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Anna Tirkkonen

Cognitive and Physical Functions Among Middle-Aged and Older People

A Special Emphasis on Executive Functions and Walking

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF SPORT AND HEALTH SCIENCES

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ABSTRACT

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Cognitive and physical functions are key factors for safe walking. Unfortunately, these functions deteriorate with age and therefore older adults may experience difficulties in outdoor mobility. In women, decline in cognitive and physical functions may start as early as middle age due to menopausal-related hormonal changes. However, cognitive and physical decline may be attenuated with cognitive and physical training. This study investigated the associations between cognitive, especially executive, and physical functions in older adults and middle-aged women. Also investigated was the role of participant characteristics in cognitive and physical training-induced change in executive functions in older adults and cognitive performance over the menopausal transition in middle-aged women. This study utilized data from two research projects: the PASSWORD (n=314) and the ERMA (n=342). In the PASSWORD, community-dwelling 70–85-year-old men and women participated in 12-month physical (n=159) or physical and cognitive training (n=155). The measurements for executive and physical functions were organized at baseline and 12 months. In the ERMA, 158 early and 184 late perimenopausal women participated in measurements for cognitive and physical functions at baseline and after reaching post-menopause (n=195). Executive functions were assessed with the Stroop test (inhibition), Trail Making Test B and B-A (set shifting), and Verbal Fluency Test (updating). Physical functions were assessed with 10-m walking speed, 6-min walking distance, dual-task walking and the Short Physical Performance Battery. The results showed domain-dependent, positive cross-sectional associations between executive and physical functions in older adults and middle-aged women. Longitudinal associations between these functions in middle-aged women were not found. Furthermore, cognitive and physical training provide additional benefits for women and participants who trained occasionally, compared to physical training alone, but the additional benefit for executive functions was domain-dependent. Finally, cognitive performance remained stable over menopausal transition. This research suggests that executive and physical functions are associated in older adults and middle-aged women. Furthermore, the results show that executive functions can be promoted with cognitive and physical training.

Keywords: cognition, executive functions, physical functions, older adults, walking, menopause

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Tirkkonen, Anna
Kognitiivinen ja fyysinen toimintakyky iäkkäillä henkilöillä ja keski-ikäisillä naisilla
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Riittävä kognitiivinen ja fyysinen toimintakyky ovat edellytyksiä turvalliselle kävelylle. Nämä toimintakyvyn osa-alueet heikkenevät ikääntyessä, jonka vuoksi ikääntyneillä henkilöillä voi olla kävelyvaikeuksia. Naisilla kognitiivisen ja fyysisen toimintakyvyn heikkeneminen voi alkaa jo keski-iässä vaihdevuosiin liittyvien hormonimuutosten vuoksi. Kognitiivista ja fyysistä toimintakykyä voidaan ylläpitää harjoittelulla. Tässä tutkimuksessa tutkittiin kognitiivisen ja fyysisen toimintakyvyn välisiä yhteyksiä iäkkäillä henkilöillä ja keski-ikäisillä naisilla. Lisäksi tutkittiin taustatekijöiden roolia kognitiivisen ja fyysisen harjoittelun aiheuttamassa toiminnanohjauksen muutoksessa ja kognitiivisen toimintakyvyn muutosta vaihdevuosien aikana. Tutkimuksessa hyödynnettiin aineistoa PASSWORD (n=314) ja ERMA (n=342) -tutkimuksista. PASSWORD-tutkimuksessa 70–85-vuotiaat henkilöt osallistuivat joko 12 kuukauden fyysiseen (n=159) tai fyysisen ja kognitiiviseen harjoitteluun (n=155). Kognitiivinen toimintakyky mitattiin tutkimuksen alussa ja 12 kuukauden jälkeen. ERMA-tutkimuksessa 158 varhaisessa ja 184 myöhäisessä perimenopaussivaiheessa olevan naisen kognitiivinen ja fyysinen toimintakyky mitattiin tutkimuksen alussa ja postmenopaussin jälkeen (n=195). Toiminnanohjaus mitattiin Stroop-testillä (inhibitio), Trail Making Test B ja B-A:lla (toiminnan joustava vaihtaminen) ja sanasujuvuustestillä (toiminnan sujuvuus, joustavuus ja työmuisti). Fyysinen toimintakyky mitattiin 10 m kävelynopeudella, 6 min kävelymatkalla, kaksoistehtävän aikaisella kävelynopeudella ja lyhyellä fyysisen toimintakyvyn testistöllä. Tulokset osoittivat toiminnanohjauksen osa-alueesta riippuvaisen, positiivisen yhteyden toiminnanohjauksen ja fyysisen toimintakyvyn välillä ikääntyneillä henkilöillä ja keski-ikäisillä naisilla. Kognition ja kävelyn välillä ei löydetty pitkittäisyhteyksiä keski-ikäisillä naisilla. Lisäksi osoitettiin, että kognitiivinen ja fyysinen harjoittelu parantaa ikääntyneiden henkilöiden toiminnanohjausta, mutta yhdistelmäharjoittelun lisäetu riippuu toiminnanohjauksen osa-alueesta. Tämän tutkimuksen perusteella toiminnanohjaus ja fyysinen toimintakyky ovat yhteydessä ikääntyneillä henkilöillä ja keski-ikäisillä naisilla. Lisäksi tutkimuksen perusteella voidaan olettaa, että toiminnanohjausta voidaan parantaa kognitiivisella ja fyysisellä harjoittelulla.

Avainsanat: kognitio, toiminnanohjaus, fyysinen toimintakyky, iäkkäät henkilöt, vaihdevuodet

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Jyväskylä 20.11.2022
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ORIGINAL PUBLICATIONS AND AUTHOR CONTRIBUTION

This thesis is based on the following original publications, which will be referred to in the thesis by their Roman numerals.

I Sipilä, S*., Tirkkonen, A*., Hänninen, T., Laukkanen, P., Alen, M., Fielding, RA., Kivipelto, M., Kokko, K., Kulmala, J., Rantanen, T., Sihvonen, S.E., Sillanpää, E., Stigsdotter Neely, A. & Törmäkangas, T. (2018). Promoting safe walking among older people: the effects of a physical and cognitive training intervention vs. physical training alone on mobility and falls among older community-dwelling men and women (the PASSWORD study): design and methods of a randomized controlled trial. *BMC Geriatrics*, *18*(215). https://doi.org/10.1186/s12877-018-0906-0*equal contributors

II Tirkkonen, A., Kulmala, J., Hänninen, T., Törmäkangas, T., Stigsdotter Neely, A. & Sipilä, S. (2022) Associations between physical and executive functions among community-dwelling older men and women. *Journal of Aging and Physical Activity 30*(2): 332–339. https://doi.org/10.1123/japa.2021-0075

III Tirkkonen, A., Törmäkangas, T., Kulmala, J., Hänninen, T., Stigsdotter Neely, A. & Sipilä, S. (2022) Participant characteristics associated with the effects of a physical and cognitive training program on executive functions. *Frontiers in Aging Neuroscience* 14:1038673. https://doi.org/10.3389/fnagi.2022.1038673

IV Tirkkonen, A., Kekäläinen, T., Aukee, P., Kujala, U.M., Laakkonen, E.K., Kokko, K. & Sipilä, S. (2022) Bidirectional associations between cognitive functions and walking performance among middle-aged women. *Menopause 29* (2): 200–209. https://doi.org/10.1097/gme.0000000000001896

Before entering doctoral studies, I had the opportunity to work as a research coordinator in the PASSWORD study. In this position I participated in the planning of the interventions and recruitment of the study participants. In addition, I designed the measurement schedule, supervised the training groups, and kept in touch with the participants during the study. In this thesis, data from the PASSWORD study was utilized in papers I, II and III. In paper IV, I was privileged to use pre-existing data. In paper I, I have a shared first authorship with Professor Sarianna Sipilä as we drafted and wrote the manuscript together. As the author of original publications II–IV, considering the comments from the co-authors, I drafted and prepared the data for statistical analyses, and performed preliminary statistical analyses and part of the final analyses. A statistician performed more challenging statistical analyses. Additionally, I had the main responsibility of interpreting the results and writing the manuscripts.

FIGURES

TABLES

ABBREVIATIONS

β	Standardized regression coefficient
B	Unstandardized regression coefficient
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CI	Confidence interval
CERAD	The Consortium to Establish a Registry for Alzheimer's Disease
DT	Dual-task
ERMA	Estrogenic regulation of muscle apoptosis
FSH	Follicle stimulating hormone
GEREC	Gerontology research center
MLR-estimator	Maximum likelihood estimation with robust standard errors and scale corrected chi-square values
MMSE	Mini-Mental State Examination
PASSWORD	Promoting safe walking among older people: physical and cognitive training intervention among community-dwelling sedentary men and women
pm	Perimenopausal
ProBDNF	Pro brain-derived neurotrophic factor
PT	Physical training group
PTCT	Physical and cognitive training group
RCT	Randomized controlled trial
SD	Standard deviations
SEM	Structural equation modelling
SPPB	Short Physical Performance Battery
Stroop	Stroop colour and word test
TMT	Trail Making test
TUG	Timed Up and Go test
Updating	Working memory updating
VF	Verbal Fluency test
wd	Walking distance
WHO	World Health Organization
ws	Walking speed

CONTENTS

1 INTRODUCTION

The world population is aging quickly. According to the World Health Organization (WHO), the world population over 60 years old will nearly double between years 2015–2050, from 12% to 22%. In addition, the number of persons aged 80 years or older is expected to triple between years 2020–2050 (World Health Organization, 2021). Aging is accompanied with changes in cognitive and physical functions that can be either non-pathological or pathological. Although the prevalence of neurodegenerative diseases, such as Alzheimer's disease (Cao et al., 2020; Overton et al., 2019) and Parkinson's disease (Beitz, 2014) increases with age, older adults without these conditions also often experience cognitive (Harada et al., 2013; Salthouse, 2019) and physical changes (Verghese et al., 2006). These changes may cause decline in the ability to solve problems, memory loss, slow walking speed, balance deficits and falls, which in turn may cause challenges to complete everyday tasks in an efficient manner.

Cognitive functions have an important role in older adults' ability to walk safely in their environment (Yogev-Seligmann et al., 2008). In addition to cognitive functions, safe walking requires lower-extremity strength, balance, endurance and power (Rantanen et al., 2001). Reduction in cognitive and lower-extremity function are associated with slow walking speed (Demnitz et al., 2018; Hirano et al., 2022; Wu & Zhao, 2021) and falls (Ambrose et al., 2013; Laurence & Michel, 2017), as well as reduction in ability to perform two simultaneous tasks, for example, talking while walking or screening traffic while talking (Yogev-Seligmann et al., 2008). For older adults, adequate walking performance is crucial, as the ability to walk independently facilitates health and participation as well as possibilities to access goods and services (Lonergan & Krevans, 1991; Satariano et al., 2012). Inability to walk independently, in turn, can lead to activity restrictions and related poor health outcomes (Hardy et al., 2011; Mantel et al., 2019; Oxley & Whelan, 2008). Therefore, in aging societies promoting cognitive and physical health is of critical importance.

Concerning cognitive functions, executive functions especially are suggested to be associated with walking performance in older adults (Morris et al., 2016). Executive functions are higher-level cognitive processes allowing flexible goal-directed action and coordinating of complex walking (Cohen et al., 2016). The association between executive functions and walking has been hypothesized to be due to partly overlapping brain structures and neuronal networks located mainly in the prefrontal and parietal cortices, regulating both actions (Morris et al., 2016; Poole et al., 2019). The anatomical overlap regulating executive functions and walking may also explain challenges that older adults experience when they must perform secondary tasks while walking.

In women, the deterioration of cognitive and physical functions may start as early as middle age due to menopausal hormonal changes. During the menopausal transition, the level of estrogen decreases dramatically (Rannevik et al., 1986), and that has been suggested to cause degradation in cognitive (Kilpi et al., 2020) and physical functions for middle-aged women (Bondarev et al., 2021). In addition, whereas the relationship between executive functions and walking in older adults has been studied to some extent, it is still unclear whether this link is present already in midlife.

While a decline in cognitive functions with aging is ubiquitous, previous research has suggested that healthy cognitive aging can be promoted with cognitive training (Ten Brinke et al., 2020) and physical exercise (Falck et al., 2019; Northey et al., 2018). In particular, executive functions seem to benefit from these training methods (Northey et al., 2018; Ten Brinke et al., 2020). In recent years, research interest has been focused on investigating whether a combination of cognitive and physical training would provide a greater benefit for executive functions compared to cognitive or physical training alone. Some of the previous studies lend support to the superior effects of a combination of cognitive and physical training on executive functions, compared to neither of these training methods alone (Eggenberger et al., 2015; Ten Brinke et al., 2020). However, all studies have not been able to find that combined training would provide additional benefit for executive functions (Hagovska & Nagyova, 2017).

The association between executive functions and physical functions among older adults is rather well documented (Berryman et al., 2013; Coppin et al., 2006; Demnitz et al., 2018; Morris et al., 2016). However, there is no consistent knowledge if executive function subdomains – namely, inhibition, set shifting and updating, and the nature of the physical task – have a role in these associations. Additionally, it is still unclear whether the link between executive functions and physical functions is present already in midlife and whether the menopausal transition has a role in longitudinal associations between executive functions and physical functions among middle-aged women. Moreover, the participant characteristics and background factors associated with intervention-induced change in executive functions have not yet been identified. To contribute to filling these research gaps, this study investigates the cross-sectional and longitudinal associations between cognitive and physical performance among older adults and middle-aged women. Especially, our interest was in investigating the association between executive functions and walking performance. In addition, we studied the effects of participant characteristics and background factors for intervention-induced change in executive functions among older adults and changes in cognitive performance over menopausal transition among middle-aged women. The information provided by this study can be utilized to promote cognitive and physical health at different ages.

