brain-behavior relationships, and increasingly, the field of cognitive neuroscience of aging has begun to move towards functional imaging methods to capture real-time relationships between brain activity and cognitive performance (Mooraj et al., 2025). Early cross-sectional studies proposed that older adults showed increased cortical activity compared to younger adults, and compensatory mechanisms were emphasized as a prominent feature for age-related differences (Cappell et al., 2010; Reuter-Lorenz & Cappell, 2008).

Longitudinal studies have nuanced this picture, instead providing evidence that aging is related to decreased cortical activity, while maintained cortical activity over time is seen for those with maintained cognitive performance. In other words, brain maintenance better explains individual trajectories of cognitive aging (Nyberg et al., 2012; Nyberg et al., 2010). Thus, while some maintain youth-like patterns of activation and cognitive performance interpreted as a sign of brain maintenance, others show distinct changes to activation, including a failure to upregulate necessary areas (Rieckmann et al., 2017), or increased activity at low levels of cognitive demand (Nyberg et al., 2022).

The question then is what factors might affect individual differences in neurocognitive aging, including where a person starts out when decline begins, and how steep their decline is. Genetics, as always, plays a large role, and several single nucleotide polymorphisms have been implicated in individual differences in cognitive performance (Andrews et al., 2016), as well as the slope of cognitive decline (Lin et al., 2017). However, research also shows that genetics interact with lifestyle- and environmental factors across a person's lifespan to determine how neurocognitive aging may occur (Nyberg et al., 2020). For example, Josefsson et al. (2012) found that a person was more likely to be classified as a maintainer of cognitive function if they had a higher education, were more physically active, were biologically female, and living with someone else, indicating how both genetic and lifestyle factors are important to consider when trying to understand individual differences in aging.

The influence of lifestyle factors has become a promising field of study, as it provides hope that behavioral changes might contribute to mitigating the risk of disease, disability, and decreased functional independence. For example, modifiable risk factors account for approximately 45% of dementia cases (Livingston et al., 2024) and an estimated 70% of cardiovascular disease cases and deaths, of which behavioral risk factors, such as physical inactivity, contribute to approximately 26% of cardiovascular mortality cases (Yusuf et al., 2020). One lifestyle factor that has been found particularly promising for preventing disease and promoting functional independence is physical activity and physical exercise (Cunningham et al., 2020).

Exercise for healthy aging

While physical activity is a broad term involving “any bodily movement produced by skeletal muscles that results in energy expenditure”, exercise instead refers to a specific type of physical activity that is structured, repetitive, and planned with the aim of increasing or maintaining fitness (Caspersen et al., 1985). Physical activity is often studied using questionnaires or accelerometer data, for example in longitudinal studies assessing how physical activity may relate to change in other variables, such as neural and cognitive measures.

Longitudinal findings

As we age, the human body declines in bodily functions such as cardiorespiratory fitness (CRF) (AlGhatrif et al., 2024) and muscular strength (Hughes et al., 2001), however maintaining physical activity can attenuate this decline to some extent. For example, physical activity can lower the risk for cardiovascular disease mortality and incidence and type II diabetes incidence (Wahid et al., 2016), as well as help maintain muscular strength (Leslie et al., 2023), which is an important factor in mitigating fall risks among older adults (Montero-Odasso et al., 2022). One main effect of physical activity is maintained or even increased CRF (Bouaziz et al., 2018; Bouaziz et al., 2020). CRF, often expressed as a person’s maximal oxygen uptake (VO_2max) or their peak oxygen uptake (VO_2peak), declines with age, and decline is accelerated at higher ages (AlGhatrif et al., 2024; Letnes et al., 2020; Letnes et al., 2023). CRF is a function of our maximum heart rate, stroke volume, and arterial-venous oxygen difference (Bassett & Howley, 2000), and is an important indicator of both present and future health status (Holmlund, 2021; Kodama et al., 2009), such as a lower risk for hypertension (Holmlund, 2021), cardiovascular disease morbidity (Ekblom-Bak et al., 2019), and being inversely associated with all-cause mortality risk (Kokkinos et al., 2023; Laukkanen et al., 2022). Age-related decline is due to age-related decreases in cardiac output and arterial-venous oxygen difference (AlGhatrif et al., 2024), as well as changes to exercise behavior (Burtscher et al., 2022).

Longitudinal evidence also suggests that physical activity may preserve cognitive function and neural measures, which is promising, considering the marked changes that occur in the aging brain. Change to physical activity over time has been shown related to cognitive performance in adults over 50, where those with decreased physical activity over time also decreased cognitive performance to a greater extent, and more rapidly, compared to those that did not (Cheval et al., 2021). Furthermore, longitudinally maintained physical activity is related to maintained WM performance (Nyberg et al., 2022). WM, which is a large focus in this thesis, is a capacity limited system of temporarily stored, very accessible representations of information (Awh & Vogel, 2025), stored for active use, and is used constantly in everyday life. It encompasses the maintenance of temporarily stored information, such as reading the ingredients from a cookbook and then remembering which four things to get out of the cupboard. It also involves mental manipulation of information, such as needing to halve the recipe as you cook (Eriksson et al., 2015). Finding ways to maintain WM is important, as age-related decreases in WM predict a decline in instrumental activities of daily living, such as medication and financial management (McDougall et al., 2019).

Physical activity has also been studied in relation to brain structure and function; however, findings are somewhat inconclusive. For example, there are indications that longitudinally maintained physical activity among older females predicts less decline in executive functions and greater volume in the left dorsolateral prefrontal cortex (DLPFC), an important area for executive functions, (Barha et al., 2020). Executive functions, which are a collection of cognitive processes encompassing mental set shifting, inhibition of prepotent responses, and information updating of WM (Miyake et al., 2000), rely heavily upon the prefrontal cortex (PFC) and age-related decline is predictive of subsequent decline to episodic memory (Memel et al., 2019). Meanwhile, the relationship between physical activity and the brain is not straightforward, and others have found no association between self-reported physical activity and gray matter volumes of the hippocampus and DLPFC (Demnitz et al., 2025). Of note, the latter study was cross-sectional, and thus may not capture the relationship between physical activity and structural outcomes in aging specifically.

Physical activity may also be related to brain function, and a common method of studying brain function is with functional magnetic resonance imaging (fMRI). fMRI measures local changes in oxygenated blood in the brain, called the blood oxygenation level dependent (BOLD) signal. The brain requires a steady flow of oxygen via the blood, with increased neural activity demanding additional supply, and by measuring changes in the BOLD signal, for example during a cognitive task, we can infer when and where brain activity is taking place. The BOLD signal, while not a direct measure of brain activity, is an indication of areas with temporarily increased metabolic requirements (Huettel et al., 2014).

This enables us to study which areas a specific cognitive task activates, as well as connectivity within- and between large neural networks. With regards to physical activity, one study found that accumulated physical activity over a decade was related to increased connectivity in the posterior cingulate cortex in the default mode network (Boraxbekk et al., 2016). However, others have found no relationship between longitudinal change in physical activity and default mode network connectivity. Rather, it seemed that within-person increases in physical activity over time were related to increased frontal-subcortical inter-network connectivity (Dorsman et al., 2020).

Taken together, physical activity is a promising lifestyle factor that can help maintain many important bodily functions, including mitigating many modifiable risk factors related to dementia and cardiovascular disease, such as hypertension, type II diabetes, and depression (Livingston et al., 2024; Yusuf et al., 2020). Furthermore, longitudinally maintained physical activity may be related to general brain maintenance (Dunas et al., 2021). While promising, there is still large heterogeneity in findings and the mechanisms underlying the relationship between physical activity and neurocognitive changes are not clear. While longitudinal observational studies provide insight into relationships between physical activity and different measures of physiological, cognitive, and neural function, testing the causal effects of exercise to neurocognitive measures is done through randomized controlled trials (RCTs).

Physiological effects of exercise

To study the effects of exercise, we manipulate exercise dose, i.e. frequency (e.g., number of sessions per week), intensity (e.g., moderate, high, very high), time (duration of a session), type (e.g., resistance vs aerobic training), volume (total amount), and progression (degree of increase within- or across sessions) (Bishop et al., 2025), and compare differences to outcomes such as CRF, muscular strength, cardiovascular function, and increasingly common, cognitive and neural measures. Both aerobic exercise, defined as an activity wherein the body's large muscles move in a rhythmic manner for a sustained period of time (e.g., running, bicycling) (WHO, 2020) and resistance training, i.e., exercise requiring skeletal muscles to push or pull against resistance until reaching neuromuscular fatigue (Bishop et al., 2025), have been widely studied among older adults. While aerobic training leads to favorable outcomes on CRF, resistance training reliably improves lean body mass (An et al., 2024), as well as measures of muscular strength (Peterson et al., 2010), and older adults are recommended to take part in both (WHO, 2020).

In this thesis, exercise intensity is of particular interest. Exercise intensity is commonly prescribed relative to maximal values that are conceptually grounded in cardiopulmonary exercise testing. These values can represent internal intensity markers such VO_2peak or maximum heart rate, or external intensity markers such as the mechanical power output achieved at VO_2peak, often referred to as maximum aerobic power (MAP). Although these maximal reference values are used to individualize training loads, they do not represent an individual's absolute maximal capacity, as very short bouts of work can exceed the external workload associated with VO_2max due to the contribution of anaerobic energy systems (MacInnis & Gibala, 2017).

In this context, submaximal intensity refers to work performed below the intensity at which VO_2max is reached, whereas supramaximal intensity refers to work performed above the external workload corresponding to VO_2max. Since oxygen uptake cannot exceed its maximal value, any additional energy demand at supramaximal workloads is met through anaerobic metabolic pathways. During the initial phase of such efforts, very high-power outputs are enabled by rapid use of intramuscular adenosine triphosphate and creatine phosphate, and during slightly longer intervals the ability to maintain power declines due to both the depletion of these immediate energy sources and the accumulation of metabolites and hydrogen ions (MacInnis & Gibala, 2017).

Exercise intensity can also be expressed using subjective responses such as perceived exertion on Borg's Ratings of Perceived Exertion (RPE) scale (6 to 20) (Borg, 1998). RPE reflects an internal perceptual response rather than a physiological maximal value but is widely used for monitoring and prescribing exercise. Because exertion and affect can fluctuate independently, especially during higher intensities, the Feeling Scale (FS) is often included alongside RPE to capture changes in affect during an exercise session (Hardy & Rejeski, 1989).

Intensity is closely linked to the duration for which an exercise bout can be sustained. For example, moderate intensity training (MIT) is typically prescribed relative to VO_2max and is commonly sustained for 30 to 60 minutes (ACSM, 2018). Higher submaximal intensities, expressed relative to either maximal VO_2max or the corresponding external workload, can only be maintained for limited periods of time and are therefore often performed as intervals, with short periods of higher effort interspersed with recovery (MacInnis & Gibala, 2017). Meanwhile, supramaximal efforts, also called supramaximal high intensity interval training (HIT) are performed as very intense and very brief intervals, typically lasting only seconds and seldom extending beyond 20 to 30 seconds.

Exercise at submaximal intensities has been studied among older adults, with widespread positive effects to the body, particularly to many mechanisms that are negatively affected by increased age. Among older adults, these include improvements to CRF (Bouaziz et al., 2018; Bouaziz et al., 2020), heart rate variability (Grassler et al., 2021), and systolic and diastolic blood pressure (Oliveira et al., 2024). Meanwhile, supramaximal HIT has primarily been studied among younger adults, due to concerns about the tolerance and safety of such high intensities among older adults (Ekkekakis et al., 2023; Hardcastle et al., 2014). Findings among younger adults suggest that supramaximal HIT and MIT elicit similar effects on CRF and blood pressure (Liang et al., 2024), and while supramaximal HIT is inferior to resistance training in producing gains to muscular strength, there are indications it may be superior to MIT (Wiens et al., 2025). However, often meta-analyses combine submaximal efforts and supramaximal HIT (Mattioni Maturana et al., 2021), making it difficult to isolate adaptations specific to supramaximal intensities. In addition, supramaximal HIT can be performed in different exercise modes, which differ in mechanical loading, and such differences may influence the adaptations observed across studies.

Few studies have assessed effects of supramaximal HIT for older adults. Findings indicate that these types of very intense and very short intervals lead to promising results on blood pressure, physical functions (e.g., timed up and go, loaded 50 m walk), cholesterol levels, and blood glucose control (Adamson et al., 2020; Adamson et al., 2019; Adamson et al., 2014). However, these studies had small sample sizes, used inactive control groups, or completely lacked a control group, limiting conclusions, and the effects of supramaximal HIT for older adults needs to be assessed more rigorously.

Neurocognitive effects of exercise

Exercise has been found to affect cognitive functions, brain structure, and brain function positively; however, the effects are smaller than physiological change and results are often inconclusive. Much is still unknown. The first meta-analysis on exercise effects on cognitive function was published over twenty years ago (Colcombe & Kramer, 2003) and since then the field of exercise neuroscience has grown exponentially, with multiple meta-analyses published annually. Recent systematic reviews of RCTs have reported small to moderate positive effects on a wide range of cognitive functions among older adults (Barha et al., 2017; Chen et al., 2020; Falck et al., 2019; Northey et al., 2018; Singh et al., 2025). However, other reviews have found no effect of exercise on cognitive functions (Ciria et al., 2023; Young et al., 2015). These differences between reviews can in part be explained by differences between exercise studies with regards to exercise dose, as well as large individual differences in cognitive response to exercise.

When it comes to exercise effects on the brain, much focus has been upon structural outcomes, and similarly, results are inconclusive. A recent meta-analysis showed that physical exercise seemed to affect structural outcomes among older adults, including volume of the frontal lobe, thalamus, and hippocampus, and found a significant positive association between exercise-induced change to brain volume and gains to cognitive function. Meanwhile, global brain volume, gray matter volume, and white matter volume was not significant (Li et al., 2025). In contrast, another meta-analysis assessing the effects of aerobic exercise specifically found no effect of aerobic exercise on hippocampal volume (Balbim et al., 2024).

Compared to brain structure, fewer studies have assessed exercise effects to brain function, especially in relation to task-based fMRI paradigms. For example, in a meta-analysis from 2021 summarizing effects of exercise on brain structure and function among older adults, the authors included 39 RCTs with structural outcomes, and only 10 that used task-based activation (Ji et al., 2021). Executive functions, which have been shown to improve in response to exercise interventions among older adults (Barha et al., 2017; Chen et al., 2020; Northey et al., 2018), have also been studied using fMRI assessing task-related functional activity during shifting and inhibition. Findings from task fMRI studies on executive functions reveal both increases and decreases to recruitment, depending upon the task and contrast assessed, however repeatedly changes to the frontal cortex have been found (Colcombe et al., 2004; Hsu et al., 2018; Liu-Ambrose et al., 2010; Voelcker-Rehage et al., 2011; Wu et al., 2018), indicating a promising cortical region for exercise-induced change. The above studies indicate that exercise can affect patterns of task recruitment to frontal, parietal, and temporal regions during executive functions, however the relationship between task-evoked activity changes and performance is not clear. Furthermore, recruitment during executive functions updating of WM has not been commonly assessed in exercise interventions.

Working memory

WM, which overlaps to some extent with executive functions, is, as previously mentioned, a major focus in this thesis. WM performance declines earlier than episodic memory, with more pronounced decline in WM manipulation, and longitudinal evidence suggests that this is accompanied by decreased recruitment of the PFC (Nyberg et al., 2022; Rieckmann et al., 2017). This is a key area in WM recruitment, and is upregulated during WM manipulation compared to maintenance (Pudas et al., 2009)There is support for exercise having positive effects on WM performance (Northey et al., 2018; Xiong et al., 2021; Zhidong et al., 2021), and resistance training may be particularly effective (Cassilhas et al., 2007). Meanwhile, few studies have examined exercise effects on WM using fMRI. One study found decreased recruitment of the bilateral PFC during a WM maintenance task fMRI following an exercise intervention, interpreted as increased efficiency, as well as exercise-induced increases to memory and executive functions (Nishiguchi et al., 2015). A follow-up study found reduced functional connectivity in key WM areas, including between the left rostral anterior cingulate cortex and left inferior frontal areas in the exercise group, while connectivity increased in the control group during WM maintenance. For the control group that increase was associated with increased general cognitive ability on the Montreal Cognitive Assessment (MoCA) test, but not for WM performance (Soshi et al., 2021). Finally, a study investigating both acute- and long-term adaptations of MIT found important WM areas affected, with acute increases in resting state functional connectivity in right- lateralized frontoparietal connections following a bout of MIT, which in turn was related to both acute and long-term increases to WM performance (Voss et al., 2020).

Taken together, these studies indicate promising effects of exercise to WM performance (Xiong et al., 2021; Zhidong et al., 2021), however large individual differences in response to exercise exist, and WM task-related functional activity, particularly for manipulation, has not been widely studied. This may be particularly important given that WM has been suggested as a task-general cognitive process shared across other cognitive domains due to its relevance when remembering and applying task rules (Unsworth et al., 2014; Voss & Jain, 2022). This may indicate that WM improvements could benefit broader cognitive functions. Furthermore, WM is not always systematically isolated in the exercise literature, rather it is often included under either executive functions or a general memory category. A closer examination of exercise effects on WM performance and underlying neural recruitment, as well as an examination of individual differences in exercise response is therefore warranted.

Mechanisms of exercise-induced neural plasticity

A key feature of the human nervous system is its ability to adapt and reorganize its structure and function, a concept called neural plasticity (James, 1890). This encompasses the growth of new neurons and synapses, called neurogenesis and synaptogenesis respectively, as well as the growth of blood vessels from pre-existing neural vasculature, called angiogenesis, and all are examples of changes that can underly changes to cognition (Stillman et al., 2020). Individual variability in exercise response regarding cognitive functions among older adults is proposed to be related to both pre-existing differences between individuals, as well as individual differences in physiological adaptations to exercise.

Baseline characteristics

When introducing exercise at an older age, pre-existing levels of physiological and neural aging are proposed to play an important role in subsequent cognitive effects. While there are numerous factors that are important to consider, including biological sex (Barha et al., 2021b), cognitive function at baseline, and genetic polymorphisms (Barha et al., 2021a), here the focus is upon baseline levels of fitness and cerebrovascular damage.

Cross-sectional studies indicate that higher CRF may be related to better performance on many cognitive functions (Oberlin et al., 2025; Wang et al., 2025), and longitudinal research shows that lower baseline CRF is related to accelerated cognitive decline (Wendell et al., 2014). The relationship between baseline fitness and exercise-induced cognitive change is however inconsistent. For example, one study found that higher baseline CRF was related to exercise-induced gains to verbal memory, pattern separation, and processing speed, however not to WM (Sokolowski et al., 2021). Taken more broadly, physical status (i.e., healthy, frail or mixed) at baseline has shown to moderate the exercise-cognition relationship, with the largest effect sizes on cognitive function for those with the healthiest physical status at baseline (Falck et al., 2019). Meanwhile others found the largest for previously sedentary adults (Chen et al., 2020). Baseline fitness measures may therefore need to be considered when understanding individual differences in exercise-induced cognitive improvements.

Pre-existing cerebrovascular damage, such as white matter lesions may also influence how well one responds to exercise. White matter lesions are tissue damage, including demyelination, axonal loss, and gliosis, that are indications of cerebral small vessel disease (Wardlaw et al., 2019). Pre-existing lesion load severity may also affect potential exercise gains to cognitive function. For example, exercise effects to WM performance were reported following a MIT intervention, however only for those with no or mild white matter lesions at baseline, while older adults with moderate to severe lesions did not see gains to WM (von Cederwald et al., 2023). This is proposed to be due to, among other things, maladaptive neurotrophic regulation impairing plasticity (Galluzzi et al., 2008). The moderating effect of baseline white matter lesion load needs to be further assessed, as it may help guide potential exercise prescription, including assessing whether lesion load severity impairs plasticity irrespective of exercise intensity. This may help identify subgroups wherein effects to WM can be expected to be smaller or non-existent.

Taken together, baseline fitness and neural measures may be important to take into consideration when assessing individual differences in WM change following exercise. Findings may help identify factors related to positive cognitive responses following exercise, with the potential for informing individualized exercise prescription. Meanwhile, individual differences in cognitive response may also be determined by the extent to which a person responds physiologically to exercise, and while there are many models proposing different mediating factors, this thesis focuses on two, namely the CRF-hypothesis and the myokine hypothesis.

Cardiorespiratory fitness hypothesis

One mechanism previously identified as important for cognitive gains is CRF. Exercise-induced gains to CRF are proposed to mediate the relationship between exercise and neurocognitive markers, as summarized in the CRF-hypothesis (Voss & Jain, 2022). This is supported by studies finding that increases to cognitive function are not associated with the exact dose of exercise, rather with individual CRF response among older adults (Billinger et al., 2017; Brown et al., 2021; Sokolowski et al., 2021; Vidoni et al., 2015; Zotcheva et al., 2022). For example, research indicates that exercise-induced gains to WM performance are positively related to increased CRF (Frost et al., 2021; Sokolowski et al., 2021). Similarly, CRF has been found related to structural and functional outcomes following exercise, such as a positive change-change relationship between CRF and hippocampus volume (Jonasson et al., 2017), as well as CRF and increased neural efficiency during executive functions inhibition (Voelcker-Rehage et al., 2011). CRF gains in this sense become a proxy for several underlying central and peripheral adaptations relevant for neural health, including increases in blood volume, capillary density, mitochondrial and metabolic efficiency, and autonomic regulation, however the exact pathways of change, including which factors are of particular importance to see cognitive gains, are not well understood (Voss & Jain, 2022). Meanwhile, a recent meta-regression found no relationship between CRF gains and change to hippocampus volume (Balbim et al., 2024), suggesting that the CRF-neuroplasticity relationship is still not entirely clear. Furthermore, meta-regressions support a positive relationship between gains to physical function, including CRF, muscular strength, flexibility, mobility, and balance, and increases in cognitive function (Falck et al., 2019), indicating that fitness variables beyond CRF may also be important in the exercise-cognition relationship.

In this sense, the relationship between exercise gains to fitness measures, such as CRF, may help explain individual differences in cognitive gains. While studies show change-change relationships between CRF and cognitive outcomes such as global cognitive function, executive function (Brown et al., 2021), attention (Billinger et al., 2017), visuospatial processing (Vidoni et al., 2015), and WM (Frost et al., 2021; Sokolowski et al., 2021), few have tested this in relation to task-based neural recruitment (Nocera et al., 2017; Voelcker-Rehage et al., 2011). Furthermore, considering support for a relationship between physical function and cognitive gains, other measures, such as exercise-induced gains to muscular strength, may also need to be considered. While there is support for resistance training affecting cognitive and neural measures (Herold et al., 2019), the relationship between gains to muscle strength and improved cognitive function, while promising (Mavros et al., 2017), needs more study.

Myokine hypothesis

While improvements to CRF reflects adaptations to cardiovascular and peripheral systems, other important mediators in the exercise-cognition relationship have been proposed, including molecular mechanisms, structural- and functional changes to the brain, and socioemotional factors such as sleep and mood (Stillman et al., 2016; Stillman et al., 2020). Here, focus is upon the molecular mechanisms, henceforth referred to as the “myokine hypothesis” (others have called it the neurotrophin hypothesis, e.g. see Herold et al. (2019)).

Exercise-induced neural and cognitive change are proposed to be mediated by several molecules released during exercise, so-called myokines (Pedersen et al., 2007). These include, among others, brain derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor A (VEGF) (Stillman et al., 2016; Stillman et al., 2020). These myokines are suggested to cross the blood-brain barrier and are proposed to trigger angiogenesis, synaptogenesis, and neurogenesis in intricate pathways. For humans, peripheral levels are most commonly measured. Resting levels of BDNF, IGF-1, and VEGF decrease with age, however exercise can increase BDNF and IGF-1, while evidence on VEGF is inconclusive (Behrad et al., 2024; Gholami et al., 2024; Song et al., 2024; Wagatsuma, 2006). However, it is unclear how closely peripheral levels relate to levels in the central nervous system (Ou et al., 2021; Pillai et al., 2010).

While upregulation of these myokines is proposed to mediate the relationship between exercise and cognitive gains, fewer studies have found clear associations or causal pathways between exercise, myokine change, and cognitive gains. Animal models show that blocking BDNF receptors also blocks cognitive benefits of exercise (Vaynman et al., 2004). Among humans, exercise-induced change to resting levels of BDNF have been found to be associated with increased functional connectivity (Voss et al., 2013) and hippocampus volume (Erickson et al., 2011). One study found that exercise induced increases to executive functions were mediated by BDNF upregulation, but only for those over the age of 71 (Leckie et al., 2014), and while a few studies have found change-change associations between BDNF and cognitive measures (Damirchi et al., 2018), others have not (Enette et al., 2020; Erickson et al., 2011; Fragala et al., 2014; Ruiz et al., 2015; Tsai et al., 2019). As for IGF-1, one study found that increased levels following a 3-month aerobic exercise intervention positively related to increased hippocampal volume and late verbal recall performance, however change in VEGF and BDNF were not related to structural or cognitive change (Maass et al., 2016). Despite evidence of exercise-induced myokine changes, their impact on WM remains largely unexplored, and additional studies are needed to evaluate this relationship.

Beyond the Randomized Controlled Trial

As outlined above, exercise has extensive health benefits. Despite this, only 14% of older adults reach exercise recommendations (Garcia-Hermoso et al., 2023). While research focused on assessing and understanding exercise effects might help with exercise prescription aimed at helping older adults maintain independence and years of healthy living, those effects are lost if the intervention is not adhered to. RCTs may be the gold standard for testing intervention efficacy, however top-down solutions often show a steep drop in effects when it comes to widespread implementation (McKay et al., 2023), which is hypothesized to be due to problems when translating rigid and controlled interventions from clinical trial settings to complicated real-life settings (Gray et al., 2021). Here, a framework for complex interventions becomes important.

Developed to help maximize research impact, the Medical Research Council's complex intervention framework challenges the notion that effectiveness trials are the primary goal when evaluating an intervention. Instead, the framework extends focus to also encompass understanding how an intervention contributes to changing the outcome of interest, including evaluating whether an intervention is implementable, transferable to new contexts, cost effective, and scalable. This framework therefore goes beyond testing effects in RCTs and includes intervention development and adaptation, feasibility testing, and planning for widespread implementation, with focus being on involving stakeholders, such as end-users, throughout this process (Skivington et al., 2021), see Figure 1.

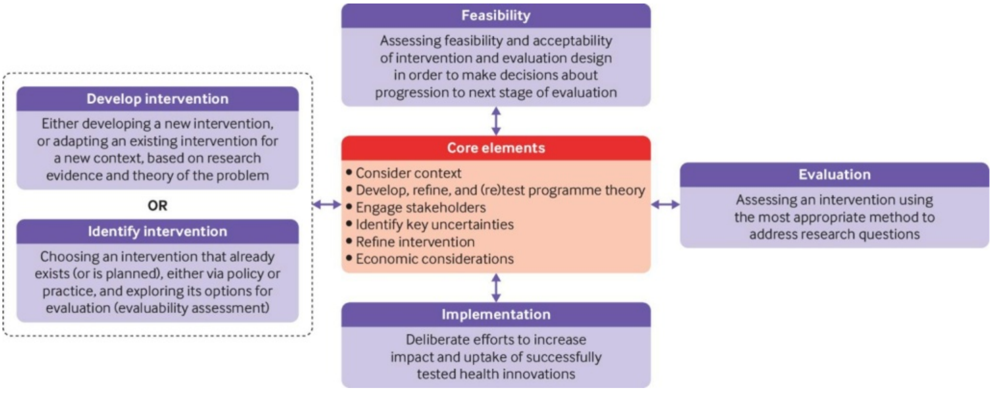

Figure 1. Framework for complex interventions (Skivington et al., 2021). Reproduced under CC BY 4.0 license.

One important factor enabling future translation of findings from clinical or research settings to real-life contexts is the careful collection of adverse events, which are common in exercise interventions (Niemeijer et al., 2020), and an important outcome and indication of the safety of an intervention. Furthermore, co-creation research is one methodological strategy for addressing the complexity in applying clinical findings to real-life settings, where the inclusion of different stakeholders' perspectives is proposed to add to the ecological validity of an intervention, potentially increasing long-term adherence (Leask et al., 2019). While co-creation aims to integrate end-users' needs and preferences into an adapted intervention, changes still need to be in line with the original intervention's program theory (Skivington et al., 2021), also called core components (Blase & Fixen, 2013). These are factors that have been identified as key to an intervention working. This thesis spans several of these steps, bringing findings from an RCT back into the development stage to work with end-users in adapting the intervention to a new context.

Rationale

All around the world people are living longer, and an important line of inquiry is how to increase the number of years of healthy living. Physical exercise is an efficient and cost-effective lifestyle factor with promising effects, targeting modifiable risk factors for dementia and cardiovascular disease. And yet, there is a large heterogeneity in response to exercise – especially with regards to cognitive and neural outcomes. One size simply does not fit all.

The evaluation of new forms of exercise, such as increasing intensity, is thus one important area in need of more research. Higher intensities may result in both similar and distinct effects as compared to exercise traditionally prescribed for older adults, but in less time. Meanwhile, understanding the exercise-cognition relationship also needs to go beyond an assessment of exercise dose, and delve into individual differences in exercise response to identify how physiological adaptations relate to cognitive benefits. This includes both individual characteristics at baseline, as well as individual differences in physiological response to exercise. Evaluating such relationships helps us begin to understand who benefits from exercise, and perhaps even why, providing a stronger basis for potential targets in future research.

Meanwhile, research is quite clear: exercise has immense benefits for the aging body. While identifying effective exercise interventions is one way to help overcome health- and societal challenges, it is equally important to adapt and make evidence-based interventions accessible so that they can benefit the population in question. This thesis spans several of these steps, from effectiveness testing to re-development of evidence-based solutions through co-creation. Through this, it attempts to provide innovative methods for maintaining physical exercise later in life, which is of importance to prevent unnecessary suffering and large societal costs, while also increasing quality of life and independence.

Purpose and Aims

The overarching aim of this thesis is to investigate the effects of supramaximal HIT compared to MIT for older adults and evaluate individual differences in change to WM. Furthermore, this thesis aims to adapt findings from an intervention setting to the home environment of older adults. The specific thesis aims are:

1. Assess the effects of supramaximal HIT compared to MIT for older adults on physiological, cognitive, neural, and quality of life outcomes.

2. Evaluate individual differences in change to WM functional activation and WM performance by testing them in relation to fitness- and neural baseline characteristics, the CRF-hypothesis, and the myokine hypothesis.

3. Evaluate safety measures of the original supramaximal HIT protocol and examine how it can be adapted for self-administered exercise in the home-settings of older adults.

Materials and Methods

Overview and Design

All four research papers in this thesis are based on the Umeå HIT study, an ongoing research project focused upon bringing controlled supramaximal HIT to older adults. The project began with a series of stepwise pilot and feasibility studies (not included in this thesis) that led to the development of the original supramaximal HIT protocol, later summarized in Hedlund et al. (2019). The protocol was later tested in a RCT conducted in 2018-2020. The RCT compared supramaximal HIT to MIT for non-exercising older adults and is registered at ClinicalTrials.gov (NCT03765385). *Papers I-III* in this thesis are based on findings from the RCT (referred to as the "Umeå HIT RCT" in this thesis). Following the trial, two branches of co-creation studies working towards future implementation of supramaximal HIT were conducted during 2022-2024; one, not included in this thesis, focused upon adapting the protocol to a gym setting (Frykholm et al., 2025) and one focused upon adapting the HIT protocol to the home environment of older adults. *Paper IV* of this thesis focused upon the latter, which is referred to as the "Umeå HIT Home Study". An overview of the *Papers I-IV* can be found in Table 1, and an overview of the HIT-study flow can be found in Figure 2.

Paper I assessed between-group differences in change (henceforth referred to as group x time interaction) of supramaximal HIT and MIT on CRF, global cognitive function, domain-specific WM function, blood pressure, isometric leg extensor strength, and health-related quality of life. *Paper II* assessed group x time interactions in WM manipulation task-related BOLD response (henceforth called functional activity) and individual differences in fitness changes related to WM functional activity and WM performance. Individual differences in exercise-induced WM performance change were further assessed in *Paper III*, including both baseline- and change-variables commonly suggested as important for exercise-induced cognitive gains. In *Paper IV*, the supramaximal HIT protocol was adapted to fit the home settings of older adults.

Table 1. Overview of Papers in this thesis				
Paper	I.	II.	III.	IV.
Umeå HIT-study	Umeå HIT RCT			Umeå HIT-Home
Study design	RCT			Co-Creation
Inclusion criteria	Older adults over 65 years not engaged in regular moderate to vigorous physical activity over the past year.			Participants from RCT HIT group
Exclusion criteria	Cardiac, lung, or neurological disease contraindicative of high-intensity exercise; exercise-induced pain; untreated arterial hypertension; insulin-treated diabetes, MMSE-SR ≤ 26; participation in a previous exercise study (PHIBRA).			
Paper-specific exclusion criteria		Contra-indications to MRI. Missing data from fMRI task	MRI subsample: Contra-indications to MRI. Missing data from FLAIR.	Phase II: cardiac contraindications to exercise at high intensities; exercise-induce pain.
Sample size	68	43	68	11
Target outcomes *and other variables of interest*	Global cognitive function, VO_2peak*, WM, blood pressure, isometric leg extensor strength, adverse events*	WM functional activity and WM performance. *VO_2peak and isometric leg extensor strength*	WM performance. *VO_2peak, BDNF, IGF-1, VEGF, white matter lesion load, isometric leg extensor strength*	Physiological and emotional reactions exercising HIT, potential exercise modalities, adaptations to HIT protocol, acute physiological response to HIT on alternative modalities, safety rankings
Method of analysis	LMMs	Flexible factorial model, LMMs, and regression models	Multivariable regression models, LMMs	Data synthesis: Phase one descriptive summaries. Phase two descriptive statistics.
My contributions (based on CRediT author statement)	Second author; Data curation; Formal analyses; Writing – original draft and editing	First and corresponding author; Formal analyses; Data curation; Methodology; Visualization; Writing original draft and editing	First and corresponding author; Formal analyses; Data curation; Visualization; Writing original draft and editing	First and corresponding author; Conceptualization; Data curation; Formal analyses; Project administration; Visualization; Writing original draft and editing
Abbreviations: BDNF = Brain-Derived Neurotrophic Factor; CRediT = Contributer Roles Taxonomy; FLAIR = Fluid-Attenuated Inversion Recovery; fMRI = functional Magnetic Resonance Imaging; HIT = High Intensity Interval Training; IGF-1 = Insulin-like Growth Factor 1; MMSE-SR = Mini-Mental State Examination; MRI = Magnetic Resonance Imaging; RCT = Randomized Controlled Trial; VEGF = Vascular Endothelial Growth Factor A; VO_2peak = Peak oxygen uptake; WM = Working Memory.				