2 REVIEW OF THE LITERATURE

Several models have been developed to describe the relationship between disease and disability. The disablement process by Verbrugge and Jette (1994) describes the pathway from pathology to functional limitations. According to this pathway, pathologies such as developmental condition, diagnoses of diseases or injury may lead to impairments that refer to dysfunctions and structural abnormalities in specific body systems, including the neurological, musculoskeletal, and cardiovascular systems. In turn, impairments may lead to functional limitations (i.e. restrictions in basic mental and physical actions). Functional limitations, such as memory loss, decline in walking performance, problems in producing intelligible speech and balance deficits, are all associated with challenges in activities of daily living among older adults (Connolly et al., 2017; Hinman et al., 2014). However, extra-individual factors such as therapy, counselling and health education, as well as such intra-individual factors as increased level of physical activity, may help to attenuate the limitations (Verbrugge & Jette, 1994).

Several different mechanisms may cause pathologies that are associated with deterioration in cognitive and physical functions in advanced age. Genes (Bai, 2018), the presence of inflammation (Campisi et al., 2019), changes in brain structure and function (Clark & Manini, 2008; Cohen et al., 2019), hormonal changes (Greendale et al., 2009; Kurina et al., 2004; van den Beld et al., 2018) and lifestyle-related factors, such as diet and physical activity, have been shown to be associated with cognitive (Kivipelto et al., 2018) and physical aging (Bloom et al., 2018; Cunningham et al., 2020). Furthermore, age-related sensory impairment has been shown to be a risk factor for reduced physical functioning (Kulmala et al., 2009; Swenor et al., 2013; Viljanen et al., 2009).

2.1 Aging and cognitive functions

Cognitive functions refer to skills and abilities related to mental processing, which can be categorized in a wide range of cognitive domains, such as executive functions, attention, memory and visuospatial functions (Brewster et al., 2018). Change in cognitive functions over the lifespan can be described with the concept of crystallized and fluid intelligence (Harada et al., 2013). Crystallized abilities such as vocabulary or general knowledge, which are based on cumulative knowledge and experiential skills, can even improve with increasing age. On the other hand, fluid abilities such as psychomotor speed and executive functions, requiring cognitive processing and the ability to manipulate and transform incoming information, are prone to decline with increasing age (Murman, 2015; Salthouse, 2012).

In women, cognitive aging may be accelerated in midlife due to menopause-related decreases in the production of estrogens and changes in estrogen receptor network (Brinton et al., 2015). The areas of brain controlling, for example, executive functions and memory are in rich of estrogens receptors (McEwen, 2001). Estrogens receptors α and β respond differently to estradiol (Patisaul et al., 1999), initiate intra- and extracellular actions in neural and peripheral substrates (Hara et al., 2015) and are differently expressed within the brain (Toran-Allerand et al., 2002). It has been suggested that age-related shifts in the ratio between estrogens receptors α and β may be affecting cognitive functions, especially memory performance (Han et al., 2013). Additionally, estrogens have been shown to induce formation and plasticity of synapses (Adams et al., 2001; McEwen, 2001; Woolley & McEwen, 1992) and affect the amount of neurotransmitters (McEwen, 2001) in experimental animal studies. Therefore, it might be that women experience a decline in cognitive functions already in midlife (Greendale et al., 2009).

2.1.1 Executive functions

Executive functions are higher-level cognitive processes that allow flexible goal-directed action (Diamond, 2013; Miyake et al., 2000). It is generally agreed that executive functions consist of three core skills: inhibition, set shifting and working memory updating (updating) (Miyake et al., 2000). According to Miyake and Friedman's unity/diversity framework (2012), these core skills are correlated yet separable, and therefore they show unity as well as diversity and serve as a base for higher order cognitive skills, such as reasoning, problem-solving and planning (Collins & Koechlin, 2012; Lunt et al., 2012).

The ability to inhibit responses that are inappropriate or maladaptive is of critical importance for adaptive behaviour, that is, meeting the changing demands of complex environments (Meyer & Bucci, 2016). Inhibition enables the ability to focus attention on relevant stimuli and suppress attention towards irrelevant stimuli. One important aspect of inhibition is self-control, which allows individuals to resist impulsive behaviour and act, for example, according to social norms (Diamond, 2013). Set shifting involves switching flexibly between multiple tasks, operations or mental sets (Miyake & Friedman, 2012; Monsell, 1996), and it concerns the ability to disengage from irrelevant tasks and engage in a relevant task (Miyake et al., 2000). Updating refers to the ability to monitor incoming information, maintain task-related relevant information and replace unnecessary information with more relevant information (Morris & Jones, 1990). The essence of updating compared to working memory is its requirement to actively manipulate relevant information instead of passively storing it (Miyake et al., 2000).

Several frontal areas of the brain including dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and the cingulate cortex has been shown to regulate executive functions (Jones & Graff-Radford, 2021; Wu et al., 2020). In addition, neuroimaging studies have shown that executive functions are associated with large-scale cerebral networks of the frontal and parietal areas of the brain (Collette et al., 2006). For example, executive functions increase activation of the frontoparietal network, the cingulo-opercular network and the striatum (Fan, 2014; Wu et al., 2018, 2020). Moreover, it has been shown that in addition to common brain regions and networks, inhibition, set shifting and updating increase activation in diverse brain structures (Jones & Graff-Radford, 2021; Wu et al., 2020). For example, the dorsolateral prefrontal cortex plays a role in set shifting and updating, and the ventrolateral prefrontal cortex plays a role in inhibition (Jones & Graff-Radford, 2021). However, all diverse activated brain areas were parts of the larger network or brain region (e.g. prefrontal cortex) that were shown to be activated while performing executive tasks (Jones & Graff-Radford, 2021; Wu et al., 2020).

Executive functions are shown to be vulnerable to age-related decline (Reuter-Lorenz et al., 2016). For example, declines in grey matter volume, fluctuation in white matter in the prefrontal cortex (Upright & Baxter, 2021) and reduced synaptic density (Harada et al., 2013) are all associated with observed declines in executive functions. Moreover, the amount of grey matter atrophy is most prominent in the prefrontal cortex which makes executive functions sensitive to decline with aging (Harada et al., 2013). However, inhibition, set shifting and updating may respond differently to age-related structural and functional changes in the brain. For example, it has been suggested that better performance in set shifting and inhibition is associated with larger prefrontal cortex volume whereas updating, assessed with Verbal Fluency Test, show no association with prefrontal cortex volume (Yuan & Raz, 2014). Additionally, it has been hypothesized that patterns of age-related functional brain changes depend on the executive subdomain that is measured (Turner & Spreng, 2012).

Several psychological tests have been developed to assess inhibition, set shifting, and updating. For example, inhibition can be assessed with the colour-word Stroop task (Graf et al., 1995), Flanker task (Eriksen & Eriksen, 1974) or go/no-go task (Cragg & Nation, 2008). Set shifting can be assessed with the Trail Making Test B and B-A (Reitan, 1958) or Wisconsin Card Sorting task (Stuss et al., 2000) and updating with an animal-naming test (Johnson-Selfridge et al., 1998) or letter fluency test (Koivisto et al., 1992).

2.1.2 Psychomotor speed

Psychomotor speed refers to the speed with which individuals execute a cognitive task and produce necessary motoric responses (Harada et al., 2013), and it is mainly regulated in the dorsolateral prefrontal cortex (Rosano et al., 2010). Among older adults, decline in psychomotor speed is associated, for example, with slow maximal walking speed (Soumare et al., 2009), and it may predict memory disorder, disability and depression (Amieva et al., 2019). In addition, many of the age-related changes in other cognitive domains are associated with decline in psychomotor speed, and therefore it may have implications for a variety of cognitive functions (Harada et al., 2013).

Psychomotor speed begins to decline already before midlife, and the decline continues throughout one's lifespan (Salthouse, 2010). Reduction in psychomotor speed has been especially associated with reduced white matter integrity (Atwi et al., 2018; Wang et al., 2020). To assess psychomotor speed, the Trail Making Test A (Reitan, 1958) and digit symbol substitution test (Wechsler, 1945) are traditionally used in clinical and research settings.

2.1.3 Memory

Memory is a complex and multifaceted cognitive domain with multiple subdomains (Harvey, 2019). Memory can be categorized as a declarative and non-declarative part. Declarative memory refers to events and facts that can be consciously recalled, whereas non-declarative memory refers to unconscious performance (Robertson, 2002). Declarative and non-declarative memories are based on neural systems that are separate but interconnected, and they can be further categorized as short-term and long-term memory (Simpkins & Simpkins, 2013). Short-term memory can be considered as the ability to remember information for seconds to hours. Long-term memories, in turn, are skills, events and facts that can be recalled after a long period of time (Robertson, 2002).

Memory processes start with incoming sensory information, which is processed in the sensory association cortex and kept in short-term memory (Robertson, 2002). If special attention is paid to the information or it is recalled several times, it will be *encoded* into long-term memory (Harvey, 2019). Encoding refers to processing sensory input into a form that can be stored in the brain (Harvey, 2019). Newly acquired information can be also transferred to long-term memory through a process called consolidation (Takehara-Nishiuchi, 2021) in which temporary memory traces are consolidated as permanent memories (McGaugh, 2000). The ability to access information storage in long-term memory when needed is possible through memory retrieval (Frankland et al., 2019).

Working memory can be defined as a type of short-term memory that includes two distinct components, one of which maintains information from seconds to hours (Norris, 2017; Robertson, 2002) and the other can manipulate it (Baddeley & Logie, 1999). Working memory can receive information from all sensory modalities and the received information can be either verbal or nonverbal (Harvey, 2019). Working memory is critical, for example, for reasoning and making sense of written and spoken language (Diamond, 2013).

Long-term memory consists of multiple structures. Declarative long-term memory involves storage of factual information and explicit memories, and it can be further divided into episodic memory, which serves for dated recollections of personal experiences, and semantic memory, which serves for general information. Non-declarative long-term memory offers storage for actions, perceptual-motor skills, conditioned reflexes, and implicit memories. Non-declarative long-term memory also has a role in skill learning (Simpkins & Simpkins, 2013).

Several brain areas are involved in controlling different facets of memory (Simpkins & Simpkins, 2013). The neural basis of short-term memory is mainly located in the same cortical regions that process sensory input, and medial temporal structures, which allow the binding of items to their context for short-term memory and retrieving items whose context is no longer in the focus of attention (Jonides et al., 2008). The neural basis of the working memory is distinct from short-term memory, as it relies mainly on the dorsolateral prefrontal cortex. The dorsolateral prefrontal cortex, which serves for higher-level cognitive functions, enables manipulating information in working memory in addition to storage of it (Diamond, 2013; McEwen & Morrison, 2013). Long-term declarative memory storage and retrieval rely mainly on the temporal and frontal areas (Simpkins & Simpkins, 2013). Moreover, hippocampus has been shown to have important role in long-term memory consolidation (Squire et al., 2015). Non-declarative memory, in turn, relies on striatum, neocortex, amygdala and cerebellum (Squire & Zola, 1996).

Age-related declines in memory are mostly seen in declarative memory (Rönnlund et al., 2005) and working memory (Fabiani, 2012), whereas non-declarative memory remains rather stable throughout one's lifespan (Fleischman et al., 2004). Age-related declines are also present in encoding (Craik & Rose, 2012) and retrieval (Economou, 2009). It has been assumed that age-related decline in different facets of memory is associated, for example, with slowed processing speed (Luszcz & Bryan, 1999), decline in ability to ignore irrelevant information (Darowski et al., 2008) and changes in brain activation patterns (Dumas, 2015).

When assessing memory in clinical and research settings, the interest is typically on assessing working memory, encoding and retrieval. The widely used and suitable test for assessing working memory is the Digit Span Test (Wechsler, 1945). Typical tests used to assess encoding are the California Verbal learning test (Woods et al., 2006) and the Rey Auditory Verbal learning test (Shin et al., 2006). Retrieval from long-term memory can be assessed, for example, simply by asking the individual to recall information presented earlier (Harvey, 2019).

2.2 Aging and physical functions

Physical functions are important contributors of mobility, which refers to the ability to go safely and reliably where you want to go and when you want to go, as well as the ability to choose how you want to go there (Satariano et al., 2012). Sufficient physical functioning is of critical importance for older adults. Limitations in physical functions may cause difficulties in activities of daily living, increased risk of falls and frailty and even mortality (Hardy et al., 2011; Lord et al., 2018). In addition to cognitive functions, menopause-related dramatic drops in estrogen production have been associated with a decline in physical functions in middle-aged women. Estrogens have been shown to maintain muscle functions (Kitajima & Ono, 2016) and homeostasis (Collins et al., 2019; Sipilä et al., 2015). It has been suggested that estrogens affect skeletal muscle strength in women by preserving muscle mass and quality of the contractile proteins. Additionally, it has been shown that estrogen deficiency impairs muscle regeneration and ultimately impact force generation (Collins et al., 2019). These factors may explain reduction in muscle strength and power in particular during the menopausal transition (Bondarev et al., 2021).

2.2.1 Muscle strength

Skeletal muscle is a dynamic and plastic tissue of the human body that contains 50–75% of body proteins and comprises approximately 40% of total body weight. Skeletal muscle relies on a balance between processes (protein synthesis and degradation) that are prone to several factors, such as nutrition, hormonal balance, physical activity and injuries (Frontera & Ochala, 2015). One of the main purposes of skeletal muscle is to produce force and power (Frontera & Ochala, 2015). Muscle strength refers to the maximal force of short duration that skeletal muscle can produce (Bohannon, 2015). Muscle power, in turn, refers to the ability to perform fast, forceful and propulsive movements (Reid & Fielding, 2012). The production of muscle force during a single contraction is a complex process that depends on appropriate cognitive and neural control, muscle architecture, contractile properties, and force transmission within muscle and from muscle to bone across a joint (McPhee et al., 2013).

The neuromuscular system includes several sites that affect voluntary force/power production, such as the excitatory drive from supraspinal centres, alpha-motoneuron excitability, muscle activity, motor unit recruitment, neuromuscular transmission, muscle mass, excitation-contraction coupling processes and muscle architecture, which can be further categorized as neurological and muscular factors (Clark & Manini, 2008). Concerning the neurological factors, the function of the cortex, spinal cord and neuromuscular junctions influence voluntary activation of the muscle fibres (Gandevia, 2001). Force production requires the recruitment of motor neurons and muscle fibres by the descending drive (Manini & Clark, 2012). When the force of the muscle contraction increases, the activation of the primary motor cortex neurons and firing of the corticospinal neuron increases (Ashe, 1997). Aging is related to several qualitative and quantitative changes of the motor cortex and spinal cord, such as reduction in neuron body size (Haug & Eggers, 1991), cortical atrophy (Salat et al., 2004), reduction in spinal excitability (Smith et al., 2009) and reduced motor unit size and number (McNeil et al., 2005). These alterations in neuronal factors contribute to the loss of muscle strength with increasing age.