Ethics

Ethical approval was given by the Regional Ethics Review Board in Umeå for the Umeå HIT RCT (2018-307-31 M, 2018-421-32 M) and the Umeå HIT-Home Study (2022-03072-01). All participants provided written informed consent prior to data collection and intervention.

Participants and Procedures

For the Umeå HIT RCT, participants were recruited through an advertisement in a local newspaper. A physiotherapist or exercise physiologist then conducted an initial telephone screening, and eligible applicants received further oral and written information about the study. Eligible applicants were screened at the Clinical Research Centre in Umeå, Sweden, which included providing written informed consent, undergoing a medical examination including a 12-lead electrocardiography by a cardiologist, and performing a Mini Mental State Examination (MMSE-SR). Further medical clearance was later conducted during baseline testing, including an oral glucose tolerance test of a capillary blood sample to rule out untreated diabetes (kP-Glucose > 12.2 mmol/L) as well as a 12-lead electrocardiography during cardiorespiratory fitness testing to rule out exercise-induced arrythmia. The study included four waves of participants, enrolled between December 2018 and September 2019. For each wave, baseline assessments were conducted, followed by a 1:1 randomization to either supramaximal HIT or MIT, stratified by age (65-69 years or ≥ 70 years) and sex (male/female). Participants then exercised twice weekly for 25 sessions (3 months). Follow-up assessments were conducted immediately after the exercise intervention period. Testing was conducted at the Sports Science Lab, the Umeå Movement and EXercise Lab of Umeå University, the Clinical Research Centre at the University Hospital of Umeå, and at participants' homes for home-based measures. A subsample of participants (n=43) was selected for magnetic resonance imaging (MRI) assessment at the University Hospital of Umeå.

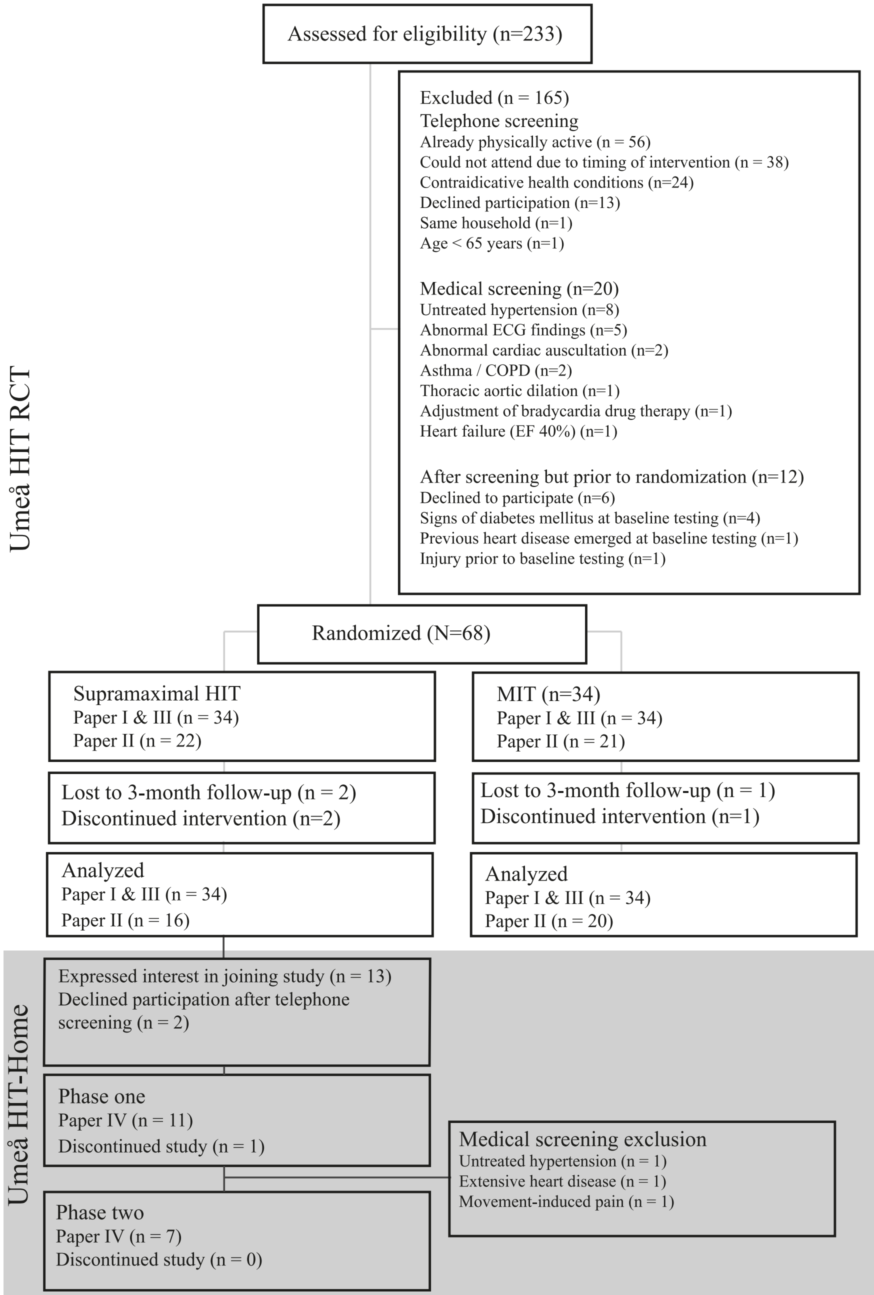

Figure 2. Umeå HIT study flow, including both RCT and HIT Home. Abbreviations: COPD = chronic obstructive pulmonary disease; HIT = high intensity interval training; ECG = electrocardiogram; EF = ejection fraction; MIT = moderate intensity training.

For the Umeå HIT-Home Study, all 34 participants from the supramaximal HIT-group of the RCT were contacted by mail, and thirteen expressed interests in participating. Following an initial telephone call depicting the extent of the study, eleven decided to join. The co-creation study included two phases. Phase one consisted of in-person co-creation workshops overseen by facilitators conducted at the UMeHealth Lab at Umeå University. Prior to phase two participants were medically screened, including a 12-lead electrocardiography, blood pressure measurements, and records of previous and current illness and medications. Phase two consisted of testing of acute physiological responses following different supramaximal HIT protocols (more details under aim three below). This was done in the Umeå Movement and EXercise Lab at Umeå University, overseen by test leaders. An overview of paper-specific participant characteristics can be found in Table 2.

Table 2. Participant baseline characteristics by paper

Paper	I. (n = (68)	II. (n = 43)	III. (n = 68)	IV. (n = 11)
Umeå HIT-study	Umeå HIT RCT			Umeå HIT Home
Demographics				
Women, n (%)	38 (56)	24 (56)	38 (56)	6 (55)
Age, years	69.7 (2.95)	69.8 (2.93)	69.7 (2.95)	70.6 (1.5)
Education, years	14.4 (3.3)	14.6 (3.0)	14.4 (3.3)	15.6 (3.4)
Anthropometrics				
Body mass, kg	76.5 (14.4)	75.3 (13.4)	76.5 (14.4)	69.5 (11.7)[a]
BMI	26.2 (3.94)	25.8 (3.2)	26.2 (3.94)	24.7 (4.4)[a]
Cardiovascular function				
Systolic (mmHg)	126 (10.8)	128 (12.0)	126 (10.8)	126.6 (7.0)[a]
Diastolic (mmHg)	80.0 (6.08)	80.4 (5.8)	80.0 (6.08)	80.3 (6.8)[a]
Diagnoses, no. (%)				
Any	53 (78)	32 (74)	53 (78)	6 (86) [a]
Hypertension	38 (56)	25 (58)	38 (56)	6 (86) [a]
Hypothyrodism	8 (12)	6 (14)	8 (12)	1 (14) [a]
Diabetes	6 (9)	2 (5)	6 (9)	1 (14) [a]
Hip prosthesis	5 (7)	2 (5)	5 (7)	0 (0) [a]

Notes: values expressed as mean (standard deviation) unless otherwise specified. [a] = data from paper IV phase two (n = 7).

Sample size

The sample size of the Umeå HIT RCT was based on power analyses for the primary outcomes global cognitive composite score and VO2peak.

For the power analysis on global cognitive function the estimated within-group change was used for supramaximal HIT (mean = 0.288, standard deviation (SD) = 0.312) and MIT (mean = 0.0657, SD = 0.246), based on data from a previous exercise intervention assessing the effects of 6 months of moderate intensity aerobic exercise with stretching and toning control group (Jonasson et al., 2017). 52 participants (26/group) were needed. For VO_2peak, an estimated between-group difference in change of 3.5 mL/kg/min (SD = 4.0) was used (Kodama et al., 2009), which revealed a need for 42 participants (21/group). Considering both power analyses, as well as including a 15% dropout rate and a margin for missing data, 70 participants were needed. The MRI-subsample size was based on the sample size in comparable exercise studies using fMRI (Prehn et al., 2019; Voelcker-Rehage et al., 2011; Wu et al., 2018). For the Umeå HIT-Home Study, the aim was to recruit 10-15 participants, based on a similar co-creation study (Mansson et al., 2020).

Aim one: Exercise effects

To assess the effects of supramaximal HIT compared to MIT, data from the Umeå HIT RCT was used.

Umeå HIT RCT

Both supramaximal HIT and MIT exercised twice weekly for 12 weeks, with a total of 25 sessions. Training was conducted in groups of 8-10 participants on Tomahawk IC7 indoor bicycles (Indoor Cycling Group, Nürnberg Germany) at a training facility in Umeå, Sweden, and training was computer-guided with two researchers present to supervise, monitor, and collect data on adherence, adverse events, and escalation criteria. Exercise intensity was individualized based on an external target power output (TPO) in absolute watts and was controlled by a standardized pedaling cadence with participants adjusting the brake resistance level to their personally prescribed intensity. Escalation and de-escalation of intensity were determined based on set criteria and individualized escalation was implemented in absolute terms in watts during the entire intervention. Further details can be found in *Paper I Supplementary Materials*. A visual depiction of the intervention as well as session intensity differences between the two exercise groups can be found in Figure 3.

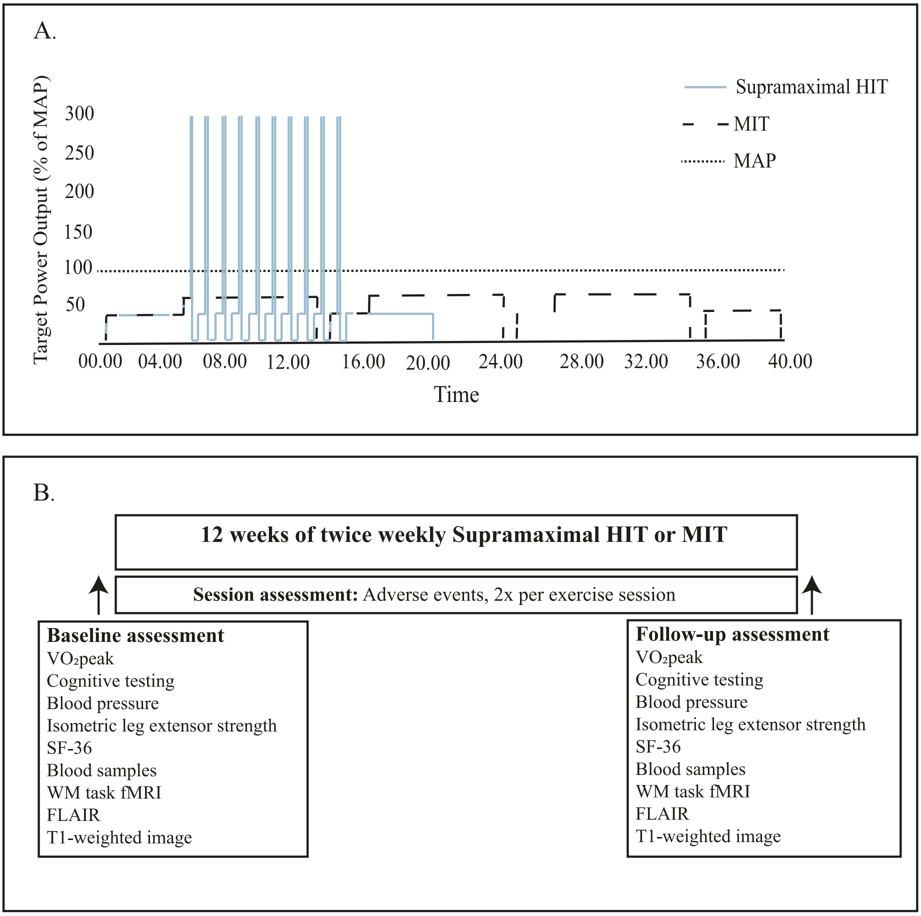

Figure 3. Umeå HIT RCT. A) Session intensity for supramaximal HIT and MIT. B) Measurement timepoints for different variables. Abbreviations: FLAIR = fluid-attenuated inversion recovery; fMRI = functional magnetic resonance imaging; HIT = high intensity interval training; MAP = maximal aerobic power; MIT = moderate intensity training; SF-36 = Swedish short form health survey; VO_2peak = peak oxygen uptake; WM = working memory.

A supramaximal HIT session consisted of a 5-minute warm-up, 10x6 second cycling sprints with 54 seconds of recovery between each interval, and a 5-minute cool-down. The session was 20 minutes in total. Prior to each interval, participants increased to interval-level cadence before adjusting the brake resistance to ensure the correct TPO was held during the entire interval. The individualized interval TPO for supramaximal HIT was calculated based on the participant's maximum mean power output for 6 seconds (MPO^6), as estimated at baseline from a modified version of the Borg Cycle Strength Test (Borg, 1982; Hedlund et al., 2019). Session 1-3 were conducted at 60% of MPO^6, after which individual escalation began, given that escalation criteria were fulfilled. All escalation was implemented between sessions, i.e., changes to interval intensity were not implemented during a session (unless indications that a participant needed to de-escalate), and escalation occurred in absolute steps of 4% of MPO[6] (in watts) if escalation criteria were reached.

The MIT-protocol consisted of a warm-up, 3x8-minute continuous cycling bouts at a moderate intensity, and a cool-down, resulting in 40 minutes total. Individual TPO was calculated based on the maximum aerobic power (MAP) in watts produced at VO_2peak during the baseline cycle ergometer ramp test. Session 1-3 were conducted at 40% of MAP, and between-session escalation occurred in absolute steps of 4% of MAP (in watts) if escalation criteria was reached.

Outcomes

The primary outcomes for *Paper I* were VO_2peak and global cognitive function, and secondary outcomes were WM performance, isometric leg extensor strength, systolic- and diastolic blood pressure, and health-related quality of life. Detailed descriptions of testing protocols and procedures can be found in *Paper I* and *Paper I Supplementary Materials*.

VO_2peak was assessed using a standardized ramp-test on an electronically braked cycle ergometer (Monark 839E Monark Exercise AB, Vansbro, Sweden), and expired air during the test was analyzed using a mixing chamber-based ergo-spirometry system (AMIS 2001 Innovision A7S, Odense, Denmark), registering the mean of 30-second intervals. The outcome of interest was the highest recorded oxygen uptake (VO_2peak, mL/kg/min).

Isometric leg extensor strength was assessed using a load cell (Lutron FG-5100, Lutron Electronic Enterprise Co., Ltd.) mounted in a Biodex dynamometer chair (Biodex System Pro X, Biodex Medical Systems, Shirley, New York). The Biodex chair was used to standardize positioning, while the load cell measured isometric force. Participants performed two maximal voluntary contractions for each leg, with two minutes of rest between trials. Joint torque (N・m) was calculated from the measured force (N) and the moment arm (m), and the outcome of interest was the maximum normalized joint torque, averaged across both legs relative to body mass (N・m/kg).

Systolic and diastolic blood pressure was assessed using a validated automatic upper arm blood pressure monitor (Omron M2). Participants registered seven days of home-based measurements with three measurements in the morning before they had eaten breakfast or taken medication, and three measurements in the evening before medication. The outcome of interest was an average of a minimum of 30 measurements for systolic and diastolic blood pressure (mmHg) respectively.

Global cognitive function was assessed using a battery of 10 tests targeting episodic memory, WM, executive functions, and processing speed. See Table 3 for tests, dependent measures, and subdomains of cognitive function. Raw scores on cognitive tasks were standardized for each participant and each timepoint using the mean and standard deviation from the entire sample at baseline. For the global cognitive composite, an average of standardized scores from the tests within all domains was computed, based on previous research (Jonasson et al., 2017; Miyake et al., 2000; Pantzar et al., 2018).

For the *WM composite*, the standardized scores for the Automated Operation Span (AOS) and Backward Digit Span (BDS) were averaged to form a composite.

Health related quality of life was assessed using the Swedish Short Form Health Survey (SF-36), and a composite mean of the 8 subscales (range 0-100, higher scores indicating a higher quality of life). Preprocessing of raw scores was managed in accordance with the survey manual (Sullivan et al., 2002).

For *paper II,* focus was on the MRI-subsample and changes to WM manipulation functional activity and performance during a WM task fMRI. This was a blocked-design fMRI task piloted by Pudas et al (2009). It consisted of three conditions: maintenance, manipulation, and control. Further information about the task can be found in *Paper II*. The contrast of interest for this study was [manipulation – maintenance].

Paper II MRI data was acquired on a GE Discovery MR 750 3T MRI-scanner, including a high-resolution T1-weighted structural image and an fMRI gradient-echo planar imaging sequence. For the high-resolution T1-weighted structural image, a 3D fast spoiled gradient echo sequence was used (180 slices, 1 mm thickness, repetition time (TR) 8.2 ms; echo time (TE) 3.2 ms, flip angle 12°; field of view (FOV) 25 cm x 25cm). The run lasted about 8 minutes. For the fMRI run, 290 volumes were collected (TR 2000 ms; TE 30 ms; flip angel 80°; FOV 25 cm; 37 transaxial slices of 3.4 mm; 0.5 mm gap) and included 10 initial dummy scans for the fMRI signal to reach equilibrium. The run lasted approximately 10 minutes.

Table 3. Cognitive test battery

Cognitive task	Dependent measure	Cognitive domain
Automated operation span (3) (Unsworth et al., 2005)	Sum of correctly remembered sets multiplied by the respective set size	Working memory
Backward digit span (5) (Wechsler, 1981)	Highest correctly completed sequence length	
Working memory manipulation[a] (Nyberg et al., 2014; Pudas et al., 2009)	Hits minus false alarms	
Free recall (2) (Murdock, 1962)	Number of correct responses	Episodic memory
Word recognition encode (4) and retrieval (8) (Nyberg et al., 1996)	Number of correct responses	
Paired Associates (10) (Rohwer et al., 1967)	Number of correct responses	
Stroop (6) (Stroop, 1935)	Difference in time between condition two and one, i.e. cost of inhibition	Executive functions
N-back, 2-back (7b) (Kirchner, 1958)	Number of correct responses	
Trail-making test (TMT) 4 (9c) (Delis et al., 2001)	Response time for switching cost (TMT 2+3)-TMT4	
Digit symbol (1) (Wechsler, 1981)	Mean response time for correct responses	Processing speed
N-back, 1-back (7a) (Kirchner, 1958)	Mean response time for correct responses	
TMT 2 (9a) & 3 (9b) (Delis et al., 2001)	Sum of response times (seconds) for TMT 2 and 3	

Notes: Numbers in parentheses indicate the order of test administration.
[a] depicts in-scanner WM task, which was not included in the WM composite

Analyses

All analyses in this thesis were conducted in R (R Core Team, 2020) and R studio (RStudio Team, 2025) using the package tidyverse (Wickham et al., 2019). For linear mixed-effects models, the lme4 (Bates et al., 2015), lmer (Kuznetsova et al., 2017), emmeans (Lenth, 2021), and effectsize packages were used. For multivariable regression models in R, the boot

(Canty & Ripley, 2021; Davison & Hinkley, 1997) package was used. For all descriptive plots, ggplot2 (Wickham, 2016) was used.

To test the hypothesis that supramaximal HIT was superior to MIT with regards to the primary outcomes VO_2peak and global cognitive function, linear mixed effects models (LMMs) were used to assess the between-group differences in change (henceforth referred to as group x time interactions), change irrespective of group, and within-group change. LMMs were further used for all other outcomes in *Paper I* and *II* except for fMRI-outcomes (these analyses are described below). The LMMs included group, time, and a group x time interaction, with subject as a random effect. For all outcomes on cognitive function, models included *a priori* adjustments for age, sex, and education as fixed effects. For non-cognitive outcomes, models included *a priori* adjustments for age and sex as fixed effects. All LMM results are reported as the LMM estimated mean change and difference in mean change and 95% CIs, with a 95% CI excluding zero as indication of statistical significance. Effect sizes were calculated using the model estimates of mean change divided by the unadjusted pooled standard deviation.

For preprocessing of fMRI data in *Paper II,* an in-house Matlab-based (Mathworks, Inc, MA, United States) software (DataZ) utilizing SPM12 was used. This included slice-timing correction (interleaved order with first image set as reference slice), movement correction to realign and unwarp all scans to the first image of each volume, coregistration of the mean functional image and the structural T1 image, normalization of each scan from each timepoint to a sample-specific template which was based on the baseline T1 images segmented into white matter, gray matter, and cerebrospinal fluid using DARTEL (Ashburner, 2007). For first-level analyses, a general linear model was set up for each scan at each time point, including regressors for each condition, convolved with a canonical hemodynamic response function, including six realignment parameters as covariates of no interest.

To test the hypothesis that WM manipulation functional activation would significantly differ in the PFC, with supramaximal HIT increasing, a flexible factorial design model was fit to assess a group x time interaction and main effects of time (Gläscher & Gitelman, 2008). All voxel-wise analyses were evaluated at $p < 0.001$, uncorrected, and with an extension threshold of 10 voxels. To decrease the risk of type I errors the search area was limited by applying an explicit mask with a rigorous threshold (Family Wise Error, $p < .01$) covering task-specific WM relevant brain regions extracted from a large sample of adults (n=363)

(Nyberg et al., 2014). For areas with significant change, the first-level beta estimates for manipulation divided by the mean of session were extracted and further explored in post-hoc change-change Pearson's correlation analyses in relation to WM performance.

Aim two: Individual differences

For aim two, data from the Umeå HIT RCT was used to test baseline fitness- and neural levels, the CRF-hypothesis, and the myokine hypothesis in relation to change (Δ) to WM functional activity and WM performance.

Variables

WM performance and WM functional activity have been described above, along with measurements of VO_2peak and isometric leg extensor strength. For all change-change analyses, baseline values were subtracted from follow-up, henceforth described as Δ[variable name].

White matter lesion load severity was collected using a fluid-attenuated inversion recovery (FLAIR) sequence with a total of 48 slices (slice thickness = 3mm, TE 120 ms, TR 8000 ms, and FOV = 24 cm x 24 cm). The run lasted approximately 5 minutes. Severity of baseline white matter lesion load was assessed by a third-year neurology resident, who was blinded to group allocation, and the Fazekas grading scale 0-3 was used for separate quantification of periventricular white matter lesion load (cingulum and corpus callosum) and deep white matter lesion load (subcortically) in line with the original Fazekas assessment (Fazekas et al., 1987). These were further subdivided into mild (Fazekas 0-1) and severe (Fazekas 2-3).

For myokine markers, blood sampling was conducted after an overnight fast. Serum samples were collected in sterile serum separator tubes and kept at room temperature for 30 minutes to allow clotting. After this the samples were centrifuged at 1500 g at room temperature for 15 minutes, and serum was harvested, aliquoted, and stored at -80°C degrees. For BDNF (pg/ml) and VEGF (pg/ml) concentrations were quantified using the Quantikine Human Free BDNF Immunoassay kit (ELISA, DBD00, R&D Systems, Inc., Minneapolis, MN, Unites States) and Quantikine Human VEGF Immunoassay kit (ELISA, DVE00, R&D Systems, Inc., Minneapolis, MN, United States) respectively, following the manufacturer's instructions. IGF-1 (ng/ml) concentrations were quantified using an automated immunoassay kit for Human IGF-1

(Siemens Immulite 2000 XPi, Siemens Healthcare Diagnostics, Erlangen, Germany). Analyses were conducted at the Department of Public Health and Clinical Medicine at Umeå University for BDNF and VEGF, and at Laboratory Medicine, Region Västerbotten for IGF-1.

Analyses

To test the hypothesis that baseline white matter lesion load severity would moderate the relationship between exercise group and WM performance (*Paper III)*, a LMM was fitted including group (HIT/MIT), time (baseline/follow-up), and lesion load severity (mild/severe), and a group x time x severity interaction, with age, sex, and education as fixed effects and individual as a random effect. This was done for periventricular white matter and deep white matter lesion loads separately.

To test the hypothesis that baseline fitness measures VO2peak and isometric leg extensor strength would be positively associated with ΔWM performance, a multivariable regression model including sex, age, education, and group allocation was run (*Paper III*).

To test the CRF-hypothesis on WM manipulation functional activity (*Paper II*) two separate regression models were fitted. First, to test the hypothesis that ΔVO_2peak would be positively related to prefrontal functional activation during WM manipulation, a multivariable regression model including sex, age, education, and ΔVO_2peak was fit, with ΔWM functional activity as the outcome. Second, to test the hypothesis that the fitness variable Δisometric leg extensor strength was positively related to prefrontal functional activation during WM manipulation in the HIT group only, a second multivariable regression model was fitted, including the same covariates as above, with ΔWM functional activity as the outcome. To test the hypothesis that areas with significant change in functional activity would positively relate to WM performance, beta estimates for significant local maxima were extracted using manipulation divided by mean of session and used as independent variables in subsequent multivariable regression models including age, sex, and education as predictors, with ΔWM in-scanner performance as the dependent variable.

To test the CRF hypothesis on ΔWM performance in the entire sample (*Paper III*), a multivariable regression was run, including Δisometric leg extensor strength and ΔVO_2peak. The hypothesis was that change in fitness measures would together positively relate to ΔWM performance.

To test the myokine hypothesis on ΔWM performance in the entire sample (*Paper III*), a multivariable regression was run, including ΔBDNF, ΔIGF-1, and ΔVEGF. The hypothesis was that change in myokine levels would together positively relate to ΔWM performance.

All *Paper III* regressions were adjusted for age, sex, education level, and group allocation. Potential-non-normality of residuals was accounted for by obtaining the 95% CIs for regression coefficients using nonparametric bootstrap resampling (1000 replications). To increase interpretability, all continuous independent variables were standardized. The model coefficients (β) and standard errors (SE) and the bootstrapped bias-corrected and accelerated (BcA) 95% CIs are reported. To assess multicollinearity, the variance inflation factor was used, and all values were below 3.9, which indicated an acceptable level of multicollinearity. To examine the potential effect of group allocation, significant variables were further examined in post hoc analyses, with a group x Δ[variable] interaction.

Aim three: Adapt Findings

For aim three, data was used from both the Umeå HIT RCT and the Umeå HIT-Home study.

Umeå HIT Home

The Umeå HIT-Home study was conducted in collaboration between older adults with experience exercising supramaximal HIT (referred to as "co-creators") from the Umeå HIT RCT, and an interdisciplinary research group of physiotherapists, a neuroscientist, an engineer, and a psychologist, see Figure 4 for the different steps of the study. As opportunities for older adults to exercise using controlled supramaximal HIT protocols are scarce, the objective was to adapt the supramaximal HIT protocol from the Umeå HIT RCT to a protocol with the intention of working in the home environment of older adults. This was done in a co-creation research study, wherein co-creators' ideas, preferences, and needs were integrated with laboratory testing of acute physiological responses to supramaximal HIT, with findings balanced with the protocol's core components. The core components were defined as 10 intervals at supramaximal intensity, the ability to systematically modulate intensity (control, increase, decrease, and individualize), and maintaining a safe protocol.

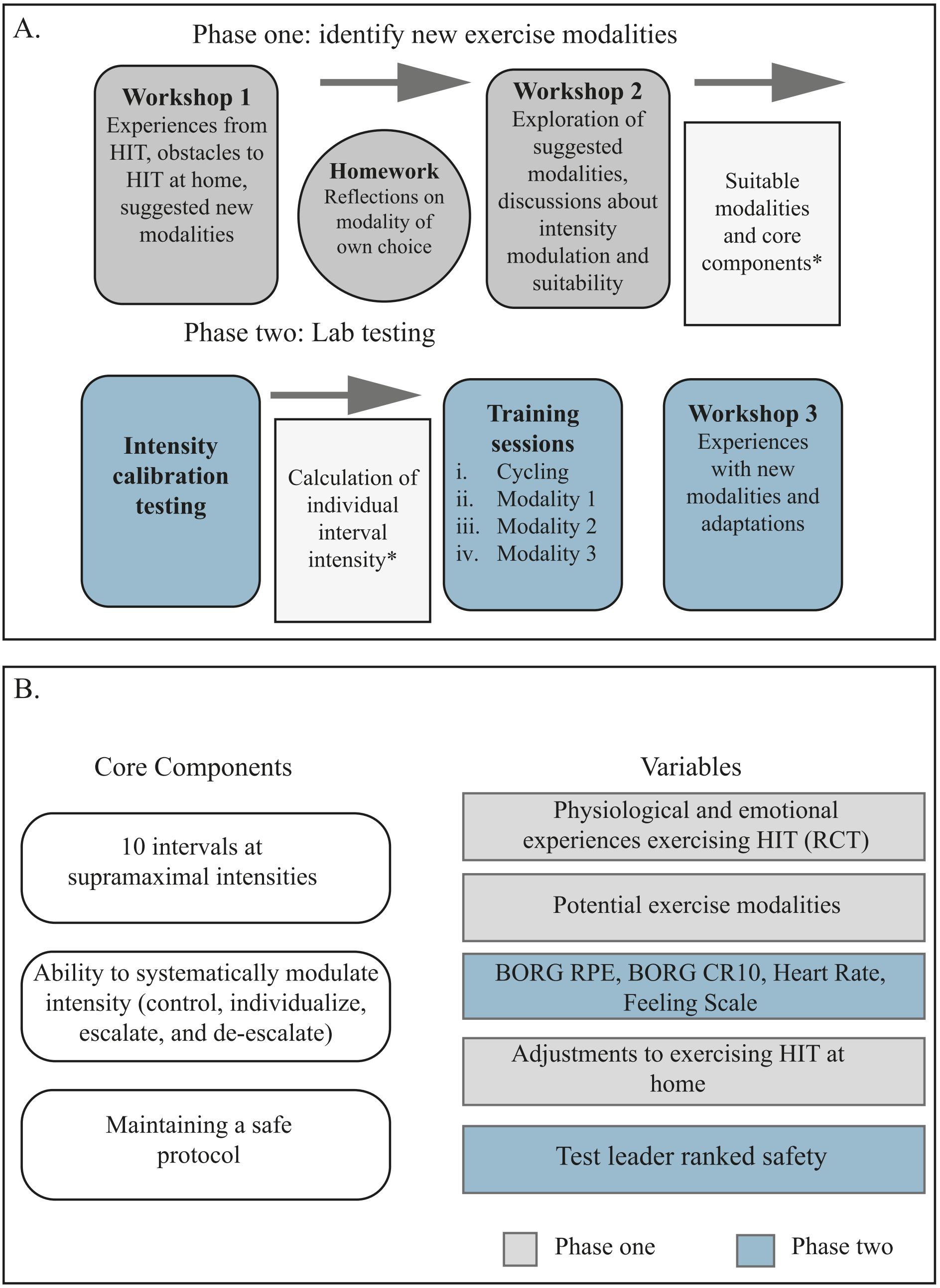

*Figure 4. Umeå HIT-home study. A) Study flow with different phases. * depicts steps where researchers worked independently from co-creators. B) Core components and study variables. Gray indicates phase one and blue indicates phase two. Abbreviations: CR10 = category ratio 10; HIT = high intensity interval training; RCT = randomized controlled trial; RPE = ratings of perceived exertion.*

Phase one: For phase one, two workshops were conducted, aimed at identifying physiological symptoms and emotional responses during the supramaximal HIT sessions from the Umeå HIT RCT, suggested alternative modalities, including ideas about how to modulate intensity, as well as suggested adjustments to the protocol when exercising at home. During the first workshop, these themes were discussed, and during the second workshop several of the suggested modalities were physically explored and discussed at a series of different stations, overseen by facilitators (five researchers from the interdisciplinary research team). Each station included 1-3 suggested modalities, and participants conducted a few slow repetitions of each modality they felt comfortable trying, for example conducting a few controlled lunges. They were explicitly asked not to exert themselves or take any risks and were reminded not to try any activity they were uncomfortable with. Discussions focused upon intensity modulation, safety, and adaptations needed to increase accessibility. Facilitators oversaw both workshops. Modalities and protocol adaptations that were considered promising by co-creators and workshop facilitators were brought to the entire interdisciplinary research group for discussion regarding how well they fit with the protocol's core components.

Phase two: Laboratory testing was conducted in the Umeå Movement and Exercise laboratory, and each co-creator conducted one intensity calibration test and one supramaximal HIT session per exercise modality, including for stationary bicycling.

The intensity calibration test was conducted to determine interval intensity. In line with the method for intensity prescription during the Umeå HIT RCT, a Borg Cycle Strength Test (Borg, 1982) was used to calculate individual interval intensity for cycling. The individual interval intensity was set to the highest completed power level, which corresponds approximately to 70% of estimated maximal power for short efforts to match the duration of the 10-second intervals. For the modalities selected from phase one, the intensity calibration tests included three 30-second self-paced trials, and participants were instructed to exert themselves at approximately 50, 75, and 100% of their perceived maximal effort. There were two minutes of rest between each trial, and the intensity calibration test method was designed to mimic the Borg Cycle Strength Test, with intensity increased in steps. The maximum trial (max30) was used to calculate interval intensity, with the number of repetitions completed recalculated into repetitions per minute and then used as the prescribed intensity for 10 second intervals. Two modalities were tested per laboratory visit for the intensity calibration testing, with a minimum of 30 minutes of rest between each modality.

Next, co-creators conducted one training session per exercise modality, including stationary bicycling. The training sessions included a warm-up, and then 10 x 10 second intervals with 50 seconds of recovery between. The individualized interval intensity was prescribed based on the intensity calibration testing described above. For non-cycling modalities, an audio metronome was used to control the repetitions per minute for intervals. Each modality was tested on a separate day and there was a minimum of one day recovery between training sessions.