Concerning the muscular factors age-related decline in muscle strength is associated with the reduction in muscle cross-sectional area (Jones et al., 2008) and in the size/number of type II muscle fibers (Verdijk et al., 2007). However, it has been shown that decline in muscle strength with increasing age is more rapid than concomitant loss of muscle mass (Goodpaster et al., 2006), and therefore it has been suggested that age-related decline in muscle strength is dependent on the intrinsic force-generating capacity of skeletal muscle rather than the size of the muscle (Kostek & Delmonico, 2011; Manini & Clark, 2012). One factor that may contribute to the decline in intrinsic force-generating capacity with aging is the age-related changes in the excitation-contraction coupling process, which refers to the physiological process of converting neural signals for muscle activation into muscle contraction (Frontera & Ochala, 2015). In addition, an increased stiffness of the whole muscle and in a single fibre (Ochala et al., 2007) as well as changes in the hormonal milieu (Bondarev et al., 2021) have been suggested to be associated with age-related decline in muscle strength. For example, several sites along the neuromuscular system that have been suggested to regulate strength, such as muscle cells (Pöllänen et al., 2011), motoneurons (Behan & Thomas, 2005) and brain tissue (Srivastava et al., 2011), are rich in estrogen receptors. Thus, estrogens may play an important role in maintaining skeletal muscle function (Kitajima & Ono, 2016) by, for example, regulating the size of the cross-sectional area of muscle fibres and increasing the growth of satellite cells (Ikeda et al., 2019) and preserving quality of the contractile proteins (Collins et al., 2019). Therefore, menopause-related hormonal changes have been hypothesized to be associated with reduced muscle strength and power. For example, a previous study showed that postmenopausal women who have experienced a dramatic decrement in estrogen levels have significantly lower-extremity strength and power compared to premenopausal women (Bondarev et al., 2018). In addition, it has been shown that muscle strength and power decrease significantly during the transition from perimenopausal stage to postmenopausal stage (Bondarev et al. 2021).

Strength measurements typically include separate assessments for the upper body and lower limbs. Typically, upper body strength is assessed with handgrip strength in research and clinical settings (Ronkainen et al., 2009). Lower body strength can be assessed with, for example, a maximal isometric knee extension test (Sipilä et al., 1996) or with a repeated chair rise test (Beaudart et al., 2019), which assess dynamic strength. The isometric knee extension test is widely used in research settings, whereas the repeated chair rise test is easy to conduct in clinical settings.

In addition to muscle strength, it is often useful to assess lower-extremity functioning on a wider scale among older adults. Lower-extremity functioning can be assessed, for example, with the Short Physical Performance Battery (SPPB) (Guralnik et al., 1994) or the Timed Up and Go Test (TUG) (Podsiadlo & Richardson, 1991). These short screening tests assess strength, balance, and walking performance, and are simple and quick to use in clinical or research settings. Both tests are widely used and considered to be suitable for assessing older adults, and they have been shown to reliably predict risk of mortality, institutional care, difficulties of daily living (Freiberger et al., 2012) and falls (Shimada et al., 2009).

2.2.2 Postural control

Postural balance can be defined as the ability to maintain one's centre of gravity within the base of support. Postural balance can be further identified as static, which refers to the ability to maintain balance when standing still, and dynamic postural balance, which refers to the ability to maintain balance during movement (Rogers et al., 2013). Maintaining balance requires interplay of the sensory systems, central nervous system and musculoskeletal system (Konrad et al., 1999). The process starts when the central nervous system receives sensory information from peripheral receptors. The information is processed in the spinal cord, the lower and mid-brain or the cortex, depending on the musculoskeletal action needed (reflexive activation, automatic activation, or voluntary movements, respectively). Finally, the processed information is sent back to the musculoskeletal system, which provides the needed action to maintain balance (Rogers et al., 2013; Winter, 1995).

Systems regulating postural balance are sensitive to age-related decline (Maki & McIlroy, 1996). For example, poor hearing (Viljanen et al., 2009), impaired somatosensory system (Whipple et al., 1993), changes in vision (Kulmala et al., 2009), muscle weakness (Manini & Clark, 2012) and increased number of chronic conditions (Rogers et al., 2013) have been suggested to explain balance deficits among older adults. It has been shown that declines in balance start already in middle age; however, the deterioration accelerates at the age of 60 years (Era et al., 2006). Postural control can be assessed by means of postural sway by mapping the centre of pressure excursions with force plates in a static position or during movement (Pollind & Soangra, 2020). Additionally, postural control can be assessed with short screening tests, such as a one-leg stance (Jonsson et al., 2004), TUG (Podsiadlo & Richardson, 1991), the Berg Balance Scale (Downs, 2015) or SPPB (Guralnik et al., 1994).

2.2.3 Walking performance

Walking is a cyclic pattern of movement where the single-support phase and the double-support phase vary when the legs are moved alternately in front of each other in a vertical position (Alamdari & Krovi 2017). Walking requires cognitive functions, especially executive functions and attention (Holtzer et al., 2006; Yogev-Seligmann et al., 2008), sufficient muscle activation, strength and power of the lower limbs (Anderson & Pandy, 2003; Rantanen et al., 2001), as well as postural balance (Winter, 1995). Age-related decline in cognitive functions and muscle strength and power, as well as increasing postural sway, increase the risk for walking limitations. It has been shown that older adults tend to have slower walking speed, shorter step length, and faster heel contact speed compared to their younger counterparts (Lockhart et al., 2003). Reduced walking performance (for example, slow walking speed) has been associated with poor health outcomes, such as increased risk for disability and morbidity (Perera et al., 2016).

In women, deterioration of walking performance may begin already in middle-age due to menopausal hormonal changes (Sowers et al., 2007). However, studies investigating associations between menopausal transition and physical performance have mostly focused on muscle strength and only a few studies have investigated the association between menopausal transition and walking performance. These few studies have showed mixed results. For example, Bondarev et al. (2021) found that maximal walking speed was not compromised during menopausal transition, whereas Sowers et al. (2007) found that self-selected walking speed significantly reduced during menopausal transition.

Among older adults, walking is often compromised in dual-task conditions, which refer to situations when secondary tasks need to be performed while walking: for example, when screening traffic, avoiding obstacles or talking while walking (Shumway-Cook et al., 2007). It has been shown that in older adults, walking under dual-task conditions is associated with reduced walking speed (Coppin et al., 2006), increased walking variability (Dubost et al., 2006) and increased numbers of missteps while walking in complex terrain (Lindenberger et al., 2000).

Several neuropsychological theories have been developed to explain reduced walking performance under dual-task conditions. The *capacity-sharing theory* suggests that the need to divide attention between two attention-demanding tasks causes reduction in at least one of the tasks because of the limited attentional capacity (Tombu & Jolicoeur, 2003). The ability to divide attention is reduced with increasing age (McDowd & Craik, 1988), and this has been suggested to explain dual-task interference among older adults. The *bottleneck theory* suggests that performing two or more tasks which are processed by the same neural processor or networks creates the bottleneck, and processing of the secondary task does not begin until the first task is processed (Pashler, 1994). The *multiple resource models* suggest that reduction of secondary tasks in dual-task conditions is task-dependent and that dual-task interference only occurs if both tasks require the same sources (Pashler, 1994).

Different procedures must be used when measuring different aspects of walking. Habitual walking speed refers to the self-selected walking speed that is used, for example, when visiting a store. Among older adults, reduced habitual walking speed has been associated, for example, with cognitive impairment, institutionalization, falls and mortality (Abellan van Kan et al., 2009). Habitual walking speed can be assessed with, for example, walking over a 2.44 meter distance (Guralnik et al., 1994). Maximal walking speed may be needed when crossing the road during a green light or trying to catch a bus. Compared to habitual walking speed, maximal walking speed requires additional physical effort and is more sensitive to different levels of cognition (Fitzpatrick et al., 2007), and it can be considered as the best marker for cognition among the walking tests in older adults (Umegaki et al., 2018). Maximal walking speed is typically assessed with a 10-meter maximal walking speed test. Community walking, which requires muscle strength, cognitive functions, and endurance, is necessary to access goods and services, and it requires strength, power, and endurance. Community walking can be assessed with, for example, a 6-minute walking test (Mänttäri et al., 2018).

Dual-task walking performance can be measured with several different test procedures. Preferred walking speed in a dual-task performance test might be habitual (Menant et al., 2014) or maximal (Kovanen et al., 2018) and the nature of the secondary task can vary. Secondary tasks can be, for example, a visuospatial task (Menant et al., 2014), talking while walking, walking over obstacles (Coppin et al., 2006) or naming words from a certain category (Kovanen et al., 2018). However, when comparing results of the walking measurements across the studies, the factors that affect them should be considered. There is still no standardized protocol for walking measurements; therefore, in addition to distance and preferred speed, the type of start (acceleration or static), path and timing instrument (Middleton et al., 2015) may vary between measurements and have an effect on the results.

2.3 Association between cognitive and physical functions

Previous research has shown that cognitive and physical functions are associated at least among older adults (Demnitz et al., 2018; Ramnath et al., 2018; van Iersel et al., 2008). For example, Demnitz et al. (2018) showed an association between better performance in set shifting and updating, processing speed and memory and faster walking speed, better postural balance and lower-extremity functioning in community-dwelling adults (mean age 62.9±10.2, range 45–87 years). In addition, Ramnath et al. (2018) found a positive association between inhibition and hand-grip strength, and van Iersel et al. (2008) showed a positive relationship between set shifting and balance among older men and women (mean age 80.6±4.0, range 75–93 years). In addition, it has been shown that reduced cognitive functioning predicts slow walking speed (Holtzer et al., 2006) and that slow gait speed predicts a decline in cognitive functions among older adults (Inzitari et al., 2007). These findings suggest that the association between cognitive functions and physical functions is bidirectional (Basile & Sardella, 2020; Krall et al., 2014). Basile and Sardella (2020) further hypothesized that reductions in cognitive and physical functions are associated, and it can therefore be considered that decline in these functions share common rather than parallel pathways.

It has been suggested that concerning cognitive and physical functions, there is an association between executive functions and walking in particular. However, knowledge is still inconsistent if some subdomain of executive functions is more strongly associated with different type of walking or physical performance compared to others. Moreover, previous research investigating the relationship between subdomains of executive functions and walking, and lower-extremity functioning have reported partially mixed results. Positive association between inhibition (Demnitz et al., 2018), set shifting (Berryman et al., 2013; Demnitz et al., 2018) or updating (Demnitz et al., 2018; Morris et al., 2016; Soumare et al., 2009) and walking have been reported in some but not all studies (Hausdorff et al., 2005; Valkanova et al., 2018). The underlying discrepancy between studies could be due to methodological differences: for example, differences in sample sizes, exclusion criterions and measurements protocols (physical and executive functions). However, the studies were mainly conducted among well-functioning, rather healthy older adults who did not have cognitive deficits.

Several brain structures and neuronal networks are included in controlling executive functions (Wu et al., 2020) and walking (Grande et al., 2019). For example, subdomains of executive functions have been shown to increase activation in the frontoparietal network (including frontal eye field, intraparietal sulcus, and dorsolateral prefrontal cortex), the cingulo-opercular network (including anterior cingulate cortex, the anterior insular cortex) and the striatum (Wu et al., 2020). Moreover, walking relies on interplay between the prefrontal (complex motor responses and adaption), motor (global motor control) and posterior parietal cortices (visuomotor transformation), basal ganglia (walking speed), thalamus and lower structures such as brainstem and cerebellum (motor coordination and error corrections), and spinal cord (central pattern generations) (Grande et al., 2019). It has been suggested that the association between executive functions and walking/physical functions may be due to the partly overlapping anatomical locations controlling both performances. Shared structures are located mainly in the prefrontal and parietal cortices as well as in the basal ganglia and cerebellum (Clouston et al., 2013; Poole et al., 2019). Overlapping brain areas of executive functions and walking are shown in Figure 1.

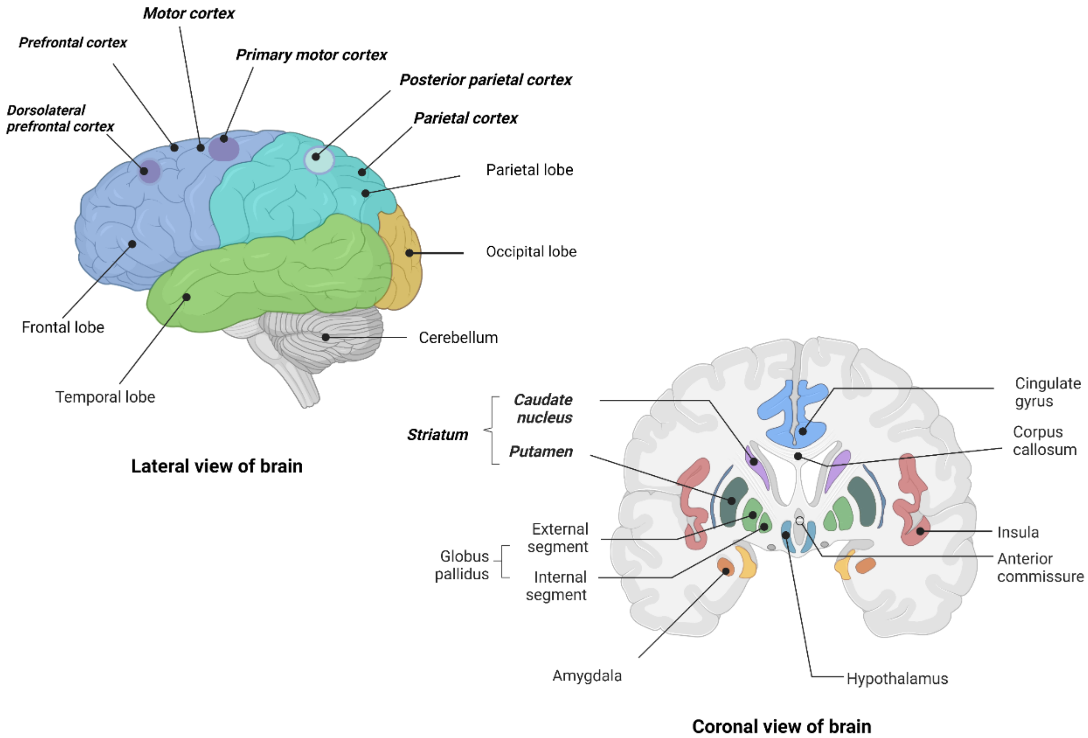

FIGURE 1 Lateral and coronal views of the brain. Overlapping brain areas of executive and physical functions are displayed in bolded italic font.