Variables

Adverse events from the Umeå HIT RCT were collected twice during each exercise session; once at the beginning of the session, wherein any discomfort experienced during or after the previous exercise session was reported, and once at the end, wherein any discomfort experienced during the current exercise session was reported. Based on the symptom descriptions the adverse events were categorized and then reviewed by external reviewers who weren't involved in the study, who assessed whether an adverse event fulfilled the criteria for a serious adverse event. Serious adverse events were defined as any event resulting in death; risk of death; hospitalization; disability or permanent damage; or requiring an intervention to prevent permanent impairment, damage, or other medical events (ICH, 2016). Cases wherein participants had discontinued the exercise intervention or withdrawn from the study were also reviewed to assess whether the case was related to the intervention, and if so, if it was a serious adverse event. The external reviewers – one medical doctor and one sports medicine researcher – assessed each event individually and then discussed their assessments to reach consensus.

For protocol adaptation during the Umeå HIT-Home study, data from phase one consisted of audio recordings, photographs of whiteboard notes, and workshop moderator notes. For phase two (lab testing), data consisted of Borg's RPE scale, Borg's Category Ration 10 (CR10) scale (Borg, 1998) for leg and arm-fatigue, hear rate (HR), FS (Hardy & Rejeski, 1989), and test-leader assessed safety ranked 1-3, with 1) the ability to perform the modality completely safely without supervision, 2) showing moderate problems maintaining safety, and 3) the modality being unsafe (e.g. losing one's balance).

Data synthesis

Adverse events from the Umeå RCT were summarized descriptively in categories and number of events and disclosed for each exercise group (supramaximal HIT/MIT).

Phase one data from the Umeå Home Study was sorted into the same content areas as questions asked during the workshop, namely *Physiological and emotional experiences when exercising supramaximal HIT, Potential exercise modalities*, and *Adjustments to Exercising HIT at home*. Following each workshop, two workshop facilitators summarized results jointly, and checked findings against other facilitator experiences to make sure nothing was missed. Summaries were also reiterated with co-creators at the beginning of each workshop. Phase one content was summarized descriptively, and was illustrated with co-creator quotes from the workshops.

Prior to phase two, the results were brought to the entire interdisciplinary research team to discuss how results could be integrated with core components, i.e., whether the suggested modalities could be conducted as 10 controlled supramaximal intervals, intensity could be modulated, and whether the suggested modalities were considered safe.

For phase two, outcomes were analyzed descriptively, with mean and standard deviations of session peak values for HR, Borgs RPE, Borg's CR10, and FS reported for different exercise modalities. Furthermore, data distributions of change within each session for HR, Borgs RPE, Borg's CR10, and FS are depicted in boxplots to illustrate subjective- and objective measures of intensity across each exercise session.

Following phase two testing, lab-results were integrated with core components in the interdisciplinary research team. Acute physiological responses were compared, safety rankings were discussed, and one modality was selected by the research team and iterated with co-creators for future adaptation and development. These findings were reiterated and discussed with co-creators in a final workshop for further feedback.

Results

Aim one: Exercise Effects

In *Paper I*, no significant group x time interactions were found for VO_2peak, systolic blood pressure, or diastolic blood pressure, see Table 4 for LMM estimates and Figure 5 for individual- and group change. For maximal isometric leg extensor strength, a significant group x time interaction was found in favor of supramaximal HIT, and supramaximal HIT also showed a significant within-group change. Overall, both groups improved in VO_2peak (mean = 1.38 mL/kg/min, 95% CI [0.77, 1.98]), systolic blood pressure (mean = -2.09 mmHg, 95% CI [-3.54, -0.64]), and diastolic blood pressure (mean = -1.27 mmHg, 95% CI [-2.31, -0.25]).

For global cognitive function there was no group x time interaction or change irrespective of group.

A significant group x time interaction in the WM composite was found in favor of supramaximal HIT, see Table 4. Supramaximal HIT did not show a within-group increase in the WM composite.

For in-scanner WM manipulation performance there was no group x time interaction or change irrespective of group.

For health-related quality of life there was no group x time interaction or change irrespective of group.

For WM functional activity, no significant group x time effects were found in the PFC. A significant group x time interaction was found in the right putamen (X = 24, Y = 20, Z = 2, number of voxels = 10, Ze = 3.22, $p < .001$, uncorrected), with HIT decreasing functional activity and MIT increasing. Both groups increased functional activity in the right cerebellum (X = 38, Y = -60, Z = -38, number of voxels = 27, Ze = 3.67, $p < .001$, uncorrected). Change in these areas was not related to change to in-scanner performance manipulation (right putamen: $r(36) = -0.05$, $p = .763$; right cerebellum $r(36) = -0.02$, $p = 0.920$).

Table 4. Within-group change and group x time interactions from baseline to follow-up										
	Within-group change						Group x time interactions			
	Supramaximal HIT			MIT						
	No.[a]	Mean	SE	No.[a]	Mean	SE	Mean	[95% CI]	P	ES
VO2peak (mL/kg/min)	34/30	1.40	0.44	34/32	1.36	0.43	0.05	[-1.17, 1.25]	.940	0.019
Blood pressure										
Systolic (mmHg)	30/27	-1.95	1.06	29/27	-2.21	1.05	0.27	[-2.63, 3.16]	.860	0.049
Diastolic (mmHg)	30/27	-1.54	0.75	29/27	-1.02	0.75	-0.53	[-2.58, 1.52]	.621	-0.122
Isometric leg extensor strength	34/31	0.07	0.02	34/31	-0.004	0.02	0.07	[0.003, 0.14]	.045	0.517
Global cognitive function	34/30	0.07	0.05	34/29	-0.04	0.05	0.11	[-0.03, 0.24]	.134	0.395
Working memory composite	34/30	0.20	0.12	34/32	-0.12	0.11	0.32	[0.01, 0.64]	.052	0.500
In-scanner manipulation[b]	21/16	0.39	0.39	21/20	0.06	0.36	0.33	[-0.69, 1.38]	.53	0.21
Quality of life (SF-36)	34/32	-1.48	2.11	33/30	1.44	2.18	-2.92	[-8.85, 3.04]	.339	-0.242

Notes: For cognitive measures, estimates of mean change from linear mixed-effects models were adjusted for age, sex, and education as fixed effects and individual as random effect. For all other outcomes, models were adjusted for age and sex as fixed effects and individual as a random effect. Data are reported as linear mixed-effects model-estimated mean change with standard error (SE) for within-group change and 95% confidence intervals (CI) for group x time interactions. Effect size (ES) was calculated based on the model estimated between-group differences in mean change and the unadjusted pooled standard deviation. Abbreviations: HIT = high intensity interval training; MIT = moderate intensity training; SF-36 = Swedish Short Form Health Survey-36; VO_2peak = Peak oxygen uptake.

[a] No. (number) of available measurements at baseline and follow-up presented as baseline/follow-up.

[b] analyses on MRI subsample.

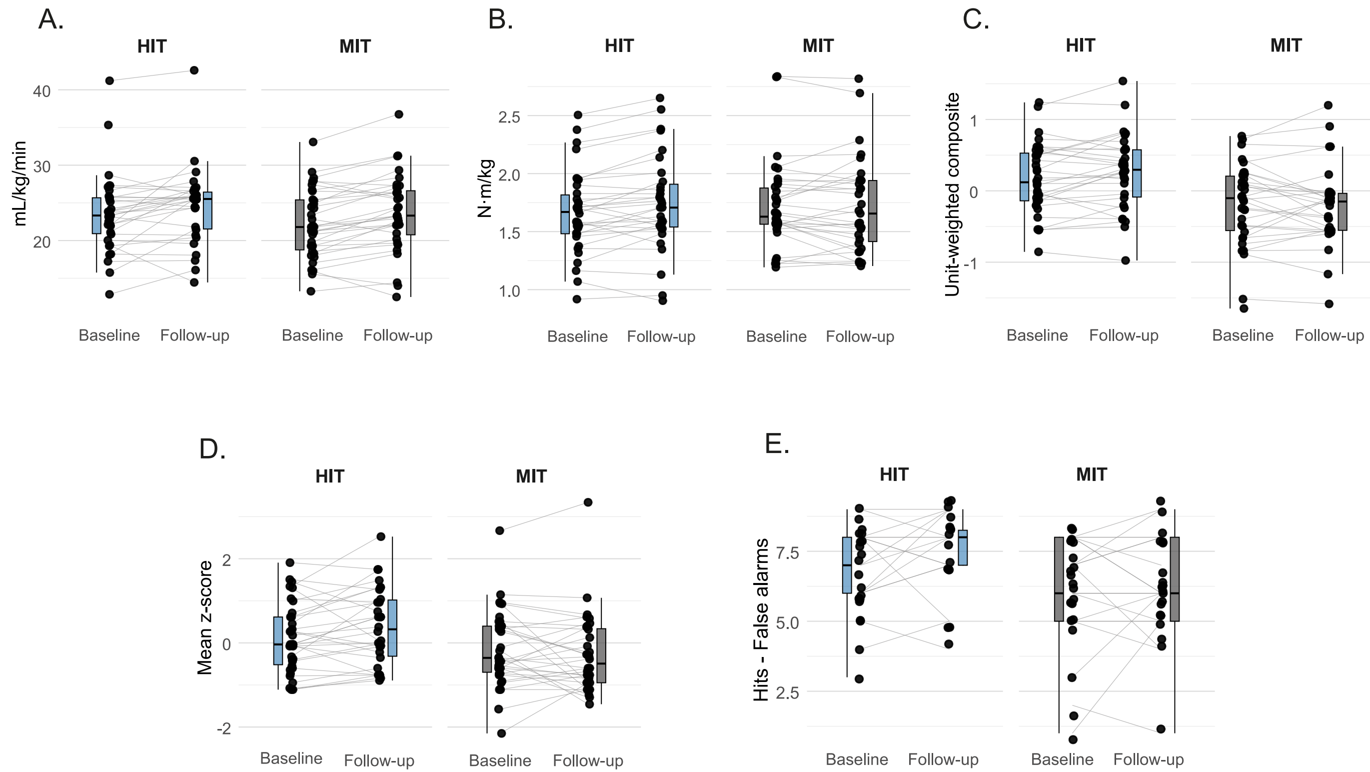

Figure 5. Individual- and group change for supramaximal HIT and MIT. A. Peak oxygen uptake. B. Isometric leg extensor strength. C. Global cognitive function. D. Working memory performance. E. In-scanner working memory performance. Abbreviations: HIT = high intensity interval training. MIT = moderate intensity training.

Aim two: Individual differences

Baseline characteristics

When testing if baseline fitness measures VO_2peak and isometric leg extensor strength were related to ΔWM performance, the overall model was not significant, $F(6, 55) = 1.38$, $p = .238$. The predictors as a set did not reliably explain variance in ΔWM (r^2adj = .04). In the model there was a significant positive association between baseline VO_2peak and ΔWM (β = 0.23, SE = 0.13, t(55) = 1.80, 95% CIs [0.02, 0.50]). Higher CRF at baseline may be linked to larger WM improvements, see Figure 6 and Table 5. This relationship did not differ by group (group x VO_2peak interaction: β = -0.08, SE = 0.17, t(54) = -0.46, 95% CI [-0.41, 0.16]).

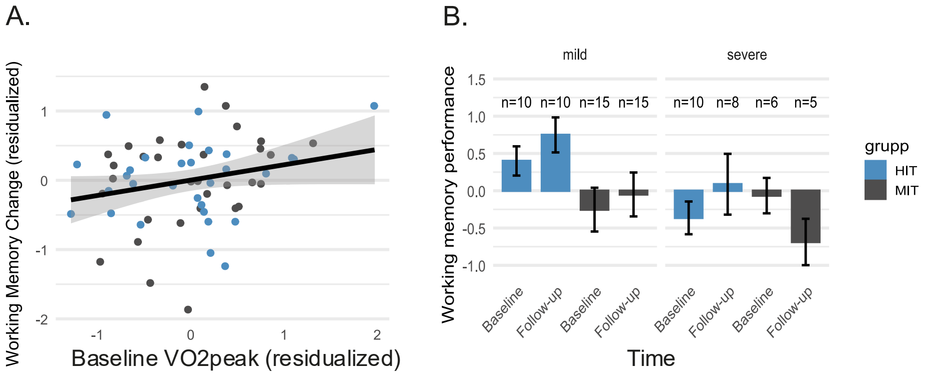

Figure 6. Baseline characteristics and working memory performance. A. Baseline peak oxygen uptake related to working memory change. B. Baseline periventricular lesion load and working memory performance by lesion load severity and group. Supramaximal HIT in blue and MIT in gray. Abbreviations: HIT = high intensity interval training; MIT = moderate intensity training; VO_2peak = peak oxygen uptake.

For baseline periventricular lesion load severity, a significant three-way interaction was found between time, group, and baseline periventricular lesion load severity (MD = -0.78, SE = 0.38, 95% CI [-1.51, -0.06]). This indicated that WM response differed depending on group and baseline periventricular lesion load severity. Simple effects analyses revealed that for severe periventricular lesion load, supramaximal HIT members significantly increased performance from baseline to follow-up (95% CI [0.02, 0.80]) while MIT members significantly decreased (95% CI [-1.02, -0.02]), see Table 6 for within-group change by severity load. For mild periventricular lesions, supramaximal HIT showed a trend towards a significant increase (95% CI [-0.00, 0.70]) while there was no change in the MIT group with mild periventricular lesions (95% CI [-0.09, 0.49]). See Figure 6 for differences between groups and severity levels.

For deep white matter lesions, there was no significant three-way interaction (MD = -0.40, SE = 0.44, 95% CI [-1.22, 0.43]).

Table 5. Baseline- and change variables in relation to Δ working memory

	Estimate	95% CI (BCa)
Baseline fitness		
Age	-0.04	[-0.26, 0.14]
Sex (Male)	-0.07	[-0.45, 0.35]
Group(MIT)	-0.21	[-0.54, 0.11]
Education	0.01	[-0.17, 0.20]
VO_2peak	0.23	[0.02, 0.50]
Isometric leg extensor strength	-0.10	[-0.41, 0.13]
Fitness change		
Age	-0.10	[-0.25, 0.06]
Sex (Male)	-0.19	[-0.54, 0.11]
Group (MIT)	-0.17	[-0.46, 0.18]
Education	0.01	[-0.17, 0.18]
ΔVO_2peak	-0.09	[-0.27, 0.11]
Δisometric leg extensor strength	0.24	[0.09, 0.44]
Myokine change		
Age	-0.15	[-0.33, 0.00]
Sex	-0.05	[-0.39, 0.26]
Group	-0.41	[-0.78, -0.08]
Education	0.03	[-0.15, 0.20]
ΔBDNF	0.27	[0.07, 0.51]
ΔIGF-1	0.01	[-0.15, 0.15]
ΔVEGF	-0.18	[-0.37, -0.02]

Notes: continuous variables are standardized. Abbreviations: Δ = change; BCa = bias-corrected and accelerated intervals.

Table 6. Within-group differences in change in working memory by severity load								
	Supramaxial HIT				MIT			
	No.	Mean	SE	ES	No.	Mean	SE	ES
Periventricular								
Mild	10/10	0.35	0.17	0.90	15/15	0.20	0.14	0.52
Severe	10/8	0.41	0.19	1.05	6/5	-0.52	0.25	-1.34
Deep white matter								
Mild	13/12	0.37	0.17	0.89	16/16	0.10	0.15	0.24
Severe	7/6	0.39	0.24	0.95	5/4	-0.27	0.29	-0.65
Abbreviations: ES = effect size; HIT = high intensity interval training; MIT = moderate intensity training; No. = number of participants contributing to baseline / follow-up; SE = standard error.								

CRF-hypothesis

When testing the CRF-hypothesis on WM manipulation functional activity, ΔVO_2peak was not related to change in functional activity irrespective of exercise group (*Paper II*).

Next, the hypothesis that change in the fitness measure isometric leg extensor strength was positively related to change in PFC WM functional activity for the supramaximal HIT group was tested. Here, Δisometric leg extensor strength was positively related to change in functional activity in the right DLPFC (X = 48, Y = 24, Z = 40, number of voxels = 32, Ze = 3.89, $p < .001$) when controlling for age, sex, and education years ($F(4, 11) = 7.26$, $p = 0.005$) and explained 63% of the variance in functional activity change (r^2adj = 0.63). Δisometric leg strength was significantly related to ΔDLPFC functional activity ($\beta = 0.87$, SE = 0.32, $t(11) = 2.67$, $p = .022$), while age ($\beta = 0.01$, SE = 0.02, $t(11) = 0.83$, $p = 0.43$), sex ($\beta = 0.13$, SE = 0.08, $t(11) = 1.64$, $p = 0.13$), and education years ($\beta = -0.01$, SE = 0.01, $t(11) = -0.89$, $p = 0.39$) were not, see Figure 7 for significant area in DLPFC.

Change to right DLPFC functional activity was in turn positively related to ΔWM in-scanner performance when controlling for age, sex, and education years ($F(4, 11) = 3.40$, $p = .05$), explaining approximately 39% of the variance in performance change (r^2adj = 0.39). In the model, Δright DLPFC functional activity was significantly positively related to change to ΔWM in-scanner performance ($\beta = 4.08$, SE = 1.36, $t(11) = 3.00$, $p = .012$), see Figure 7, while age ($\beta = 0.27$, SE = 0.15, $t(11) = 1.85$,

p = .09), sex (β = −0.51, SE = 0.68, t(11) = -0.74, p = 0.47), and education years (β = 0.02, SE = 0.13, t(11) = 0.19, p = .85) did not.