2.4 Improving executive functions with physical and cognitive training

In recent years, there has been growing interest in investigating whether cognitive functions can be improved with cognitive or physical training, or a combination thereof. Some of the previous studies on the effect of training on executive functions have suggested that computer-based cognitive training (Ten Brinke et al., 2020), physical training (Northey et al., 2018) as well as combination of cognitive and physical training may improve, especially, executive functions among healthy older men and women (Ten Brinke et al., 2020). However, some of the studies have not been able to find positive effect of the cognitive (Lampit, Hallock, & Valenzuela, 2014) and physical training (Voss et al., 2013). In addition, it is still unclear whether a combination of cognitive and physical training provides any superior benefit for executive functions, compared to cognitive or physical training alone. However, when interpreting the results of the previous research it must be noted that study designs, methods and interventions differ across the studies and controversies in previous finding may at least partly be explained by these differences.

2.4.1 Cognitive training

It has been suggested that computer-based cognitive training may improve executive functions among healthy, cognitively intact community-dwelling men and women (mean age 65.0±0 and 72.4±4.8, respectively) (Corbett et al., 2015; Ten Brinke et al., 2020). However, the previous research investigating effect of cognitive training on executive functions has partly reported conflicting results. Some studies have found that among healthy older adults who had intact cognition, cognitive training benefit executive functions related to inhibition (Ten Brinke et al., 2020), set shifting (Marusic et al., 2022) and updating (Fu et al., 2020) whereas other studies have found that cognitive training did not improve inhibition (Lampit, Hallock, Moss, et al., 2014) or set shifting (Simpson et al., 2012). Gajewski et al. (2020) suggested that cognitive training might be beneficial for fluid cognitive domains, which require cognitive processing and the ability to manipulate and transform incoming information, such as executive functions and attention, but not for crystallized cognitive domains, such as memory. Moreover, the systematic review and meta-analysis by Nguyen et al. (2019) suggested that cognitive training targeted at inhibition, set shifting and updating provides immediate as well as long-term benefits for these subdomains among healthy older adults.

Training response of cognitive and physical training may be dependent on the type of the training and training frequency. It has been hypothesized, that computer based cognitive training is most beneficial when it is performed one to three times a week in supervised conditions (Lampit, Hallock, & Valenzuela, 2014). In addition, meta-analyses by Karbach and Verhaeghen (2014) and Nguyen et al. (2019) have showed that cognitive training targeted to executive functions is beneficial for targeted domain but also untrained domains and overall cognitive functions. Although, the transfer effect to untrained domains might be relatively small and cognitive training including exercise for multiple executive domains has been shown to produce broadest benefit for overall executive functions subdomains (Nguyen et al., 2019).

Several factors have been hypothesized to explain the positive effects of cognitive training on executive functions. First, it might be that practising cognitive tasks makes the underlying cognitive and neural processes more automatic, which in turn allows more efficient processing, and thus performing the same task becomes quicker and more accurate (Jonides, 2004). In addition, cognitive training has been shown to increase expression of the Brain-Derived Neurotrophic Factor (BDNF) (Ledreux et al., 2019) and activity in the prefrontal cortex (Nouchi et al., 2020), which might be beneficial for executive functions. It has also been suggested that cognitive training promotes compensatory recruitment of additional neural circuitry to complement or provide alternative ways to solve cognitive challenges. This "scaffolding" occurs mainly in the prefrontal cortex and therefore it might be especially beneficial for executive functions (Park & Reuter-Lorenz, 2009). Moreover, in a recent study, Ten Brinke et al. (2021) suggested that computerized cognitive training targeting on visual, focus, speed, memory, problem-solving and language improves executive functions among healthy, cognitively intact men and women over the age of 70 by decreasing the correlation between the default mode network and the frontoparietal network.

2.4.2 Physical training

Multiple meta-analyses (Colcombe & Kramer, 2003; Northey et al., 2018) and randomized controlled trials (Langlois et al., 2013; Nouchi et al., 2014) have suggested that aerobic, resistance as well as multimodal physical training improve executive functions related to updating (Colcombe & Kramer, 2003; Northey et al., 2018), set-shifting (Langlois et al., 2013) and inhibition (Nouchi et al., 2014) among older adults. However, for example, a randomized controlled trial by Voss et al. (2013) and meta-analysis by Young et al. (2015) found that aerobic training did not induce benefits in these domains. Additionally, the meta-analysis by Barha et al. (2017) suggested that women's and men's executive functions respond differently to physical training interventions. Thus, the effects of the physical training intervention on executive functions may be dependent on training type and sex.

Previous meta-analyses investigating the role of type of physical training on executive functions have shown partially mixed results. For example, in their meta-analysis, Barha et al. (2017) showed that aerobic training benefitted executive functions related to inhibition, updating and set shifting more, compared to resistance or multimodal training. On the other hand, according to the meta-analysis by Colcombe and Kramer (2003) multimodal physical training including aerobic and strength training is most beneficial for executive functions. Additionally, meta-analysis by Northey et al. (2018) suggest that performing both aerobic training and resistance training in 45–60-minute sessions of at least moderate intensity may be the most beneficial practice to improve subdomains of executive functions among healthy older adults.

Concerning the role of sex in training response, meta-analysis by Barha et al. (2017) found that aerobic exercise, resistance training and multimodal physical training, including aerobic and resistance training, provide greater benefit to women's executive functions related to inhibition, set shifting and updating, compared to men. The sex differences in the training response of physical exercise for executive functions may be due to smaller age-related decline in executive functions in women compared to men (McCarrey et al., 2016) and the different neural circuits and/or molecular mechanisms utilized to solve executive tasks between men and women (Grissom & Reyes, 2019). It might be that the neural circuitry underlying executive functions remains more intact among older women, compared to men, and therefore they are more responsive to targeted exercise interventions (Barha et al., 2017).

The mechanisms by which physical training improves executive functions are not fully understood. It has been shown that a higher level of physical activity has been associated with larger total brain volume and larger grey matter volume, especially in the frontal lobes (Rovio et al., 2010). In addition, physical training increases expression of the BDNF (Tsai et al., 2021), which has an important role in facilitating neural repair and promoting synaptic plasticity, neurogenesis and angiogenesis (Vaynman et al., 2004; Yang et al., 2014), as well as activity in the prefrontal cortex (Nouchi et al., 2014), which has been suggested to improve executive functions. Moreover, physical training increases cerebral blood flow, decreases oxidative stress (De la Rosa et al., 2020) and has positive effects on cardiovascular risk factors such as hypertension (Lesniak & Dubbert, 2001), insulin resistance (Kwon et al., 2019) and high cholesterol levels (Wilund et al., 2009), which have been shown to be beneficial for executive functions (Krivanek et al., 2021).

2.4.3 Cognitive and physical training

Previous randomized controlled trials (Eggenberger et al., 2015, 2016; Ten Brinke et al., 2020) have suggested that a combination of cognitive and physical training is an effective way to improve inhibition (Eggenberger et al., 2016), set shifting (Eggenberger et al., 2015; Ten Brinke et al., 2020) and updating (Eggenberger et al., 2015) among healthy, cognitively intact older adults. However, it is still under debate if combined training provides greater benefits to executive functions, compared to cognitive training alone or physical training alone. For example, concerning the comparison between cognitive and physical training and physical training alone, Hagovska & Nagyova (2017) found that computer-based multidomain cognitive training combined with multicomponent physical training improves inhibition more, compared to multicomponent physical training alone, among older adults with mild cognitive impairment. In addition, Eggenberger et al. (2015) found that attention-demanding cognitive training performed simultaneously with aerobic training improved inhibition, set shifting and updating more, compared to treadmill walking among healthy older adults. Recent meta-analysis (Guo et al., 2020), in turn, found that combined training is more effective in improving set shifting but not inhibition or updating, compared to physical training alone among healthy older adults and older adults with mild cognitive impairment.

A similar phenomenon is present concerning the studies comparing the effects of combined training and cognitive training alone among healthy older adults. Ten Brinke et al. (2020) showed that multidomain computer-based cognitive training complemented with aerobic training benefits set shifting (but not inhibition) significantly more, compared to cognitive training alone, in healthy older adults. Similar results were reported also in meta-analysis by Guo et al. (2020). They found that a combination of cognitive and physical training compared to physical training alone provides superior benefit for set shifting but not for inhibition and updating among healthy older adults and older adults with mild cognitive impairment. However, Rahe et al. (2015) were not able to show that a combination of cognitive training and physical training provides additional benefit for inhibition and updating compared to cognitive training alone in healthy older adults. These findings suggest that an additional benefit of combined cognitive and physical training might be domain-dependent.

Previous reviews and meta-analyses investigating the relationship between training protocol and combined cognitive and physical training-induced positive effects on executive functions in older adults have shown partly mixed results. It has been suggested that for executive functions, a low level of practising (≤ 3 session/week) is more efficient than a high level of practising (≥5 times/week) (Guo et al. 2020). Interventions that last less than 6 months have been shown to be more effective for executive functions than interventions that last over 6 months (Gavelin et al., 2021; Guo et al., 2020). In addition, Zhu et al. (2016) suggest that the best practice for performing combined training is under supervised conditions, whereas Gavelin et al. (2021) did not find moderating effects of supervision. In addition, it has been suggested that performing cognitive and physical training simultaneously might be important for interaction effects between cognitive and physical components (Fissler et al., 2013) and therefore simultaneously performed training is more beneficial for cognitive functions, including executive functions. This suggestion is in line with findings of meta-analysis by Gavelin et al. (2021). However, for example Guo et al. (2022) were not able to find additional benefit of simultaneous training compared to sequential training.

The combination of cognitive and physical training may benefit executive functions through two mechanisms. It has been suggested that physical training increases the plastic potential of the brain, whereas cognitive exercise guides it to induce beneficial plastic change by increasing the number of surviving new-born neurons and integrating new neurons and synapses into pre-existing neural networks (Bamidis et al., 2014; Fissler et al., 2013).

3 PURPOSE OF THE STUDY

The purpose of this study was to investigate if cognitive and physical functions are associated among community-dwelling older adults. A further objective was to explore if participant characteristics such as age and sex were associated with the effects of physical training and a combination of cognitive and physical training on executive functions among community-dwelling older adults. In addition, the cross-sectional and longitudinal relationships between cognitive and walking performance as well as changes in cognitive functioning over the menopausal transition were investigated in middle-aged women. The specific research questions were:

1. Are executive functions associated with different aspects of walking performance and lower-extremity functioning among community-dwelling 70–85-year-old men and women who do not meet physical activity guidelines?

2. Are baseline characteristics (age, sex, compliance with training intervention, global cognition) associated with the effects of physical training or a combination of cognitive and physical training on executive functions among community-dwelling 70–85-year-old men and women who do not meet physical activity guidelines?

3. Does performance in cognitive functions change over the menopausal transition from perimenopause to post menopause among 47–55-year-old women?

4. Are executive functions associated with walking speed and dual-task cost in walking speed in 47–55-year-old perimenopausal women? Are cognitive functions measured at perimenopause associated with walking performance at post menopause or vice versa?

4 MATERIALS AND METHODS

4.1 Study design and participants

This study utilizes data from the two large research projects conducted at the Gerontology Research Center (GEREC) and the Faculty of Sport and Health Sciences, University of Jyväskylä: "Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women" (PASSWORD study, Sipilä et al., 2021) and "Estrogenic Regulation of Muscle Apoptosis" (ERMA study, Kovanen et al., 2018). The study designs, participants and outcomes are summarized in Tables 1 and 2.

TABLE 1 Summary of the datasets, study designs and participants.

Paper	Dataset	Design	n	Age (mean ± SD)
I	PASSWORD	Design and methods	Target 310	70–85
II	PASSWORD	Cross-sectional	314 Women n=188 Men n= 126	74.5±3.8 Women 74.5±3.8 Men 74.4±3.9
III	PASSWORD	Subgroup analysis of a randomized controlled trial	PT n=159 PTCT n=155	74.5±3.8 PT 74.5±3.7 PTCT 74.4±3.9
IV	ERMA	Cross-sectional and longitudinal	342 Early pm n=158 Late pm n=184 Follow-up n=195	51.2±1.9 Early pm 50.6±1.9 Late pm 51.7±1.9 Follow-up 51.8±1.9

Note. SD=standard deviation, PASSWORD= Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women, ERMA= Estrogenic Regulation of Muscle Apoptosis, PT=physical training, PTCT=physical and cognitive training, pm=perimenopausal.

TABLE 2 Summary of outcomes and statistical methods used in the papers.

Paper	Dataset	Outcomes	Statistical method
1	PASSWORD	Design and methods of a randomized controlled trial	
2	PASSWORD	**Executive functions:** TMT B-A, the Stroop test, the Verbal Fluency test **Physical functions:** 10m maximal walking speed, 20m habitual walking speed, 6-min walking distance, dual-task cost in walking speed, SPPB **Covariates:** age, sex, education, physical activity, MMSE scores, smoking	Multiple linear regression analysis
3	PASSWORD	**Executive functions:** TMT B, the Stroop test, the Verbal fluency test **Participant characteristics for the subgroup analysis:** age, sex, CERAD, adherence to training sessions	Longitudinal two-group linear path model
4	ERMA	**Cognition:** TMT A and B, the Verbal Fluency test, the Digit Span Test, the Word List Test, Family pictures test	Related samples t-test, Wilcoxon signed rank test
4	ERMA	**Executive functions:** TMT A and B, the Verbal Fluency test **Physical functions:** 6-min walking distance, 10m maximal walking speed, dual-task cost in walking speed **Covariates:** age, education, menopausal symptoms, physical activity (regression models) follow-up time (structural equation modelling)	Multiple linear regression analysis, structural equation modelling

Note. PASSWORD= Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women, ERMA= Estrogenic Regulation of Muscle Apoptosis, SPPB=Short Physical Performance Battery, TMT= Trail Making Test, MMSE=Mini-Mental State Examination, CERAD=Consortium to Establish a Registry for Alzheimer's Disease.

4.1.1 Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women (PASSWORD, papers II & III)

The PASSWORD study (ISRCTN52388040) was a 12-month randomized controlled trial (RCT) that investigated whether a combination of physical and cognitive training (PTCT) provides additional benefits to walking performance and executive functions, compared to physical training (PT) alone, among community-dwelling older adults who did not meet physical activity guidelines at baseline (Sipilä et al., 2018). The sample of 314 participants were recruited into the study from the population register of the city of Jyväskylä. Participants were eligible for the study if they were: aged 70–85 years, lived independently in the city of Jyväskylä, walked less than 150 minutes per week and had no regular resistance training, were able to walk 500 meters without assistance (cane was allowed) and had intact cognition (Mini-Mental State Examination (MMSE) scores ≥24 and acceptable The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores). Participants were excluded from the study if they had a severe chronic condition or medication that affected cognitive or/and physical functions, had excessive use of alcohol, another household member was a participant in the PASSWORD study, or any contraindications for physical exercise or walking tests were found. The participants were randomized into physical and cognitive training (n=155) or physical training alone (n=159) groups after the baseline measurements. The follow-up measurements were organized at six months and 12 months. The current study utilizes baseline (paper II) as well as follow-up data (paper III) from the PASSWORD study. The study flow of PASSWORD is shown in Figure 2.

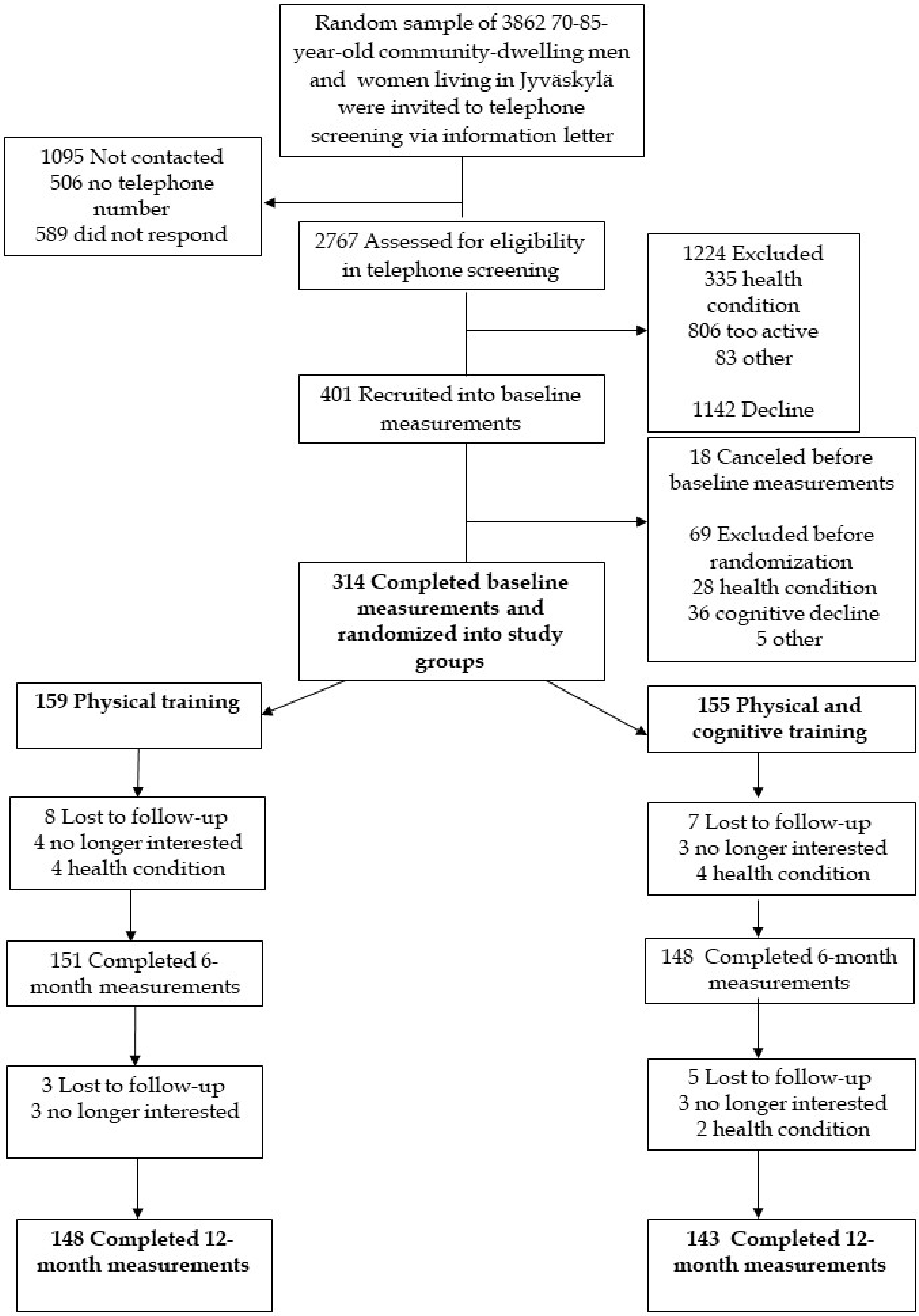

FIGURE 2 Flow chart of the PASSWORD study.

4.1.2 Estrogenic regulation of muscle apoptosis (ERMA, paper IV)

The ERMA study investigated the associations between sex hormones, muscle biology, and the physical and cognitive functions among 47–55-year-old women living in the city of Jyväskylä or neighbouring municipalities (Kovanen et al., 2018). Participants were eligible for the study if they were willing to participate, had self-reported body mass index (BMI) of <35, were not currently pregnant or lactating, did not have a condition affecting ovarian functions (bilateral ovariectomy, estrogen-containing hormonal preparations, other medication affecting ovarian function) or medication seriously affecting muscle functions.

The recruitment started with an information letter and prequestionnaire sent to a total of 6878 women who were at the age of 47 to 55 and lived in the city of Jyväskylä or neighbouring municipalities. In the next phase of the recruitment, potential participants who were willing to participate (n=1627) were invited for a laboratory visit to give fasting blood samples and fill in the health screen questionnaire. After the first laboratory visit, 1393 women were assigned to four groups: premenopausal, early perimenopausal, late perimenopausal, and postmenopausal, based on their menopausal status. The group assignment was based on follicle-stimulated hormone (FSH) levels and self-reported menstrual cycle. The final phase of the recruitment included examination by the study nurse or physician and measurements for, for example, cognitive and physical functions. Participants who had reported unclear medical conditions or arrhythmia during the second phase of the recruitment underwent a medical examination to ascertain safe participation in physical performance measurements. Participants who had any contraindications for physical performance measurements were excluded from the study. Finally, 1158 women participated in the laboratory measurements at baseline (physiological and psychological abilities). Out of these, the women included in the perimenopausal groups (n=381) were regularly screened until they received postmenopausal stage. After reaching postmenopausal stage, the measurement procedure was repeated. This study utilized baseline data from the participants whose cognition was measured at baseline (n=342) and follow-up data from the participants who were screened over the menopausal transition and who reached postmenopausal stage and did not start hormone therapy during the study (n=195). The study flow of ERMA is shown in Figure 3.

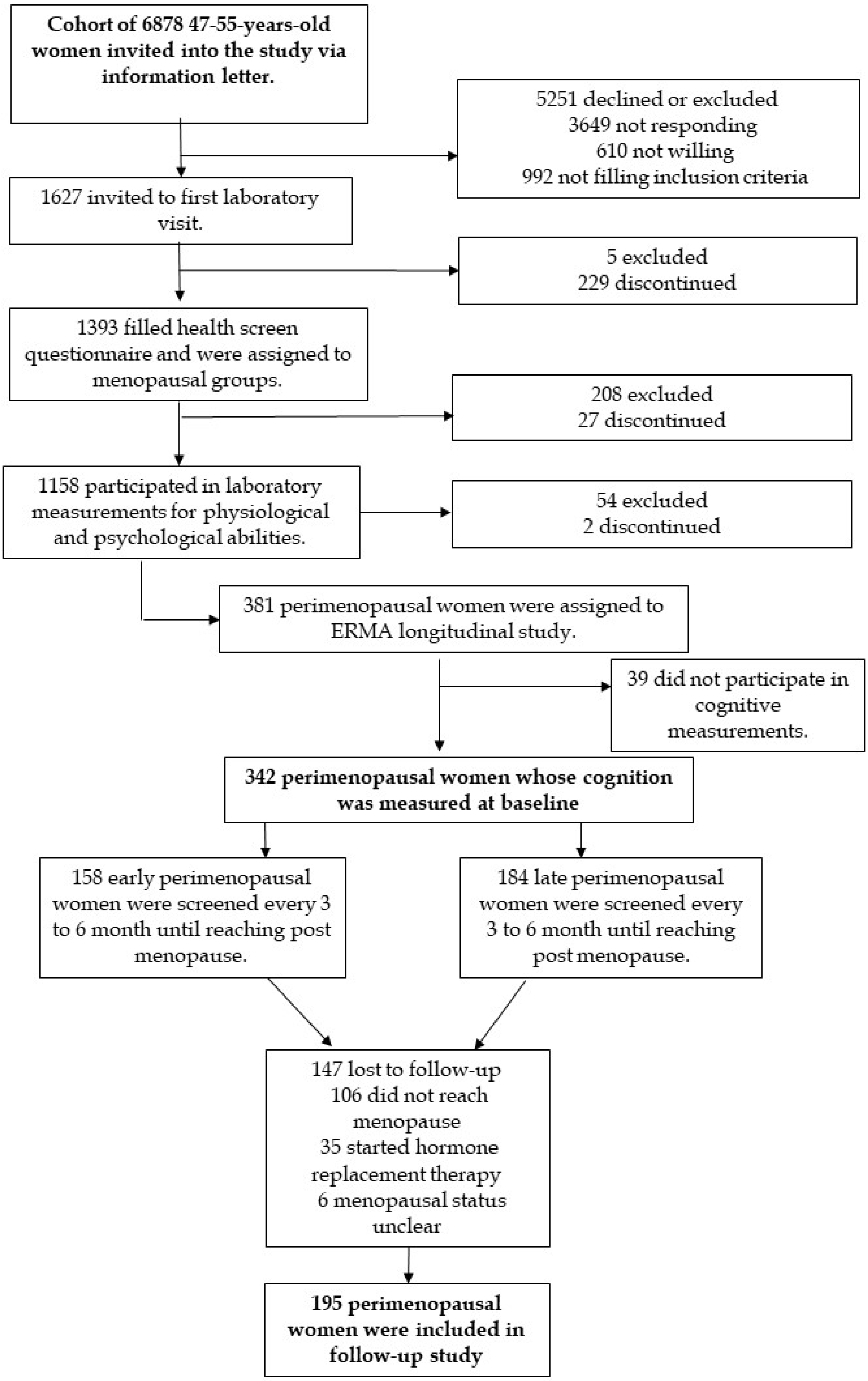

FIGURE 3 Flow chart of the ERMA study.

4.2 Ethics

Both studies were performed according to good scientific practice and approved by the ethics committee of the Central Finland Health Care District (the PASSWORD study, K-S shp Dnro 11U/2016; the ERMA study, K-S shp Dnro U/2014). All participants received written information explaining the risks and personal benefits associated with laboratory examinations and gave permission for use of the data for research purposes and publications. All participants signed informed consent before baseline measurement or tissue/blood sample collection. All participants had the right to end participation at any point in the studies without any ramifications. In the PASSWORD study, exercise-induced falls and injuries were monitored during the study. All data of the studies was handled and analysed confidentially.

4.3 Measurements

4.3.1 Executive functions and psychomotor speed

The Trail Making Test (TMT) was used to assess psychomotor speed and executive functions related to set shifting (papers II, III and IV) (Reitan, 1958). TMT is a paper-and-pencil test composed of two parts, A and B. In part A, participants were instructed to combine as fast as possible numbers from 1 to 25 in the correct order by drawing a line between the numbers (i.e. from 1 to 2 and from 2 to 3, etc.). The numbers were placed on the paper in random order. In part B, participants were asked to alternately combine numbers (1–13) and letters (A–L) in correct order as fast as possible by drawing a line between a number and a letter (from 1 to A and A to 2, etc.). If the participant made an error during the test, the examiner informed him/her immediately, after which the error was corrected, and the test was continued normally. The time (in seconds) to complete the parts was measured with a stopwatch and the time difference between the parts (TMT B–A) was calculated. In each part, shorter time indicates better performance.

The Stroop Colour and Word test (Stroop) was used to assess executive functions related to response inhibition (papers II and III) (Graf et al., 1995). In Stroop, participants were asked to name colours in congruent and incongruent conditions. First, the participants were asked to read aloud the names of the colours printed in black. Next, the participants were asked to name the colours of the ink in which the set of X's were printed. Finally, the participants were asked to name in which colour ink the colour word was printed while ignoring the word itself (for example, the right answer is red when the word 'green' is printed in red). The time to complete each condition was measured with a stopwatch and the time difference between conditions (i.e. inhibition cost) was calculated by subtracting the time spent in naming colours from the time spent in naming colours printed in an incongruent colour. Shorter inhibition cost indicates better performance.

An animal-naming test (Johnson-Selfridge et al., 1998) (paper IV) and a letter-fluency test (papers II and III) were used to assess executive functions related to updating. In the animal-naming test, participants were asked to list as many animals as they could during the one-minute trial. The total number of the listed animals was used as an outcome. In the letter-fluency test (Koivisto et al., 1992), participants were asked to list as many words as they could, starting with prespecified letters (P, A and S) during the three separate one-minute trials. The number of words listed in each trial were summed and used as an outcome. A higher number of listed words indicates better performance in both tests.