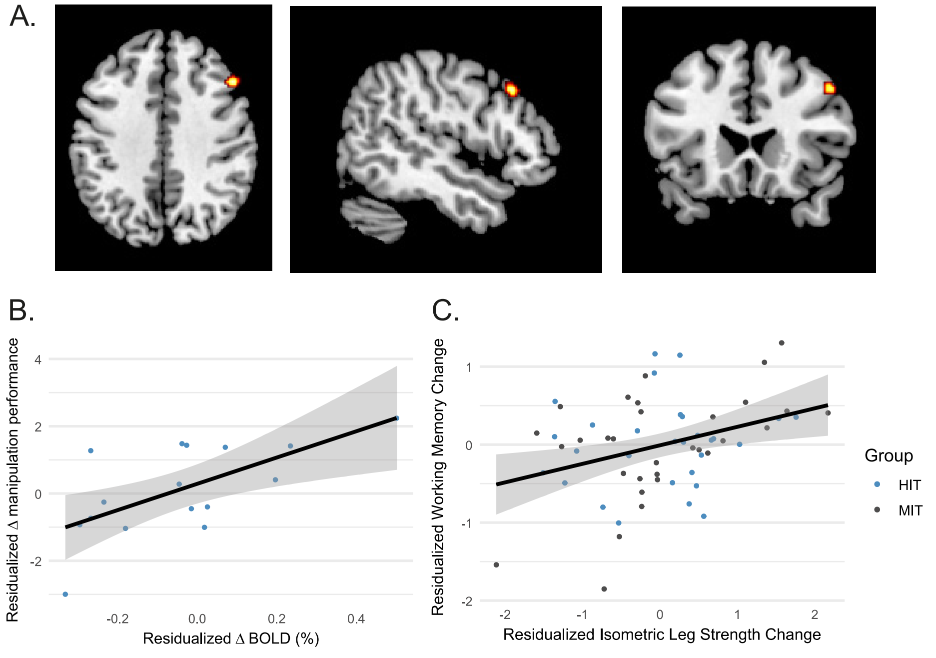

Figure 7. Fitness changes related to working memory change. A) Isometric leg extensor strength positively related to right dorsolateral prefrontal cortex activation in supramaximal HIT. Significant cluster is highlighted and overlaid on ch2better.Nii.Gz template using MRIcron. B) Increased dorsolateral prefrontal cortex activation related to increased in-scanner working memory performance in supramaximal HIT. C) Isometric leg extensor strength related to working memory performance change irrespective of group. Figures A. and B. adapted from Sandstrom et al. (2025). Supramaximal HIT in blue and MIT in gray. Abbreviations: BOLD = blood oxygen level dependent; HIT = high intensity interval training; MIT = moderate intensity training.

In *Paper III*, the CRF-hypothesis was tested on the entire sample with ΔWM performance as the outcome of interest. The model, which included ΔVO_2peak, Δisometric leg extensor strength, sex, age, education, and group allocation (supramaximal HIT/MIT) was not significant (F(6, 53) = 2.21, p = .056, r^2adj = 0.11). Δisometric leg extensor strength was positively related to ΔWM performance (β = 0.24, SE = 0.09, t(53) = 2.72, 95% CIs [0.09, 0.44]), while other predictors were not significant. A post-hoc analysis revealed this relationship was independent of group allocation (group x Δisometric leg extensor strength interaction: β = 0.29, SE = 0.17, t(52) = 1.71, 95% CI [-0.12, 0.25]).

Myokine hypothesis

When testing the myokine hypothesis on ΔWM performance , the overall model, which included ΔBDNF, ΔIGF-1, and ΔVEGF was not significant (F(7, 54) = 1.71, *p* = .126, r^2adj = 0.13), while group (MIT) (β= -0.41, SE = 0.17, t(54) = -2.43, 95% CI [-0.78, -0.08]), ΔBDNF (β = 0.27, SE = 0.11, t(54) = 2.55, 95% CI [0.07, 0.51]), and ΔVEGF (β = -0.18, SE = 0.10, t(54) = -1.80, 95% CI [-0.37, -0.02]) were significant predictors. A post-hoc analysis revealed that the negative relationship between ΔVEGF and ΔWM performance was independent of group allocation (β = -0.06, SE = 0.20, t(52) = -0.30, 95% CI [-0.64, 0.19]), while there was a significant group x ΔBDNF interaction in relation to ΔWM performance (β = 0.50, SE = 0.22, t(52) = 2.29, 95% CI [0.17, 0.99]), suggesting the relationship was stronger in the MIT group. See Figure 8 for myokine findings.

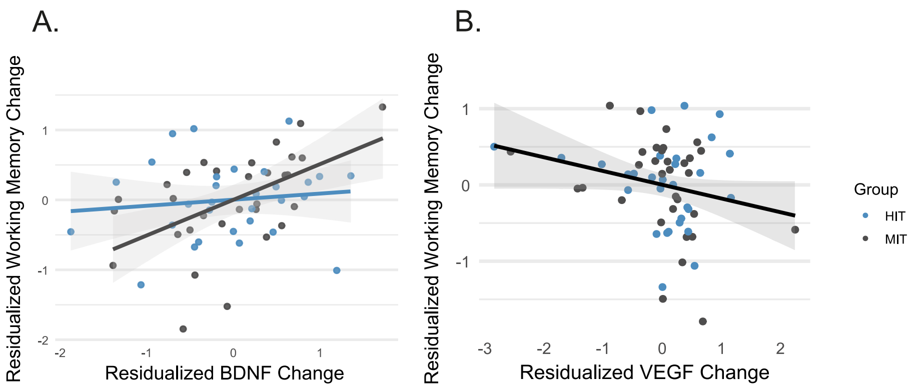

Figure 8. Myokine changes related to working memory performance change. A) Upregulated brain-derived neurotrophic factor (BDNF) related to increased working memory performance, with a significant group x BDNF interaction. B) Decreased vascular endothelial growth factor related to increased working memory performance in both groups. Supramaximal HIT in blue and MIT in gray. Abbreviations: BDNF = brain-derived neurotrophic factor; HIT = high intensity interval training; MIT = moderate intensity training; VEGF = vascular endothelial growth factor.

Aim three: Adapt findings

Adverse events

In total, 146 adverse events were reported, 52 of which were in HIT (36%) and 94 in MIT (64%), and none of the adverse events were considered serious adverse events as evaluated by external reviewers. Participants reported discomfort since the previous training session in 83 of the total 1497 sessions attended, which indicated a rate of 5.5%. For discomfort experienced during the current training session, 63 adverse events were reported, corresponding to 4.2% of all training sessions. Table 7 depicts the number of different events reported sorted by category for HIT and MIT.

Table 7. Adverse events by category in HIT and MIT

Category	HIT	MIT	Total
Musculoskeletal	39 (18/34)	63 (25/34)	102
Respiratory/circulation	3 (3/34)	4 (3/34)	7
Psychological/general vitality	1 (1/34)	7 (6/34)	8
Illness	0 (0/34)	3 (3/34)	3
Equipment related	3 (3/34)	13 (11/34)	16
Multiple reasons	1 (1/34)	0 (0/34)	1
Session-induced effects	3 (3/34)	4 (4/34)	7
Unspecified	2 (2/34)	0 (0/34)	2
Total	52	94	146

Notes: Events are depicted as session-level occurrences, i.e., total number of occurrences. Participant counts (in parentheses) indicate the number of unique participants (n) who experienced at least one event in each category out of the total number of participants in the category (N). Participant counts are not summed across categories as one individual may have events in multiple categories.

Protocol adaptation: Phase one

For phase one of the Umeå HIT-Home study, results were summarized into three categories*: Physiological and emotional experiences when exercising supramaximal HIT*; *Potential Exercise modalities*; and *Adjustments to exercising HIT at home*, and all can be found in Figure 9.

For *Physiological and Emotional Experiences Exercising HIT*, both positive and negative experiences were described. Positive experiences included being out of breath, feeling lactic acid in one's legs, being completely focused upon the exercise, and feeling that the session felt easy due to the short duration of each interval. However, co-creators also described experiencing stress due to the numerous bicycle brake adjustments during the session, as well as pain in their hands.

All *Potential Exercise Modalities* can be found in Figure 9. For each modality, intensity modulation was discussed, such as adjusting speed, incline, size of the movement, number of different body parts involved or adding weight. For some modalities, no solution to intensity modulation was found. Discussions also focused on availability aspects such as modalities not being outdoors, or weather-, or equipment-dependent, and that the modality should work for a wide range of people with common physical limitations, such as balance issues or sore knees.

For *Adjustments to Exercising HIT at Home*, several potential changes were discussed, and a list can be found in Figure 9.

Integrating phase one results with core components: As indicated by Figure 9, the three modalities that co-creators considered most promising were chair stand, home cross-country skiing (XC), and walking up steps. For chair stand, co-creators repeatedly stood up and sat down from a chair. For home XC, an exercise rubber band was fastened over a door frame, and participants held one end in each hand, pulling downwards and upwards repeatedly with their entire upper body, using cross-country skiing double poling technique. For walking up steps, co-creators climbed a staircase. These modalities were considered promising by the interdisciplinary research team. All three had the potential of eliciting acute physiological responses similar to supramaximal HIT on a stationary bicycle with intensity that could be modulated using a metronome. Furthermore, the interdisciplinary research team had experience prescribing similar exercises to older adults and had found them to be safe.

Physiological and emotional experiences exercising HIT (RCT)

"It was exhausing, I was out of breath, and that means my heart and lungs were working. But it felt very nice afterwards, it passed quickly."

"It [the training session] was incredibly easy, I was barely sweating. But that highest intensity, it was hard, you could barely complete it. But it was very short."

"But I also thought it was stressful, because you were trying to make the adjustments correctly. The only thing I was thinking about was to turn the knob at the right time."

Potential exercise modalities

Suggested exercise modality	Comments on advantages and challanges	Phase two?
Jumping in place or with jump rope	Sore knees, hips, ankles. Balance issues	No
Running, Nordic walking	Sore knees, hips. Weather- and season dependent	No
Walking	Not HIT	No
Chair Stand	Promising	Yes
Squats, lunges	Balance issues, especially lunges	No
Cross-country skiing	Weather-, season, and equipment-dependent	No
Home XC	Promising	Yes
Housework and yardwork	Not everyone has a yard	No
Yoga, stretching, and toning	No solutions for intensity modulation, not HIT?	No
Biking upphill	Season- and equipment dependent	No
Step-up board	Step-up board caused balance issues	No
Walking up steps	Promising	Yes

Adjustments to exercising HIT at home

"I think the problem is the timing. Because you get fixated upon it. One would need somebody on the side to tell you... Or to help you... Or an app. I can't both take the time and do the movement."

"That is why you don't see any results just from going on your walks. You don't push yourself, and you don't have anybody to push you."

Suggested adjustments:

- Help keeping track of time
- Using an app
- Having a cue to push yourself (metronome?)
- Extending intervals to 10 s

Figure 9. Phase one findings. Abbreviations: HIT = high intensity interval training; Home XC =indoor cross-country skiing double-poling using a rubber band; RCT = randomized controlled trial.

Protocol adaptation: Phase two

Phase two testing revealed that chair stand and walking up steps both elicited acute physiological responses that resembled exercise on a stationary bicycle with regards to interval HR, interval RPE, interval CR10, interval FS, and max RPE, see figure 10 and table 7. However, home XC did not elicit a similar interval HR, interval RPE, and max RPE to stationary bicycling, indicating intensities below supramaximal HIT.

Test-leader safety rankings indicated that walking up steps received two incidents of level 2) safety rankings, i.e., co-creators showing signs of problems maintaining safety when performing the modality.

Table 8. Physiological Responses for Potential Modalities and Cycling

	Waking up steps	Chair Stand	Home XC	Stationary bicycle
Max HR	130.7 (12.4)	114.7 (12.4)	114.3 (11.5)	121.7 (12.4)
Max RPE	15 (1)	15 (1.5)	13.4 (1.5)	14.9 (1.1)
Session RPE	14.3 (1.1)	14.1 (0.9)	12.7 (2.1	13.7 (0.8)

Notes: Values are depicted as mean (standard deviation).

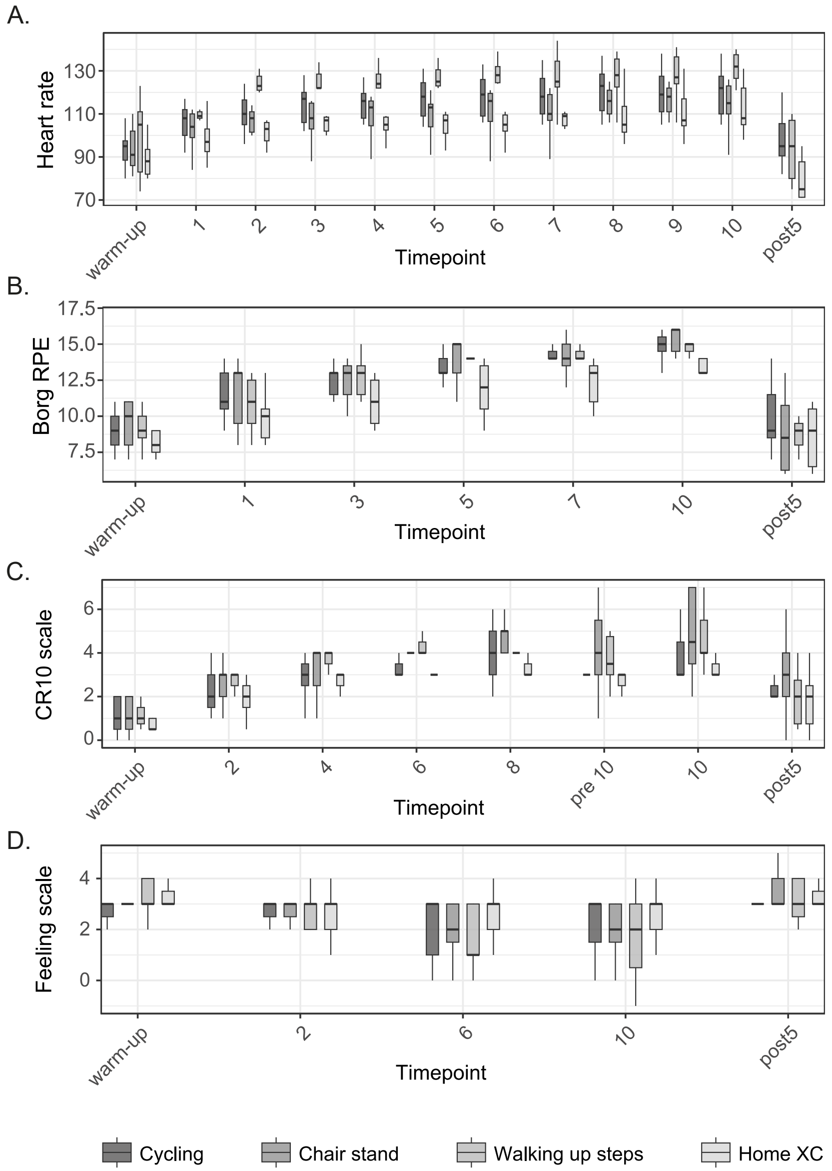

Figure 10. Phase two findings on acute physiological responses by exercise modality. A) Heart rate. B) Borg's ratings of perceived exertion. C) Borg's category ratio 10 scale. D) Feeling scale. Each plot depicts warm-up, interval measurements (digits depict which interval), and five-minutes post exercise. Abbreviations: CR10 = category ratio 10; post5 = five minutes post exercise; pre 10 = measurement timepoint during recovery between interval 9 and 10; RPE = ratings of perceived exertion.

Co-creators experienced all three alternative modalities as enjoyable. For home XC, they liked using their upper body, however they found it far less exhausting than exercise on a stationary bicycle and had issues correctly adjusting the rubber bands. For walking up steps, they found it physiologically exhausting, however they also expressed safety concerns, as well as concerns about the availability of tall staircases. For chair stand, they appreciated the simple instructions, how efficient the session was, and that the movement itself felt good. However, most co-creators had experienced muscle soreness the days following the exercise trial, and while they weren't bothered by it, they believed future end-users should be notified about side effects.

> *"I thought that [Chair Stand] was a nice movement. And then you get sweaty and a high heart rate, and something happens in your whole body. My legs were completely gone, I was sore for three days."*

In addition, co-creators expressed a need to have the metronome built into a mobile application.

Integrating phase two results with core components: Phase two results indicated that home XC did not elicit acute physiological responses similar to supramaximal HIT on a stationary bicycle and was therefore not considered in line with core components. Walking up steps did not fulfill core components either due to safety concerns. Furthermore, a few co-creators required more stairs than expected, which also became a limiting factor due to a lack of available tall buildings. Meanwhile, chair stand fulfilled all core components and was considered promising for further development.

Discussion

Key findings

Aim one: Twelve weeks of controlled supramaximal HIT resulted in similar- to superior physiological effects compared to MIT, and while a significant group by time interaction was found for WM performance in favor of supramaximal HIT, exercise effects to global cognitive function were not found.

Aim two: Individual differences in exercise-response to WM were further studied in relation to baseline characteristics as well as change to fitness- and myokine markers, in line with mechanisms proposed in the CRF- and myokine hypotheses. Regarding baseline characteristics, pre-existing periventricular lesion load severity moderated the effect of intervention group on WM performance, with supramaximal HIT increasing WM performance despite severe lesions at baseline, while MIT decreased significantly. Baseline CRF was positively related to WM change irrespective of group. For fitness change factors, leg strength gains emerged as a promising fitness factor. First, increased leg strength was related to increased DLPFC functional activity in supramaximal HIT, which were in turn positively related to in-scanner performance. Furthermore, leg strength gains was related to increased performance in the broader WM composite for both groups. Of the myokines assessed, upregulated BDNF was related to improved WM performance, but differed by group, indicating the relationship may be stronger in MIT. Surprisingly, VEGF was negatively related to WM improvements in both exercise groups.