4.3.2 Memory

Working memory (paper IV) was assessed with the Digit Span Test (Richardson, 2007) and with the Word List Test (Wechsler, 1997). In the Digit Span Test, participants were instructed to repeat extended number sequences after the examiner as long as they could remember the sequence. The sequences were first repeated forwards and then backwards. The total scores were summed from both (forwards and backwards) tasks. In the Word List Test, the examiner first read aloud 12 words. After that, participants were required to recall and repeat as many words as possible from 12 words read aloud previously by the examiner. The test was performed four times. Finally, after at least 15 minutes, participants were required to recall and then recognize all words that they could from the same list of words without hearing the list again. The total scores of the Word List Test were calculated from the number of words remembered and recalled from all lists. Visual memory (paper IV) was assessed with the Family Pictures Test (Wechsler, 1997). In the Family Pictures Test, four pictures including family members in different situations were shown to participants. The pictures were shown at 10-second intervals. After showing all four pictures, the examiner asked the participants to recall which family members were in a specific picture, where they were and what they were doing. After at least 15 minutes, the test was repeated without showing the pictures again. The test was scored according to the number of recalled details, with higher scores indicating better performance.

4.3.3 Walking performance

Walking performance was assessed with maximal walking speed, walking distance, dual-task cost in walking speed (papers II and IV) and habitual walking speed (paper II). In the maximal walking speed test, participants were asked to walk as fast as possible down a 10-meter laboratory corridor. To achieve maximum speed over the full 10-meters, 2–3-meter acceleration was allowed. The walk was repeated twice, and the fastest time (m/s) measured with photocells was accepted as a result. A six-minute walking test was used to assess community walking (papers II and IV). In this test, participants were required to walk for 6 minutes at their self-selected speed (Mänttäri et al., 2018). The test was carried out on a 20-meter indoor track where the participants travelled back and forth. The distance travelled in 6-minutes was used as an outcome. Habitual walking speed was assessed over 20 meters in the laboratory corridor (paper II) (Abellan van Kan et al., 2009). The time to complete the walk, in seconds, was measured with photocells and walking speed was calculated. The dual-task cost in walking speed was assessed with two different tests. In the PASSWORD study (paper II), participants first performed the previously mentioned 20-meter habitual walking speed test. After the habitual walking speed test, they were instructed to repeat the walk with simultaneous visuospatial cognitive tasks (Menant et al., 2014). The tasks involved three boxes set side by side and labelled A, B and C in the display. Participants were instructed to visualize a star that randomly moved from one box to another. After the three imagined movements, participants were encouraged to name the box containing the star. The starting position of the star and the direction of each movement were informed to participants through headphones during the walk. The new sequence of movements started within one second of the participant answering the previous question. The difference between the two walks, that is, the dual-task cost(s), was calculated. In the ERMA study (paper IV), participants first walked for 10-meters at their maximal walking speed and then repeated the walk with a simultaneous word-naming cognitive test. In the word-naming cognitive test, participants were required to enumerate as many Finnish first names starting with a pre-specified letter as they could, during the 10-meter walk. The time difference between the single-task and the dual-task walks was measured in seconds and the dual-task cost (m/s) calculated.

4.3.4 Lower-extremity functioning

Lower-extremity functioning was measured with the Short Physical Performance Battery (SPPB) (paper II) (Guralnik et al., 1994). The SPPB is composed of three sub-tests: a standing balance test, walking over a short distance and a repeated chair-rise test. In the walking test, participants were instructed to walk for 2.44 meters at their habitual speed. The test was repeated twice, and the scoring was performed according to the faster time. In the repeated chair-rise test, participants were asked to rise from the chair five times as fast as they could. Their arms were supposed to be kept crossed over their chest during the test, if that was possible for the participant. In the standing balance test, participants were first asked to stand with feet side by side, then in the semi-tandem position and finally in the tandem position. If the participant was not able to complete some of the positions, the test was discontinued. The time (max 10s) spent at each position was measured with a stopwatch. Finally, all sub-tests were scored from 0 to 4, and total scores (0–12) were calculated. In the SPPB, higher points indicate better performance.

4.3.5 Participant characteristics and covariates

The sex and date of birth were drawn from the Finnish Digital and Population Data Services Agency and the age was calculated (papers II, III and IV). BMI was calculated from body height and weight measured by the nurse after overnight fasting (papers II and IV). In the PASSWORD study, Finland's integrated patient information system and self-reports were used to collect information about chronic diseases (paper II). Information about the number of indoor and outdoor falls in the previous year and smoking (current, former, never) were self-reported (paper II and III). For the analyses, information about falls and smoking were dichotomized as fallers and non-fallers and smokers and non-smokers.

MMSE (Folstein et al., 1975) was used to assess cognitive status (paper II and III) and CERAD was used to assess global cognition (paper III). The CERAD is a neuropsychological battery that was developed for identifying the prodromal phase of Alzheimer's disease, and it includes five subtests: Category verbal fluency, Modified Boston naming test, Mini-Mental State Examination, Word List Memory and Constructional Praxis. Total scores of the CERAD have been shown to be an accurate measure for detecting cognitive impairment (Paajanen et al., 2010). A seven-point scale was used to assess self-reported physical activity (Hirvensalo et al., 2000) (papers II, III and IV). For the statistical analyses, self-reported physical activity was re-categorized as 1=low level, 2=moderate level, and 3=high level of physical activity. Education was categorized as 1=basic (primary or secondary school), 2=college (applied science or bachelor's degree), 3=university (master's degree or PhD) (papers II, III and IV).

Serum FSH hormone and estradiol levels were assessed by immunoassay (IMMULITE 2000 XPi, Siemens Healthcare Diagnostics, Camberley, UK) (paper IV). The self-reported information about menopausal symptoms experienced, such as hot flashes, joint aches, sexual reluctance, or depression, were categorized as vasomotor symptoms, somatic and pain symptoms, psychological symptoms, and urogenital symptoms (paper IV). The follow-up time was defined by calculating the number of days between the baseline and the follow-up measurements (paper IV).

Training compliance of the PASSWORD study was based on participation in the supervised training sessions and was monitored by the instructors of the training sessions. In the physical training group, training compliance was based on participation in supervised physical training sessions. In the physical and cognitive training group, training compliance was based on participation in supervised physical training sessions and the number of cognitive trainings performed a week. After the intervention, training compliance was calculated and further categorized as high compliance and low compliance. In the physical training group, the high compliance subgroup participated in at least 50% of the supervised physical training sessions. In the physical and cognitive training group, the high compliance subgroup participated in at least 50% of the supervised physical training sessions and performed cognitive training at least twice a week. Low compliance group participated less than 50% into supervised physical training sessions and/or performed cognitive training less than two times a week (paper III).

4.4 Interventions of the PASSWORD study

Both training groups (PT and PTCT) received a 12-month structured physical training program including two 45–60-minute supervised sessions per week (Sipilä et al., 2021), with one aiming to increase muscle strength and postural balance and the other aerobic fitness, walking performance and dynamic balance. The training protocol was adapted from the physical activity guidelines at the time and the previous studies (Fielding et al., 2011; Portegijs et al., 2008) The supervised resistance training session took place in local senior gyms equipped with resistance training machines utilizing air-pressure technology. The resistance training sessions started with approximately 10 minutes of warm-up, which included, for example, balance exercises. After the warm-up, 8 to 9 exercises for the lower body, trunk and upper body were performed. The supervised aerobic training sessions were performed outdoors except during winter months, when training took place in an indoor sports hall. The aerobic training started with a 10–15-minute warm-up, which included short walks at habitual walking speed and dynamic balance exercises. After the warm-up, the training session continued with a continuous walk for 10 to 20 minutes. The target intensity of the continuous walk was 13 to 15 (somewhat hard to hard) on the Borg Scale (Borg, 1982). The intensity, resistance and difficulty of all exercises increased progressively during the training period. In addition to supervised sessions, participants were encouraged to perform a structured and progressive home-based exercise program (including walking, balance exercises, strengthening activities with resistance bands and stretching) 2 to 3 times a week and accumulate at least 150 minutes of aerobic exercise (for example, walking) per week in periods of at least 10 minutes.

The combination group also received a 12-month computer-based cognitive training program. The cognitive training was developed to improve especially working memory and executive functions that are sensitive to aging processes (Dahlin et al., 2008; Ngandu et al., 2015). The difficulty level of the exercises increased individually while training proceeded. Participants were instructed to perform all tasks as fast and accurately as possible. Cognitive training started with supervised sessions. After 2 to 3 supervised sessions, participants who had the necessary computer skills and a computer available at home were able to start cognitive training at home. Those who did not have a computer at home had an opportunity to train at the university computer class. Support for computer skills was available during the supervised sessions. Participants were encouraged to perform cognitive training 3 to 4 times a week.

4.5 Statistical methods

As descriptive statistics, means and standard deviations for continuous variables and frequencies and percentages for categorical variables were reported (papers II, III and IV). The normality of the distribution of the continuous variables was tested with the Shapiro-Wilk test and Kolmogorov-Smirnov test. An independent samples t-test (papers II and IV) was used to compare means for normally distributed variables and Mann-Whitney's U-test (papers II and IV) was used to compare non-normally distributed variables. A chi-square test was used to compare categorical variables (papers II and IV). The correlation between the main outcomes and covariates (paper II) was tested with the Pearson correlation coefficient and Spearman's rank correlation coefficient. All descriptive analyses were conducted with IBM SPSS version 26. The significance level was $p<.05$ at all analyses.

Multiple linear regression analyses were used to assess cross-sectional associations between physical functions and executive functions (papers II and IV). In paper II, the main effect model, the executive functions-sex interaction model, and the sex-stratified models were constructed to explain physical function tests. In the main effect model, the main predictors were executive function and sex. In the executive functions-sex interaction model, the main predictors were executive functions, sex, and the executive function sex interaction. In the sex-stratified models, the main predictor was executive function, and the analyses were conducted separately for both sexes. Bonferroni correction was used to adjust main effect models and sex-interaction models for multiple testing. The results were interpreted from the main effects models when the sex-interaction p-value was non-significant and from the sex-stratified models when the sex-interaction p-value was significant. All model sets were adjusted for age, MMSE scores and smoking. In paper IV, regression models were conducted separately for early and late perimenopausal women. Moreover, separate models were constructed for each executive function subdomain. The main explanatory variable in models was a walking test (maximal walking speed, dual-task walking speed or 6-minute walking distance), which was separately entered in the models. Models were adjusted for age, physical activity, education, vasomotor, psychological, and somatic or pain symptoms. In both papers (II and IV), two dummy variables were constructed from three-class variables: education and physical activity. Multiple linear regression analyses were conducted with IBM SPSS version 26.

Longitudinal two-group linear path models were used to assess associations of participant characteristics and background variables with the intervention-induced changes in executive functions (paper III). In these models each outcome was regressed on the exposure independent variable within the measurement's waves while accounting for the within-subject correlation. The path model approach permits more general outcome covariance structure specification and flexible handling of missing data compared to repeated measurements ANOVA that otherwise has a similar fixed effects model structure. Differences in the regression coefficients from the measurement waves as the within-group change in the association over time (time effect) were assessed using custom contrasts. The interaction contrast tested the between-group difference in PTCT and PT group changes. A similar model was used for binary exposure variables. All three outcomes were continuous variables.

Structural equation modelling (SEM) using a cross-lagged path model was used to investigate longitudinal bidirectional associations between cognitive functions and walking performance among middle-aged women. Maximum likelihood estimation with robust standard errors and scale-corrected chi-square values (MLR estimator) was used in all the SEM models. The analyses started with invariance testing, which was conducted through several models (Widaman et al., 2010) and continued with multigroup modelling which tested the model structure suitability for early and late perimenopausal groups. In the final models, correlation between cognitive functions and walking performance in perimenopause as well as longitudinal paths from baseline cognitive functions to follow-up walking performance and vice versa were included. In addition, stability over time in cognitive functions and walking performance was investigated. The longitudinal models were adjusted for follow-up time. Structural equation modelling was conducted with Mplus statistical package version 7.3 (Muthen & Muthen, 2017).

Change in cognitive performance over the menopause transition was investigated among middle-aged women (paper IV). The analysis was conducted separately for early and late perimenopausal women. A paired samples t-test was used to compare performance in cognitive functions in the perimenopausal stage and after reaching the postmenopausal stage among normally distributed variables. The same comparison among non-normally distributed variables was conducted with a Wilcoxon signed rank test. Paired samples t-test was conducted with IBM SPSS version 26.

5 RESULTS

5.1 Characteristics of participants (papers I–IV)

The participants' characteristics and performance in physical and cognitive functions in the PASSWORD and ERMA studies are summarized in Tables 3, 4 and 5. The mean age of the participants was 74.5 (SD 3.8) years in the PASSWORD and 51.2 (SD 1.9) years in the ERMA. Moreover, 21% of the PASSWORD participants and 45% of the ERMA participants had a high education. Concerning the self-reported physical activity, 87% of the PASSWORD and 39% of the ERMA participants reported that their physical activity level was low or moderate. The PASSWORD participants performed TMT B on average in 131.5 seconds, whereas the ERMA participants performed TMT B on average in 62.1 seconds. The mean maximal walking speed was 2.0 m/s among the PASSWORD participants and 2.6 m/s among the ERMA participants. The PASSWORD participants walked approximately 475.4 meters during the six-minute walking test, whereas the walked distance among ERMA participants was 663.7 meters.

TABLE 3 Background characteristics at baseline among PASSWORD and ERMA participants. Means and standard deviations or frequencies and percentages.

	PASSWORD					ERMA			
	All (n=314)	Women (n=188)	Men (n=126)	PT (n=159)	PTCT (n=155)	All (n=342)	Early pm (n=158)	Late pm (n=184)	Follow-up (n=195)
Age	74.5±3.8	74.5±3.8	74.4±3.9	74.5±3.8	74.4±3.9	51.2±1.9	50.6±1.9	51.7±1.9	51.8±1.9
Height (m)	1.66±0.1	1.61±0.1	1.74±0.1	1.66±0.1	1.66±0.1	1.65±0.1	1.65±0.1	1.65±0.1	1.65±0.1
Weight (kg)	76.9±14.2	71.9±13.1	84.3±12.5	76.9±14.0	76.9±14.5	70.0±11.2	69.9±11.5	70.2±11.0	69.6±11.3
BMI	27.9±4.7	28.0±5.3	27.9±3.6	27.9±4.5	28.0±4.9	25.7±3.9	25.6±3.9	25.8±3.9	25.6±4.0
Education (%)									
Low	48 (15)	21 (11)	27 (21)	25 (16)	23 (15)	6 (2)	1 (1)	5 (3)	5 (3)
Medium	200 (64)	122 (65)	78 (62)	106 (67)	94(61)	180 (53)	91 (58)	89 (49)	103 (53)
High	66 (21)	45 (24)	21 (17)	28 (18)	38 (25)	154 (45)[a]	65 (41)[b]	89 (49)[c]	86 (44)[d]
Current physical activity (%)									
Low	126 (40)	73 (39)	53 (42)	70 (44)	56 (36)	35 (10)	20 (13)	15 (8)	16 (8)
Moderate	148 (47)	95 (51)	53 (42)	68 (43)	80 (52)	99 (29)	41 (26)	58 (32)	56 (29)
High	40 (13)	20 (11)	20 (16)	21 (13)	19 (12)	206 (61)[a]	96 (61)[b]	110 (60)[c]	122 (63)[d]
Fall in previous year (%)									
Yes	164 (52)	93 (50)	71 (56)	92 (58)	72 (47)	N/A	N/A	N/A	N/A
No	150 (48)	95 (51)	55 (44)	67 (42)	83 (72)	N/A	N/A	N/A	N/A
Smoking (%)									
Never	191 (61)	135 (72)	56 (44)	97 (61)	94 (61)	N/A	N/A	N/A	N/A
Former	109 (35)	48 (26)	61 (48)	57 (36)	52 (34)	N/A	N/A	N/A	N/A
Current	14 (4)	5 (3)	9 (7)	5 (3)	9 (6)	N/A	N/A	N/A	N/A
No. of the chronic diseases	2.4±1.5	2.5±1.5	2.6±1.5	2.6±1.5	2.4±1.6	N/A	N/A	N/A	N/A

TABLE 3 continued

	PASSWORD					ERMA			
	All (n=314)	Women (n=188)	Men (n=126)	PT (n=159)	PTCT (n=155)	All (n=342)	Early pm (n=158)	Late pm (n=184)	Follow-up (n=195)
Vasomotor symptoms (%)									
yes	N/A	N/A	N/A	N/A	N/A	201(59)	86 (55)	115 (63)	123 (63)
no	N/A	N/A	N/A	N/A	N/A	139 (41)[a]	71 (45)[b]	68 (37)[c]	71 (37)[d]
Psychological symptoms (%)									
yes	N/A	N/A	N/A	N/A	N/A	167 (49)	71 (45)	96 (52)	100 (52)
no	N/A	N/A	N/A	N/A	N/A	173 (51)[a]	86 (55)[b]	87 (48)[c]	94 (48)[d]
Somatic/pain symptoms (%)									
yes	N/A	N/A	N/A	N/A	N/A	95 (28)	42 (27)	53 (29)	53 (27)
no	N/A	N/A	N/A	N/A	N/A	245 (72)[a]	115 (73)[b]	130 (71)[c]	141 (73)[d]

Note. [a]n=340, [b]n=157, [c]n=183, [d]n=194, PASSWORD=Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women, ERMA=Estrogenic Regulation of Muscle Apoptosis, pm=perimenopausal, BMI= Body Mass Index, PT=physical training, PTCT=physical and cognitive training.

TABLE 4 Cognitive functions at baseline among PASSWORD and ERMA participants. Means and standard deviations.

	PASSWORD					ERMA			
	All (n=314)	Women (n=188)	Men (n=126)	PT (n=159)	PTCT (n=155)	All (n=342)	Early pm (n=158)	Late pm (n=184)	Follow-up (n=195)
STROOP	46.7±25.0	46.5±22.4	46.9±28.6	48.1±28.5	45.1±20.8	N/A	N/A	N/A	N/A
TMT A (s)	43.4±13.7[a]	42.7±12.8[b]	44.6±15.0	43.4±13.3[c]	43.5±14.2	24.2±7.0	23.7±6.7	24.7±7.2	25.0±7.2
TMT B (s)	131.5±60.0[a]	126.4±57.0[b]	139.0±61.2	132.2±55.0[c]	130.7±62.9	62.1±19.7[c]	63.0±20.2	61.4±19.3[d]	61.9±18.8
TMT B-A	88.0±52.2[a]	83.8±50.8[b]	94.4±53.8	88.9±49.4[c]	87.2±55.0	38.1±18.3[c]	39.3±19.2	37.0±17.5[d]	36.9±17.9
Verbal Fluency (no. of words)	41.6±13.0	44.4±12.1	37.5±13.2	40.9±12.9	42.3±13.1	28.5±6.2	28.1±6.7	28.8±5.7	28.8±6.2
Digit Span test (score)	N/A	N/A	N/A	N/A	N/A	15.7±3.3	15.8±3.3	15.7±3.4	15.7±3.3
Word List test (score)	N/A	N/A	N/A	N/A	N/A	63.9±7.0	64.4±7.0	63.6±7.0	64.1±7.1
Family Pictures (score)	N/A	N/A	N/A	N/A	N/A	79.0±18.9	81.4±19.5	77.0±18.1	79.2±18.8
MMSE (score)	27.6±1.5	27.8±1.5	27.5±1.4	27.4±1.5	27.9±1.4	N/A	N/A	N/A	N/A
CERAD (score)	79.2±8.1	80.1±8.1	77.8±7.9	78.8±8.2	79.5±8.0	N/A	N/A	N/A	N/A

Note. [a]n=313, [b]n=187, [c]n=341, [d]n=183. PASSWORD=Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women, ERMA=Estrogenic Regulation of Muscle Apoptosis, PT=physical training, PTCT=physical and cognitive training, pm=perimenopausal, TMT=Trail Making Test, MMSE=Mini-Mental State Examination, CERAD=The Consortium to Establish a Registry for Alzheimer's Disease.

TABLE 5 Physical functions at baseline among PASSWORD and ERMA participants. Means and standard deviations.

	PASSWORD					ERMA			
	All (n=314)	Women (n=188)	Men (n=126)	PT (n=159)	PTCT (n=155)	All (n=342)	Early pm (n=158)	Late pm (n=184)	Follow-up (n=195)
10m ws (m/s)	2.0±0.4	1.9±0.3	2.1±0.4	2.0±0.4	2.0±0.4	2.6±0.48[a]	2.6±0.48[d]	2.6±0.49[f]	2.6±0.46[i]
20m ws (m/s)	1.3±0.2	1.3±0.2	1.3±0.2	1.3±0.2	1.3±0.2	N/A	N/A	N/A	N/A
DT cost (s)/(m/s)	4.2±5.4	4.8±6.3	3.2±3.5	3.8±4.0	4.5±6.6	0.34±0.26[b]	0.35±0.28[d]	0.33±0.25[g]	0.32±0.26[j]
6-min wd (m)	475.4±81.7	457.3±70.3	502.4±89.9	472.0±88.0	478.9±74.8	663.7±66.6[c]	672.0±64.9[e]	656.7±67.4[h]	658.48±61.0[k]
SPPB (score)	10.1±1.5	9.8±1.5	10.6±1.4	10.1±1.6	10.2±1.5	N /A	N/A	N/A	N/A

Note. [a]n=337, [b]n=336, [c]n=311, [d]n=156, [e]n=143, [f]n=181, [g]n=180, [h]n=168, [i]n=192, [j]n=191, [k]n=181, PASSWORD=Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women, ERMA=Estrogenic Regulation of Muscle Apoptosis, PT=physical training, PTCT=physical and cognitive training, pm=perimenopausal, ws=walking speed, wd=walking distance, DT=Dual-Task, SPPB=Short Physical Performance Battery.

5.2 Cross-sectional and longitudinal associations between executive and physical functions (papers II and IV)

The cross-sectional associations between executive functions and physical functions were investigated among older women and men and middle-aged women. The results are presented in Table 6. In addition, sex differences in associations between executive and physical functions were investigated (Table 7). Better performance in updating (assessed with Verbal Fluency Test) was positively associated with higher maximal and habitual walking speed, longer 6-minute walking distance and better lower-extremity functioning among 70–85-year-old men and women and with higher maximal walking speed and longer 6-minute walking distance among late perimenopausal women. In addition, better performance in set shifting (assessed with TMT B and TMT B-A) was associated with better lower-extremity functioning among older adults and with 6-minute walking distance with late perimenopausal women. No significant associations between inhibition and physical functions among older adults or any of the executive functions subdomain among early perimenopausal women were found. However, unexpectedly we found that better performance in updating was negatively associated with dual-task cost in walking speed among late perimenopausal women. In addition, we investigated sex differences in associations between executive functions and physical functions between older women and men. However, after adjusting the models for multiple comparison, all sex interactions were non-significant (Table 7).

TABLE 6 Cross-sectional association between physical functions and executive functions among 70–85-year-old men and women and middle-aged women.

	Maximal walking speed			Dual-task cost[b]			6-min walking distance			Habitual walking speed			SPPB		
	β	R^2	p	β	R^2	p	β	R^2	p	β	R^2	p	β	R^2	p
PASSWORD															
Main effect models[a]															
VF	0.273	0.272	<0.001	-0.050	0.032	1.000	0.242	0.291	<0.001	0.184	0.127	0.009	0.234	0.184	<0.001
TMT B-A	-0.100	0.214	0.409	0.144	0.046	0.121	-0.130	0.253	0.107	-0.111	0.108	0.360	-0.236	0.178	<0.001
STROOP	-0.063	0.213	1.000	0.110	0.042	0.267	-0.057	0.245	1.000	-0.052	0.101	1.000	-0.058	0.142	1.000
ERMA															
Early perimenopausal															
VF	0.082	0.086	0.309	0.082	0.086	0.305	0.035	0.107	0.681	N/A	N/A	N/A	N/A	N/A	N/A
TMT A	-0.100	0.006	0.235	-0.115	0.009	0.165	-0.138	0.029	0.118	N/A	N/A	N/A	N/A	N/A	N/A
TMT B	-0.036	0.049	0.663	0.057	0.051	0.482	0.106	0.087	0.214	N/A	N/A	N/A	N/A	N/A	N/A
Late perimenopausal															
VF	0.264	0.100	0.001	0.160	0.064	0.034	0.198	0.064	0.018	N/A	N/A	N/A	N/A	N/A	N/A
TMT A	-0.025	0.037	0.755	-0.106	0.050	0.162	-0.055	0.022	0.522	N/A	N/A	N/A	N/A	N/A	N/A
TMT B	-0.110	0.053	0.175	-0.001	0.042	0.991	-0.178	0.058	0.036	N/A	N/A	N/A	N/A	N/A	N/A

Note. [a]Bonferroni-corrected p-value for five outcome variables. [b]In main effect models distribution shifted by adding a constant 2.724 and Box-Cox transformed with λ=-0.39. PASSWORD=Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women, ERMA=Estrogenic Regulation of Muscle Apoptosis, TMT=Trail Making Test, VF=Verbal Fluency test, SPPB= Short Physical Performance Battery. Main effect models were adjusted age, education, level of physical activity, smoking and Mini-Mental State Examination scores. Models for perimenopausal women were adjusted for physical activity, education, vasomotor symptoms, psychological symptoms and somatic or pain symptoms.

TABLE 7 Associations between physical functions and executive functions among 70–85-year-old men and women. Sex-interaction and sex-stratified models.

	Maximal walking speed			Habitual walking speed			Dual-task cost[c]			6-min walking distance			SPPB		
	β	R^2	p	β	R^2	p	β	R^2	p	β	R^2	p	β	R^2	p
PASSWORD															
Sex-interaction effect models[a]															
VF*sex			0.120			0.799			0.357			0.110			1.000
TMT B-A*sex			1.000			1.000			0.109			1.000			1.000
STROOP*sex			0.788			1.000			1.000			0.544			1.000
Sex-stratified models[b]															
Women															
VF	0.204	0.153	0.053	0.107	0.085	1.000	-0.165	0.020	0.353	0.151	0.207	0.323	0.209	0.214	0.030
TMT B-A	-0.193	0.138	0.185	-0.133	0.087	1.000	0.285	0.054	0.010	-0.172	0.206	0.287	-0.211	0.205	0.075
STROOP	-0.007	0.116	1.000	-0.023	0.075	1.000	0.160	0.020	0.340	0.018	0.187	1.000	-0.050	0.177	1.000
Men															
VF	0.363	0.217	0.001	0.285	0.169	0.020	0.095	<0.001	1.000	0.318	0.265	0.003	0.256	0.048	0.090
TMT B-A	-0.076	0.106	1.000	-0.108	0.108	1.000	-0.027	<0.001	1.000	-0.079	0.182	1.000	-0.248	0.041	0.140
STROOP	-0.122	0.116	1.000	-0.113	0.110	1.000	0.064	<0.001	1.000	-0.122	0.191	1.000	-0.068	<0.001	1.000

Note. [a]Bonferroni-corrected p-value for five outcome variables. [b]Bonferroni-corrected p-value for five outcome variables within sexes. [c]distribution shifted by adding a constant 2.724 and Box-Cox transformed with λ=-0.39. PASSWORD=Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women, SPPB=Short Physical Performance Battery, TMT=Trail Making test, VF=Verbal Fluency test. Models were adjusted for age, education, level of physical activity, smoking status, and Mini-Mental State Examination scores.

Longitudinal associations between cognitive and physical functions over the menopausal transition are shown in Figure 4. The longitudinal paths in SEM models showed no statistically significant associations between cognitive and physical functions. However, high stability over time was observed in cognitive functions, maximal walking speed and 6-min walking distance. Moderate stability over time was observed in DT cost. Evaluations for model fit showed adequate fit for all models.