Aim three: No serious adverse events occurred, and supramaximal HIT had fewer adverse events compared to MIT. This indicated that supramaximal HIT is a time-efficient, effective, and a safe exercise option for older adults. The protocol was subsequently adapted through a co-creation study, wherein a metronome-controlled supramaximal chair stand HIT protocol was developed for future home-use.

Exercise effects of supramaximal HIT and MIT

Physiological adaptations

The overall increase in CRF irrespective of group is encouraging, given the importance of CRF in relation to present and future health status, morbidity, and mortality (Ekblom-Bak et al., 2019; Kodama et al., 2009; Kokkinos et al., 2023), especially considering that supramaximal HIT exercised half the amount of time. Given previous findings that an increase of 1 ml/kg/min has been considered clinically meaningful (Kavanagh et al., 2003), the current study's finding that participants increased with 1.38 mL/kg/min irrespective of group is promising. The average overall increase was 5.9%, which goes against the age-expected decline. CRF decline has been found to accelerate from approximately 5% per decade from age 30 to over 20% per decade at 70 years and beyond (Fleg et al., 2005), and with only three months of twice-weekly exercise, both groups reversed the equivalent of approximately three years of expected decline. For supramaximal HIT, this was done with only 40 minutes of exercise per week. Meanwhile, the hypothesized between-group difference in effect was not found, which may be due to the exercise groups not being load-matched, as research on younger adults indicate similar findings (Bonafiglia et al., 2022). In this sense, supramaximal HIT may be seen as a time-efficient alternative to MIT, rather than an exercise form leading to superior CRF gains.

Blood pressure improved in both groups, despite untreated hypertension being an exclusion criterion, i.e., this was not a group that was in need of improved blood pressure. However, the overall decrease in systolic blood pressure of 2.09 mmHg is encouraging, considering a decrease of 2mmHg is clinically meaningful, for example being related to a 10% lower stroke mortality (Cormick et al., 2022). Hypertension is a modifiable risk factor contributing to cardiovascular disease (Yusuf et al., 2020) and dementia (Livingston et al., 2024). Findings further indicate a dose-dependent relationship between increased systolic blood pressure and increases in white matter lesions (Alateeq et al., 2021), as well as decreased cognitive function, making these findings particularly interesting in the context of neurocognitive aging, indicating potential for disease prevention. However, with regards to cognitive decline, it may be midlife hypertension that best predicts subsequent cognitive decline (Ding et al., 2023), indicating a population that also is important to target in future research aimed at decreasing cognitive decline with exercise. Whether similar improvements can be found in clinical groups, such as patients with hypertension, remains to be seen.

One area where supramaximal HIT saw superior gains compared to MIT was leg strength. The 4% within-group increase in supramaximal HIT can be contrasted to an expected annual decline of 3-4% (Goodpaster et al., 2006). Despite the promising increase in leg strength, it is still inferior to effects following resistance training for the same amount of time (Marzuca-Nassr et al., 2024), and supramaximal HIT is therefore not suggested to be an alternative to resistance training among older adults. However, in the context of aging, this result is important, as maintained lower limb strength helps mitigate falls, which are one of the most common reasons for hospitalization among older adults (Montero-Odasso et al., 2022). Furthermore, lower limb strength is important for maintaining mobility (Hicks et al., 2012). Finding exercise forms that help maintain lower limb strength is important, and here supramaximal HIT is a promising candidate, targeting both cardiorespiratory, cardiovascular, and muscular function.

Taken together, physiological adaptations to supramaximal HIT resemble previous findings on younger adults (Liang et al., 2024; Wiens et al., 2025). HIT may provide similar cardiorespiratory and cardiovascular benefits as aerobic exercise, while providing increased benefits with regards to muscle strength. These adaptations are clinically meaningful with the potential of having a positive impact on older adults' daily lives (Wang et al., 2020). It seems controlled supramaximal HIT works similarly in older adults as younger and is therefore an important addition to the menu of exercise options for older adults.

Neurocognitive adaptations

Exercise-effects to cognitive functions were not as clear as physiological effects. While a group x time interaction was found on WM performance in favor of HIT, global cognitive function did not change in either group, which was not in line with the study's hypothesized effect.

The global cognitive score was a composite of multiple tasks, tapping into several tasks across numerous domains. This offers a more robust measure compared to common screening tools often used in the field (e.g., MMSE) and reduces measurement error (Jonaitis et al., 2019). However, such a composite also aggregates the performance of many different cognitive processes and is therefore less sensitive to early and/or domain-specific change. Questions remain as to whether exercise effects are the largest for global measures of cognition or for subdomains, as well as the timing and magnitude of change in different domains. Early research in the exercise-cognition field indicated that cognitive domains such as executive functions and WM were particularly sensitive to exercise-induced change (Colcombe & Kramer, 2003; Erickson & Kramer, 2009), with effects to WM increasing in strength with age (Smith et al., 2010). Meanwhile, a recent meta-meta-analysis confirmed larger effect sizes for general cognition compared to executive functions (including WM) (Singh et al., 2025); however, general cognition was based on the measures MMSE, MoCA, and Alzheimer's Disease Assessment Scale. These types of screening tests don't capture variability in healthy populations, and therefore are vulnerable to practice effects (Cooley et al., 2015) and ceiling effects (Franco-Marina et al., 2010). Others have found that WM and executive functions are particularly sensitive to change (Barha et al., 2017; Northey et al., 2018; Zhidong et al., 2021), and have proposed that WM may be a task-general component that is particularly important to target with exercise, as it may benefit other cognitive domains (Voss & Jain, 2022). In consideration of this, our rather short exercise intervention with an arguably low dose of exercise may indicate early sensitivity to WM improvements, while a larger exercise dose may have been necessary for such improvements to generalize to global gains. Future studies should consider assessing temporal differences in change for different cognitive domains to further examine which cognitive domains show early effects, and how domains affected early might relate to subsequent cognitive gains.

Our lack of effect to global cognitive function may also need to be considered in the light of a power calculation based on a large effect size. A recent umbrella review of exercise effects to cognition raised numerous methodological considerations that the field should better address, including inadequately powered RCTs, general publication bias, and large variations in methods for how cognitive measures are pre-processed and analyzed (Ciria et al., 2023). For example, our study was underpowered to detect small- to moderate effect sizes in line with those reported in the exercise neuroscience literature (Falck et al., 2019; Northey et al., 2018). While we did not find evidence of a treatment effect, the sample size was sufficient only to reliably detect large effects (Ciria et al., 2023). Consequently, these results should not be interpreted solely as evidence of no effect, but rather as indicative of limitations in finding small, realistic effects in the current sample size. While many studies do show positive effects to measures of global cognitive function, planning interventions based on smaller effect sizes is important.

This between-group difference in change found for WM performance corresponds to a medium effect size. However, since the composite WM score is expressed in z-scores, the magnitude in the context of cognitive aging is more difficult to interpret than measurements such as VO_2peak (ml/kg/min) and blood pressure (mmHg). The use of z-scores thus makes comparisons to age-expected decline somewhat problematic, given that this study had no control group indicating age-expected change (or maintenance, given the intervention was three months). Furthermore, as the current study lacked a long-term follow-up, we don't know how WM performance changed following the end of the exercise intervention, and whether exercise-induced increases were maintained. For example, our effect size of 0.50 can be contrasted to studies showing expected decline in WM composites of about 3.5% SD per year (Zahodne et al., 2011), indicating a promising effect. However, such comparisons should be interpreted with caution due to different tasks being included in the composite measures. This is, in general, a challenge in the field, where cognitive functions are assessed in a multitude of different ways, using screening tools (as discussed earlier), single tasks, composites of tasks, or latent variable analysis, and while effect sizes help interpret the size of effects, findings are harder to compare to normative population data. Caution is also needed when interpreting group-level change due to there being large individual differences in cognitive aging (Nyberg et al., 2020), and thus a closer look at individual differences in WM response to exercise was a natural next step.

The significant difference between the groups with regards to change in WM functional activity in the putamen, while interesting, are hard to interpret given the lack of relationship to performance changes. The same goes for the finding that both groups increased functional activity in the right cerebellum. Both areas are important for WM, for example the putamen is proposed to serve a role as a gating mechanisms, controlling when PFC representations should be maintained or updated (O'Reilly, 2006). The absence of a correlation between change to functional activation and performance does not negate that this change may be functionally relevant (Poldrack, 2006). BOLD signal change doesn't capture neural activity directly, rather it reflects changes to blood flow, oxidative metabolism, and blood volume (Gauthier & Fan, 2019) and thus a change in functional activity may not reflect mechanisms that directly map onto cognitive performance. However, inferring meaning is also problematic. For example, it has been common to interpret BOLD signal increases as improved recruitment (good) and BOLD signal decreases as increased efficiency (good), an approach that has been criticized (Morcom & Henson, 2018). Thus, rather than viewing the findings in the right putamen as a sign of increased efficiency in gating mechanisms of WM for HIT, these findings might just be spurious, and until replicated, the interpretation remains unclear.

Factors related to working memory change

Individual differences in cognitive response to exercise are large, and here we found that baseline fitness- and neural characteristics, as well as individual differences in response to physiological measures were related to WM response, as discussed below. For certain measures, exercise intensity mattered, while in others, the relationship was consistent across both exercise groups. While these are exploratory, hypothesis-generating analyses on change-change relationships, the findings are interesting, as they may point to factors that future study designs could target.

Baseline characteristics

While baseline CRF was positively related to WM response irrespective of exercise group, periventricular lesion load severity moderated exercise effects to WM depending on exercise group, indicating potential exercise-general and intensity-specific mechanisms in relation to individual differences in response.

White matter integrity is important for maintained WM performance during older age, especially at higher loads such as WM manipulation (Li et al., 2022). Thus, we had expected that pre-existing lesion load severity would inhibit exercise-related plasticity, in line with previous findings (von Cederwald et al., 2023). However, we instead found that supramaximal HIT increased WM performance despite severe lesions, while MIT showed similar patterns to previous findings on aerobic exercise (von Cederwald et al., 2023). While surprising, this finding is hopeful, as it indicates that improvements to WM may be possible, despite severe lesions to periventricular areas, which constitute important white matter microstructure for WM (Bettcher et al., 2016). While our findings do not offer a mechanistic explanation as to how supramaximal HIT increased WM performance in those with severe lesions, we suggest that other mechanisms may need to be explored. These include changes in autonomic nervous system and heart rate variability (Forte & Casagrande, 2025), and assessing potential compensatory neural mechanisms (Cappell et al., 2010) in subgroups with severe lesions. These findings are promising in the context of cognitive aging, as severe lesions are related to cognitive decline (Luo et al., 2023), and increase the risk of stroke (Debette & Markus, 2010) and Alzheimer's (Hu et al., 2021). While we did not assess the effects of exercise to lesion severity, finding ways to circumnavigate the reduced plasticity of pre-existing cerebrovascular disease is important for exercise prescription alleviating cognitive decline. These findings need to be directly tested on larger samples with groups balanced with regards to lesion severity, as they indicate that supramaximal intensities may increase neuroplasticity for older adults with severe lesions.

The relationship between CRF and maintained cognitive functions has support in longitudinal research (Wendell et al., 2014); however, questions remain regarding the direction of the relationship. For example, one study found that, while CRF and cognitive functions during midlife were positively associated, this may be due to neuroselection rather than neuroprotection, as the relationship did not hold when accounting for childhood cognitive performance (Belsky et al., 2015). The question remains: does higher CRF protect against cognitive aging, or does higher cognitive function early in life lead to a healthier, fitness-promoting lifestyle?

The importance of testing exercise in causal rather than observational study designs thus becomes clear. Our findings that baseline CRF may be related to subsequent WM change indicate that neuroplasticity may require a certain level of CRF before gains to WM are possible. This finding is in line with previous findings indicating that exercise improvements to several other cognitive functions (Sokolowski et al., 2021) and positive structural outcomes (Jonasson et al., 2017) were related to baseline CRF. In the context of exercise prescription for neurocognitive aging, this finding may indicate that participants with lower CRF at baseline may need a larger exercise dose before cognitive gains can be expected. In contrast, others have found that sedentary older adults have the most to gain cognitively by introducing exercise (Chen et al., 2020). While we assessed this relationship linearly, future studies with larger sample sizes and larger variability in baseline CRF may consider exploring non-linear effects to assess whether there are threshold- or ceiling effects. In this sense, both baseline- and change to CRF are important to consider when examining cognitive change.

Fitness adaptations in relation to working memory change

While the CRF-hypothesis emphasizes CRF gains as an important physiological mechanism related to cognitive improvements (Voss & Jain, 2022), we instead found that the fitness measure leg strength was related to increased WM. Leg strength gains were first tested in relation to functional activity during WM manipulation, where increases to leg strength in the HIT group were found to be related to increased DLPFC functional activity during WM manipulation. Changes in DLPFC functional activation were in turn related to increased performance on the in-scanner test (*Paper II*). When we later tested the relationship between exercise-induced changes to fitness in relation to the WM composite in the entire sample, we found that changes to leg strength, and not CRF, was positively related to improved WM, irrespective of exercise group (*Paper III)*. These exploratory findings indicate that, in addition to CRF, other aspects of fitness are important to consider in future research on the exercise-cognition relationship.

Leg strength gains in the HIT group were related to increased functional activity in the DLPFC, a key area for WM manipulation (Eriksson et al., 2015; Pudas et al., 2009). Among older adults functional activity in the PFC during WM has been shown to decrease longitudinally, together with a decline in performance, however older adults with longitudinally stable PFC activity also maintain WM performance (Nyberg et al., 2022; Rieckmann et al., 2017). The increased BOLD signal we found could be interpreted as a sign of brain maintenance, or returning to a youth-like pattern of activation (Nyberg et al., 2012). However, cross-sectional research has also proposed increased activity as a sign of neural compensation (Cappell et al., 2010; Reuter-Lorenz & Cappell, 2008). As our study had no younger group (cross sectional or longitudinal) enabling a comparison, we were unable to test these hypotheses against each other. Rather, our results may reflect brain maintenance, compensation, or potentially both, considering there are likely subgroups within the study sample, as indicated by our findings on pre-existing white matter lesion load severity discussed above. Recent evidence using multimodal imaging suggests that WM-related BOLD overactivation in line with compensatory models for neurocognitive aging do not correspond to increased glucose metabolism (Stiernman et al., 2023). Future research might consider using multi-modal imaging methods to tease apart exercise-induced changes to neurovasculature and metabolism. Despite these difficulties interpreting our findings, leg strength emerged as a promising potential physiological mechanism related to WM improvements.

A relationship between leg strength and cognitive measures have been found in earlier studies as well. Cross-sectional evidence suggests that leg strength is associated with higher executive functions and episodic memory (Frith & Loprinzi, 2018), and longitudinal research indicates that baseline leg power (average age 55 at baseline) was significantly positively related to ten-year change in cognitive function and total gray matter (Steves et al., 2016). These studies indicate a potential connection between strength and cognitive measures, however only a few studies have tested this in RCTs to assess relationships between exercise-induced strength gains and change to cognitive function.

One study tested a similar hypothesis as ours, namely whether CRF and leg strength gains following progressive resistance training was related to global cognitive function. Similarly, they found that leg strength gains, but not CRF was related to improvements in both global cognitive function and executive functions (Mavros et al., 2017). Another study found that both multicomponent training and resistance training improved executive functions; however, for resistance training, improvements were mediated by gains in muscular strength (Forte et al., 2013). These resistance training protocols differ from supramaximal HIT, with supramaximal HIT showing superior gains to CRF and inferior gains to muscle strength. Our expectation was that changes in these factors together would be related to WM improvements. Surprisingly, leg strength, but not CRF, was related to increased WM.

While we did not find support for the relationship between improved CRF and WM, our findings do not refute the importance of CRF, rather we suggest the addition of another potentially important mechanism. Our lack of findings with regards to CRF were surprising, considering previous research showing a relationship between increased CRF and increased WM specifically (Frost et al., 2021; Sokolowski et al., 2021). Our findings may be due to limited variability in CRF change, with both groups increasing to a similar extent. While that increase was statistically significant, the 1.38mL/kg/min was smaller than the proposed 3.5mL/kg/min increase that is suggested to be necessary to see cognitive gains (Zotcheva et al., 2022). Historically, research has primarily focused upon the effects of aerobic exercise to cognitive functions, with fewer studies focused on resistance training (Singh et al., 2025). Taken together, these findings indicate the importance of continuing to assess both distinct and overlapping physiological effects of resistance and aerobic training and how they relate to cognitive functions, as well as how muscular adaptations may be related to neuroplasticity.

Myokine adaptations in relation to working memory change

The myokine hypothesis proposes that physical activity and exercise lead to an upregulation of myokines, which are related to both neural and cognitive change (Stillman et al., 2016; Stillman et al., 2020). Variability between people in exercise-induced cognitive response are thus proposed to be related to individual differences in upregulated BDNF, IGF-1, and VEGF, among others. When testing individual differences in WM performance in relation to changes in peripheral resting-levels of serum BDNF, IGF-1, and VEGF, upregulated BDNF was related to increased WM performance, with a group x time interaction indicating that the relationship was stronger in MIT. This is in line with previous findings on aerobic exercise regimes, implicating BDNF in relation to hippocampal volume (Erickson et al., 2011), executive functions (Leckie et al., 2014), and functional connectivity (Voss et al., 2013).

Support for the importance of BDNF in exercise-induced plasticity has primarily been found in animal models, wherein BDNF can be studied *in vivo* in rodent brains, and study designs allow for direct manipulation of BDNF. For example, by blocking BDNF uptake in the hippocampus of mice, exercise effects to cognition were inhibited (Vaynman et al., 2004), and several other studies have revealed the importance of exercise-induced BDNF to cognitive gains in rodents, e.g., Berchtold et al. (2010) and Siette et al. (2013). While BDNF is proposed to work in similar ways in the human brain (Barde, 2025), human studies measure peripheral levels in the blood. This indirect measure has been thought to be related to central levels (Rasmussen et al., 2009), however current studies have questioned this relationship (Barde, 2025; Ou et al., 2021). BDNF is produced in both the central nervous system (Park & Poo, 2013) and in peripheral tissues. In the brain, it is expressed in the hippocampus, cerebral cortex, and the cerebellum (Hofer et al., 1990). Peripheral BDNF reflects further sources of secretion, among them skeletal muscles, where it is proposed to be secreted in response to a muscle contraction (Matthews et al., 2009). While exercise interventions increase peripheral resting levels (Behrad et al., 2024; Dinoff et al., 2016) and acute levels in response to exercise (Fernandez-Rodriguez et al., 2022; Wang et al., 2022), there are many mechanistic questions that need answered before we can understand how peripheral BDNF may be related to neural plasticity.

The significant interaction, indicating that the relationship between increased BDNF and WM was stronger in MIT is somewhat surprising, given support for higher intensities increasing BDNF levels to a greater extent, at least acutely (Fernandez-Rodriguez et al., 2022; Reycraft et al., 2020; Tarassova et al., 2025). However, given that we did not compare our intervention groups with regards to acute effects to BDNF, we do not know if that relationship holds for our study, or the manner in which acute increases relate to long-term upregulation. Future studies should further assess effects of both acute- and chronic upregulation of BDNF in relation to cognitive function, as well as the role of exercise intensity in the relationship.

The methodological challenges described above make interpretations of this study's results somewhat problematic. Nevertheless BDNF, including peripheral levels, is an important biomarker to continue to study in relation to neuroplasticity and neurocognitive aging. It has been implicated in Alzheimer's disease (Ng et al., 2019), depression (Tiwari et al., 2022), bipolar disorder, and schizophrenia (Nuernberg et al., 2016). Furthermore, the Val66Met polymorphism, a common genetic variation in the BDNF gene affecting the efficiency of BDNF release from brain cells, has been shown to moderate longitudinal hippocampal and cognitive decline, with accelerated decline among Met-carriers with elevated amyloid burden (Lim et al., 2014). Assessing the role of BDNF in the exercise-cognition relationship is therefore warranted. Research should further assess exercise-induced molecular changes in relation to other levels of mechanisms proposed by Stillman et al. (2016), including in relation to neural measures as well as the mediating effect of socioemotional changes. Furthermore, a closer inquiry into the relationship between acute increases in BDNF and long-term cognitive gains is an interesting area for future study. For example, one study assessing combined exercise and cognitive training found that individual differences in acute increases of plasma BDNF following exercise were related to greater cognitive training gains, i.e., a post-exercise advantage in learning related to increased BDNF (Nilsson et al., 2020). Designing studies that include measures of acute changes to myokines may be one important step in untangling potential mediators of exercise-induced cognitive change.

Towards scalability

Taken together, the first two aims of this thesis provide support for exercise effects following supramaximal HIT and point to potential mechanisms related to increases in an age-sensitive cognitive function. However, these findings are from controlled and rigid research settings, and to reach people in their everyday lives, steps need to be taken towards future implementation. This thesis can thus be placed into the framework for complex interventions, spanning both evaluation and intervention development stages (Skivington et al., 2021), including efficacy testing, understanding how an intervention might be working, and finally, re-developing and adapting findings to new contexts through co-creation research. Finding effective methods to increase exercise among older adults is important to reduce the risk of dementia (Livingston et al., 2024), cardiovascular disease morbidity and mortality (Yusuf et al., 2020), and increase functional independence, and is particularly pressing given that few older adults reach current recommendations for physical activity (Garcia-Hermoso et al., 2023). While the question of how to get more people to exercise is immensely complex, spanning fields of exercise physiology, psychology, economics, community planning, and politics, one small step in the right direction is developing innovative and effective exercise interventions, and bringing findings from controlled research settings to real-life environments. The Umeå HIT study is a good example of this kind of complex intervention, and has thus far included steps of pilot studies and feasibility testing (Hedlund et al., 2019), efficacy testing (*Papers I and II*), assessing how the intervention might be working (*Papers II and III*) and intervention re-development (*Paper IV*). So why is metronome-controlled supramaximal chair stand HIT a promising item to add to the menu of options for older adults, and what questions remain?

Supramaximal intensities may be particularly interesting in the context of exercise and aging, given that aerobic capacity decreases steadily over time, while anaerobic capacity is better preserved (Ganse et al., 2018). While exercise at aerobic intensities is still important, and is recommended for older adults, exercise intensity may decrease over time, potentially limiting exercise gains. Exercise intensities utilizing anaerobic capacity are thus an interesting loophole, preserving anaerobic power while also, as we found, affecting aerobic capacity. Findings from *Paper I* align with this proposal, with similar cardiorespiratory and cardiovascular gains in supramaximal HIT and MIT, and superior muscular effects for supramaximal HIT. The shift from stationary bicycling to chair stand may further increase potential muscular adaptations, by involving both excentric and concentric muscle contractions, targeting the stretch-shortening cycle, which is an age-sensitive function (Vaczi et al., 2014). Increased muscular adaptations – especially lower limb muscular adaptations, are important to mitigate fall risk among older adults (Montero-Odasso et al., 2022). An intervention targeting both CRF and muscular gains may also be promising given previous research on the importance of CRF and cognitive function (Frost et al., 2021; Vidoni et al., 2015) and the current findings in *Papers II* and *III* implicating leg strength as a potentially important factor related to WM gains. However, the effects of a supramaximal chair stand protocol on CRF, muscular strength, and cognitive functions need to be assessed in future studies.

A key aspect to the protocol, from early feasibility testing (Hedlund et al., 2019), to the RCT, as well as during the co-creation study, was prescribing a controlled intensity. This was important to avoid overshooting exercise intensity (Buchheit & Laursen, 2013), potentially limiting adherence due to negative affective responses and physical discomfort (Merrells et al., 2021), as well as to diminish potential long-term adaptations due to undershooting intensity (Hebisz et al., 2016). Stationary bicycling enabled watt-controlled intervals with supramaximal intensity prescribed based on baseline performance during the Borg Cycle Strength Test (Borg, 1982), however stationary bicycles are not widely available to older adults. The shift to non-cycling modalities required a new solution for intensity prescription, and the idea of controlling intensity using an audio metronome was an important result from phase one workshops. The similar physiological responses between metronome-controlled chair stand and watt-controlled stationary cycling revealed that this shift seemed successful. Previous studies have used audio metronomes to help pace exercise, for example in clinical populations with Parkinson's (Hutin et al., 2024), multiple sclerosis (Moumdjian et al., 2019), post-stroke (Shaw et al., 2022), and following unilateral transtibial amputations (Kline et al., 2021). Participants in the current study appreciated the metronome, and wished to see it built into a mobile application. While beyond the scope of this thesis, a mobile application would allow for programming clear escalation- and de-escalation criteria, thus enabling individualized starting points and controlled progression of intensity over time, in compliance with the core components of the protocol.

An important question to consider when adapting an intervention is for whom this intervention is intended. Who is the end-user? The aim of the Umeå HIT study was never to create a solution that fits everyone – rather the aim was to assess whether supramaximal HIT might be another option that can be offered to older adults. Findings support the use of the exercise form for older adults, both with regards to physiological and, to some extent, cognitive benefits, adverse events (*Paper I*), applicability (Frykholm, Simonsson, et al., 2024), muscle capacities, physical function (Frykholm, Hedlund, et al., 2024), as well as findings that participants found supramaximal HIT to challenge negative age stereotypes about what older adults can manage (Fridberg et al., 2025). An unanswered question is for whom self-managed supramaximal HIT is appropriate. Of the ten participants medically screened for phase two, three were excluded based on similar medical criteria they had passed only a few years prior when entering the Umeå

HIT RCT. This indicates the complexity of identifying both who should begin an exercise intervention (Armstrong et al., 2018; Whitfield et al., 2014), as well as how different aging trajectories may lead to said intervention becoming less appropriate over a long-term perspective. There is support for long-term exercise interventions not influencing health-related or mortality-related drop-out rates (Garcia-Hermoso et al., 2020), however whether this can be applied to supramaximal HIT is not clear. While the adapted version aims to maintain the more conservative approach of individualized progression of intensities with built-in escalation and de-escalation, future implementation needs to include a plan for both pre-intervention screening and regular safety checks throughout.

Adapting the protocol for future implementation in the home environment involves transferring from a researcher-monitored intervention to one that is self-monitored. Such a transfer from RCTs to real-life settings is a major challenge for researchers, and subsequent decline in effect sizes has been referred to the efficacy-effectiveness gap (Nordon et al., 2016). Differences in effect sizes drop dramatically when comparing exercise RCTs with subsequent scaled up interventions (Lane et al., 2021). Despite this potential drop in effect, it is important to reach those who need an intervention, and co-creation research, while not solving the entire issue of the efficacy-effectiveness gap, offers one potential solution for increasing the ecological validity of an intervention (Leask et al., 2019). With regards to the currently suggested intervention, there is support for home-based training and digitally delivered home-exercise improving fitness, as well as reducing fall risks and number of falls among older adults (Chaabene et al., 2021; Pettersson et al., 2025; Solis-Navarro et al., 2022). Future steps should also include applying psychological theories on goal-setting (Locke & Latham, 2002), reinforcement learning (Zhou et al., 2018), and motivation to potentially increase long-term adherence to new exercise behaviors.

Methodological considerations

The Umeå HIT study has many strengths, the foremost perhaps being that it involves many different steps within a framework for complex interventions, bringing together findings from feasibility testing (Hedlund et al., 2019), an RCT (Paper I and II), a pragmatic feasibility study (Frykholm et al., 2025), and a co-creation study , with the aim of future implementation (Skivington et al., 2021). The RCT was a large study compared to others assessing supramaximal HIT among older adults (Adamson et al., 2020; Adamson et al., 2019; Adamson et al., 2014), was pre-registered to prevent reporting bias, outcome assessors were blinded to group allocation, and statistical analyses on primary outcomes were conducted on a masked data set.

Regarding exercise effects, findings under aim one may be limited due to a potentially optimistic power calculation. As alluded to earlier, the power calculation for global cognitive function was based on a larger effect size than what is usually found in the exercise neuroscience literature (Falck et al., 2019; Northey et al., 2018), and the current study was therefore likely underpowered. Meanwhile, change to VO_2peak was also considered in the power calculation, increasing the number of participants, however again, the expected between-group difference in change was quite large (3.5mL/kg/min). Taken together, an underpowered study increases the risk for Type II errors, meaning that true but more modest effects may have gone undetected, as well as overestimating effect sizes when effects are detected. This may be important to keep in mind when interpreting effect sizes for outcomes such as WM and isometric leg extensor strength. The sample size was nearly halved for the MRI-analyses and due to this, fMRI analyses did not include rigorous corrections for multiple comparisons, which increases the risk for Type I errors (Poldrack et al., 2008). Interpretations of the results from *Paper II* should therefore be viewed as exploratory and hypothesis generating.

Furthermore, due to the COVID-19 pandemic, the long-term follow-up for half the participants was canceled for safety reasons, as the study sample was a risk group. This thesis was therefore unable to include the originally planned long-term follow-up data in *Papers I* and *III*, and the analysis plans were adjusted accordingly. In *Paper I*, LMMs were used, which account for individual differences in baseline levels through random intercepts. However, with only two measurement occasions available, it was not possible to model more complex change-trajectories. Nevertheless, the analyses still offer valuable insights into group-level change over time, even with this limitation. A similar limitation applies to *Paper III*, where exercise-induced change to WM was captured using a change-score (post minus pre). While such change-change analyses may compound measurement error and partly reflect regression to the mean, they nonetheless provide a pragmatic way to examine short-term within-person change. These analyses, however, do not allow for individual differences in trajectories and limit directional or causal interpretation. Had there been a third measurement occasion, more powerful longitudinal models could have been applied, even with the modest sample size, for example simple latent growth curve models that better capture individual differences in change over time.

Another important aspect to consider is the choice of a comparison group (MIT) that exercised more than supramaximal HIT. From an exercise physiology perspective, this comparison is important, as the two groups exercised in quite different ways, and piecing apart distinct effects is important for exercise prescription. Exercise neuroscience however, may still have something to gain from including more traditional control conditions, including the ability to account for learning effects, and when studying older adults, account for age-expected decline in cognitive functions. Meanwhile, the use of inactive controls is ethically problematic, given the extensive support for exercise to important health outcomes.

As always, something needs to be said about how representative this study sample was, and whether findings thus can be considered generalizable to broader populations. For example, while the study aimed to recruit a wide age-range of participants, the oldest participant was 79, and future studies should consider recruitment strategies that may capture an even broader age-range (i.e., people over 80 as well). Furthermore, participation in the Umeå HIT Home study was limited to participants with experience exercising in the supramaximal HIT group of the RCT. While that previous experience was considered necessary for the aim of the co-creation study, this sample likely doesn't represent true end-users, and upcoming steps need to involve more representative participants.

When it comes to the Umeå HIT Home study, it is important to note that, while the aim was to adapt the protocol to the home environment, no research (besides the participant's homework assignment in phase one) was conducted in the home environment. Future work will need to assess whether the adapted protocol can be implemented in the homes of older adults. Furthermore, it is important to note that phase one findings were summarized descriptively and were not subjected to a qualitative analysis. This was in line with the original plan of the study, where the workshops were used as a pragmatic tool to identify concrete adaptations, suggested alternative modalities, and creative solutions for intensity modulation. Nevertheless, this limits the depth of insight that might have been obtained regarding co-creators' experiences, perspectives, and motivations.

Practical implications and future directions

In the end, this thesis barely scrapes the surface of all that we know and all that we should find out about how exercise affects the aging body and brain, and as always with research, each answered question has only led to new questions being asked. There are many important directions this research can continue in, many have already been mentioned, and below a few overarching ideas have been outlined.

This thesis aimed to assess individual differences in exercise-induced change to WM, however to conduct more rigorous research on the mechanisms underlying cognitive gains, future studies should consider a few design changes. As previously mentioned, more timepoints for measurement is one important factor. This would enable piecing apart temporal differences between variables in change. Another interesting direction would be to combine acute- and long-term adaptations. This may be particularly important for mechanisms such as myokines, where long-term upregulation may only be telling part of the story.

A second area of interest is placing findings into a broader context of neurocognitive aging. This thesis looks at three months out of a person's life. As was made clear in the above discussion on effects to WM, the cognitive results are more complicated to understand in relation to age-expected decline, as compared to many of the physiological effects in this thesis. While inactive controls and long-term follow-ups may help to some degree, another direction might be including measures of cognitive function already present in large longitudinal studies, enabling comparisons with pre-existing large cohorts, or using cognitive batteries with established normative data.

With that said, the question is not whether to encourage exercise, but rather how to increase the number of active older adults. While not included in this thesis, the Umeå HIT Home study also included a third phase, wherein an exercise mobile application was co-created, and feasibility testing is currently being planned. Designing exercise studies, not just for an increased mechanistic understanding of effects, but also with the long-term goal of broader implementation needs to be a key aim in scientific research, to ensure that complex findings can be translated to real-life effects among those who need it the most.

Conclusions

This thesis found that three months of controlled, supramaximal HIT is a time-efficient and effective way for older adults to exercise, with similar- to superior effects on both physiological and cognitive outcomes. These effects can be contrasted to the decline that otherwise is expected in this age group, however as the intervention length was quite short, and the potential maintenance of long-term effects were not studied, questions remain as to the extent that supramaximal HIT may affect global cognitive function, as well as the extent to which improvements are maintained in the long-run.

On a group-level, exercise-induced changes to WM performance differed between the groups, and individual differences in WM performance and WM functional activation were further examined. Here we found that baseline brain integrity did not affect gains to WM in supramaximal HIT, rather participants with severe white matter lesions at baseline increased WM, while MIT did not. This finding is an addition to previous research indicating that neural plasticity in relation to WM performance following aerobic exercise was impaired for those with severe lesions and indicates that supramaximal HIT may provide effects despite severe lesions. However, the exact mechanisms need to be tested in future studies. Furthermore, leg strength gains emerged as a potential target for future studies to examine, as it was related to increased WM functional activation in a key WM area in the HIT group, which in turn was related to increased performance. Furthermore, leg strength gains irrespective of exercise group were found to be related to WM performance on a broader composite of tasks.

Given the promise of supramaximal HIT for improving age-sensitive physiological and cognitive functions, the protocol was adapted in a two-phase co-creation study aimed at re-developing the protocol to one with the potential of being conducted at home. The original watt-controlled supramaximal HIT protocol on stationary bicycles was thus re-developed in collaboration with a group of older adults, to a metronome-controlled supramaximal HIT protocol using chair stand as an exercise modality. Future studies should evaluate the feasibility and efficacy of this home-based supramaximal HIT protocol with regards to both physiological and cognitive measures, with the aim of future implementation in the real-life settings of older adults.

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