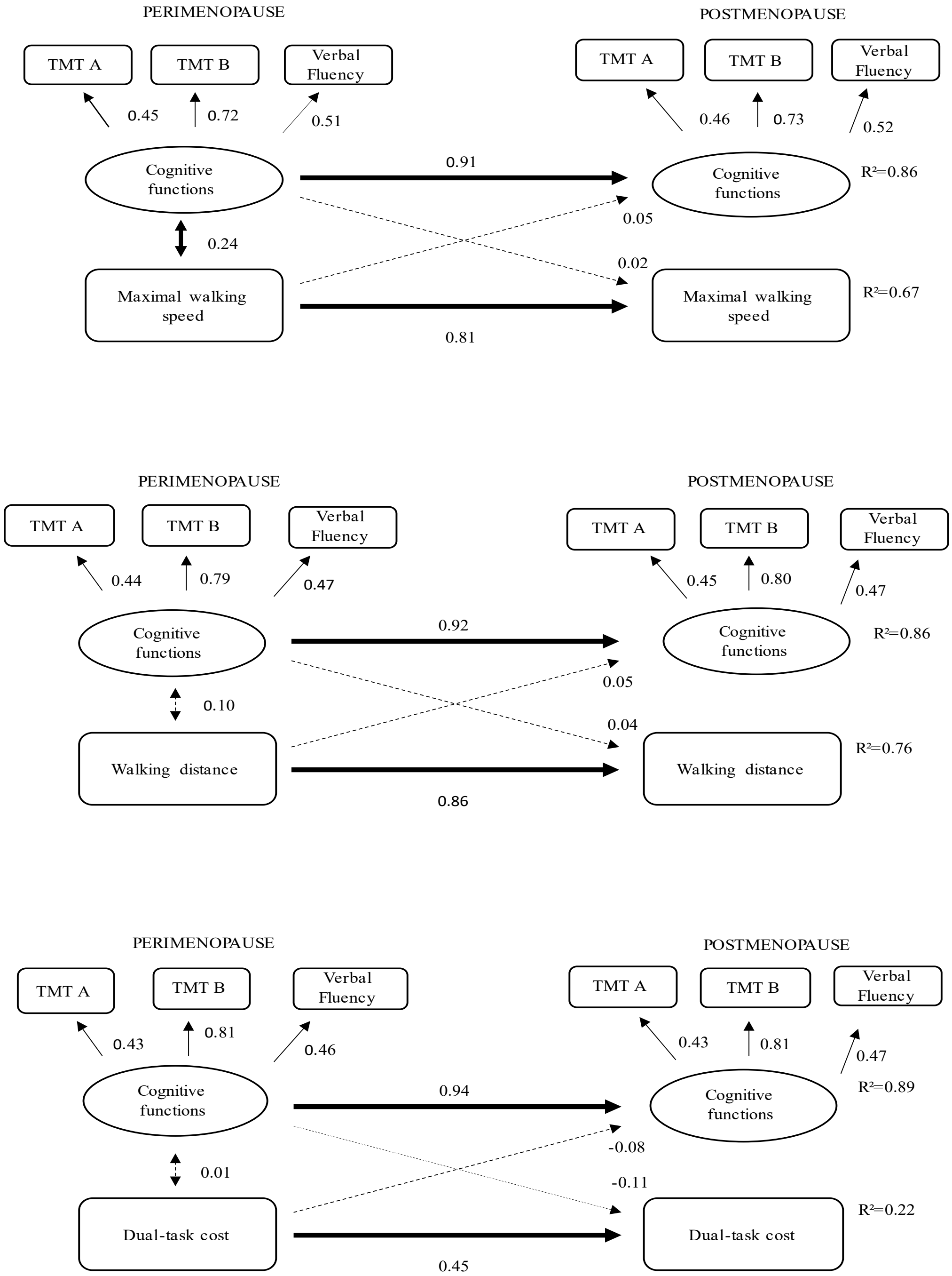

FIGURE 4 Longitudinal associations between walking speed and cognitive functions among middle-aged women. TMT=Trail Making Test. Models were adjusted for follow-up time. Modified from Tirkkonen et al. 2021.

5.3 Participant characteristics associated with the effects of physical and cognitive training program on executive functions (paper III)

The associations between participant characteristics and the effects of physical and a combination of physical and cognitive training programs on executive functions were investigated among 70–85-year-old men and women (Tables 8, 9 and 10). The results showed that women and PTCT participants who performed less than half of the training improved inhibition significantly more, compared to corresponding participants who received PT alone. No significant differences in change in inhibition between the study groups were observed among men and participants who performed more than half of the training. In addition, PTCT participants who performed less than half of the training had significantly greater improvement in set shifting compared to the corresponding PT participants. Among men, women or participants who performed more than half of the training, no differences in intervention-induced change in set shifting were observed. Age and global cognition were not associated with intervention-induced change in inhibition or set shifting. Concerning updating, intervention-induced change was not associated with participant characteristics. Moreover, no significant difference in intervention-induced change in updating was observed between the study groups among participants who performed less than half of the training or participants who performed more than half of the training.

TABLE 8 Means with 95% confidence intervals and unstandardized regression coefficients with 95% confidence intervals for the subgroup analysis of the Stroop outcome.

PASSWORD													
STROOP			PTCT				PT			PTCT-PT			
				95% CI				95% CI			95% CI		
		N	Mean	Lower	Upper	N	Mean	Lower	Upper	Difference	Lower	Upper	p-value
Overall	0kk	155	45.1	41.9	48.4	159	48.1	43.7	52.6	-6.766	-11.111	-2.421	0.002
	12kk		34.0	31.2	36.8		43.8	40.5	47.1				
Men	0kk	59	42.5	38.0	47.1	67	50.8	42.5	59.2	-3.575	-10.942	3.793	0.342
	12kk		34.6	29.8	39.4		46.5	40.8	52.2				
Women	0kk	96	46.7	42.3	51.2	95	46.2	41.6	50.8	-8.758	-13.873	-3.643	0.001
	12kk		33.6	30.2	37.0		41.8	38.0	45.7				
Low compliance	0kk	95	46.2	42.1	50.2	55	48.2	42.5	53.9	-8.405	-14.780	-2.031	0.010
	12kk		35.1	31.5	38.7		45.5	39.9	51.1				
High compliance	0kk	60	43.5	38.1	48.9	103	48.3	42.2	54.4	-5.966	-12.736	0.804	0.084
	12kk		32.3	28.0	36.6		43.0	39.0	47.1				
			B	Lower	Upper		B	Lower	Upper	Difference	Lower	Upper	p-value
Age	0kk	155	0.860	0.026	1.695	159	1.037	-0.126	2.200	0.654	-0.482	1.790	0.259
	12kk		1.368	0.686	2.049		0.890	0.032	1.749				
CERAD[a]	0kk	141	-0.538	-0.939	-0.136	147	-0.691	-1.141	-0.241	-0.090	-0.655	0.474	0.754
	12kk		-0.514	-0.810	-0.218		-0.577	-0.902	-0.252				

Note. [a]Comprises verbal fluency, modified Boston naming test, word lists constructional praxis, word list recall and word list recognition discriminability (total sum score range 0-100). PASSWORD=Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women, 0kk=baseline, 12kk=follow-up, B=unstandardized regression coefficient, CI=confidence interval, PTCT=physical and cognitive training, PT=physical training, CERAD=Consortium to Establish a Registry for Alzheimer's Disease.

TABLE 9 Means with 95% confidence intervals and unstandardized regression coefficients with 95% confidence intervals for subgroup analysis of the TMT-B outcome.

PASSWORD													
TMT-B			PTCT				PT			PTCT-PT			
				95% CI				95% CI			95% CI		
		N	Mean	Lower	Upper	N	Mean	Lower	Upper	Difference	Lower	Upper	p-value
Overall	0kk	155	130.7	120.8	140.6	158	132.2	123.7	140.8	-5.349	-13.620	2.922	0.205
	12kk		119.3	108.6	129.9		126.1	117.7	134.6				
Men	0kk	59	134.4	120.3	148.4	67	143.1	127.4	158.7	-13.486	-27.924	0.952	0.067
	12kk		117.2	104.7	129.7		139.4	123.0	155.8				
Women	0kk	96	128.5	115.1	141.9	91	124.3	115.3	133.3	-0.494	-10.190	9.202	0.920
	12kk		119.9	104.8	135.0		116.2	108.6	123.7				
Low compliance	0kk	95	137.4	123.2	151.6	54	125.8	112.8	138.7	-15.034	-28.769	-1.299	0.032
	12kk		127.9	112.0	143.8		131.3	115.2	147.4				
High compliance	0kk	60	120.2	108.6	131.8	103	135.9	124.8	147.1	-1.775	-13.150	9.599	0.760
	12kk		106.7	95.5	117.8		124.2	114.3	134.1				
			B	Lower	Upper		B	Lower	Upper	Difference	Lower	Upper	p-value
Age	0kk	155	5.358	2.941	7.774	158	3.741	1.537	5.945	-1.574	-3.747	0.599	0.156
	12kk		4.470	1.802	7.138		4.427	2.276	6.578				
CERAD[a]	0kk	141	-1.317	-2.148	-0.486	147	-2.939	-3.788	-2.089	0.268	-0.826	1.362	0.631
	12kk		-1.136	-1.968	-0.303		-3.026	-3.830	-2.222				

Note. [a]Comprises verbal fluency, modified Boston naming test, word lists, constructional praxis, word list recall and word list recognition discriminability (total sum score range 0–100). PASSWORD=Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women, 0kk=baseline, 12kk=follow-up, B=unstandardized regression coefficient, CI=confidence interval, PTCT= physical and cognitive training, PT=physical training, CERAD=Consortium to Establish a Registry for Alzheimer's Disease.

TABLE 10 Means with 95% confidence intervals and unstandardized regression coefficients with 95% confidence intervals for subgroup analysis of the Verbal Fluency outcomes.

PASSWORD													
VERBAL FLUENCY			PTCT				PT			PTCT-PT			
				95% CI				95% CI			95% CI		
		N	Mean	Lower	Upper	N	Mean	Lower	Upper	Difference	Lower	Upper	p-value
Overall	0kk	155	42.3	40.3	44.4	159	40.9	38.9	42.9	0.291	-1.753	2.335	0.780
	12kk		46.0	43.7	48.3		44.3	42.2	46.4				
Men	0kk	59	39.5	36.0	43.0	67	35.7	32.7	38.7	-0.937	-4.116	2.241	0.563
	12kk		41.4	37.6	45.1		38.6	35.4	41.7				
Women	0kk	96	44.1	41.6	46.6	92	44.7	42.3	47.1	0.894	-1.725	3.514	0.503
	12kk		48.8	46.1	51.5		48.5	46.0	50.9				
Low compliance	0kk	95	41.2	38.8	43.9	55	40.9	37.8	44.0	-0.436	-3.551	2.676	0.784
	12kk		44.2	41.4	47.0		44.3	40.9	47.7				
High compliance	0kk	60	44.1	40.9	47.3	103	40.9	38.2	43.5	1.424	-1.284	4.133	0.303
	12kk		48.9	45.1	52.7		44.2	41.6	46.9				
			B	Lower	Upper		B	Lower	Upper	Difference	Lower	Upper	p-value
Age	0kk	155	0.141	-0.392	0.675	159	-0.449	-0.975	0.078	-0.173	-0.705	0.360	0.525
	12kk		-0.099	-0.689	0.492		-0.516	-1.066	0.035				
CERAD[a]	0kk	141	0.539	0.328	0.749	147	0.409	0.207	0.611	-0.075	-0.350	0.200	0.593
	12kk		0.510	0.296	0.724		0.455	0.252	0.659				

Note. [a]Comprises verbal fluency, modified Boston naming test, word lists, constructional praxis, word list recall and word list recognition discriminability (total sum score range 0-100). PASSWORD=Promoting safe walking among older people: Physical and cognitive training intervention among older community-dwelling sedentary men and women, 0kk=baseline, 12kk=follow-up, B=unstandardized regression coefficient, CI=confidence interval, PTCT=physical and cognitive training, PT=physical training.

5.4 The effect of menopausal transition on cognitive functions (paper IV)

The change in cognitive functions over the menopausal transition was investigated among middle-aged women. Results are presented in Table 11. Among early perimenopausal women, results showed small but significant improvement in psychomotor speed and working memory (assessed with the Word List Test) after menopausal transition. Among late perimenopausal women, significant improvements in psychomotor speed, set shifting, visual memory and working memory (assessed with Word List Test) were observed. No significant change in updating over the menopausal transition was observed.

TABLE 11 Performance in tests for memory and executive functions in middle-aged women assessed in perimenopause and post menopause. Means and standard deviations.

	Early perimenopausal		
	Baseline (n=64)	Follow-up (n=64)	p
ERMA			
TMT[a] A (s)	25.9±7.3	23.5±5.4	0.007[d]
TMT[a] B (s)	64.0±19.6	62.3±18.1	0.656[d]
Verbal Fluency[b] (No. of words)	28.3±7.1	28.0±6.2	0.671[c]
Family Pictures[b] (scores)	83.8±18.8	81.9±21.6	0.331[c]
Word List Test[b] (scores)	64.9±6.6	68.0±7.0	<0.001[c]
Digit Span Test[b] (scores)	15.7±3.1	16.0±2.8	0.297[c]
	Late perimenopausal		
	Baseline (n=129)	Follow-up (n=129)	p
TMT[a] A (s)	24.5±7.2	22.5±5.9	0.001[d]
TMT[a] B (s)	60.7±18.6	57.6±17.3	0.015[d]
Verbal Fluency[b] (no. of words)	29.0±5.7	29.0±5.9	0.943[c]
Family Pictures[b] (scores)	76.9±18.4	82.2±18.5	0.002[d]
Word List Test[b] (scores)	63.6±7.3	66.9±7.2	<0.001[c]
Digit Span Test[b] (scores)	15.7±3.3	16.0±3.4	0.065[d]

Note. [a]smaller time indicates better performance; [b]higher number of words or scores indicates better performance; [c]paired samples t-test [d]Wilcoxon signed rank test. ERMA=Estrogenic Regulation of Muscle Apoptosis, TMT=Trail Making test.

6 DISCUSSION

The aim of this study was to investigate the relationship between executive functions and physical functions among older adults and middle-aged women. Additionally, the participant characteristics associated with cognitive and physical training intervention-induced change in executive functions among older adults were investigated. Further, we examined changes in cognitive performance over the menopausal transition among middle-aged women.

The results of this study showed that executive and physical functions were associated cross-sectionally among older adults and middle-aged women. However, the associations were dependent on the executive functions' subdomain and the nature of the physical task. Moreover, the results did not indicate sex differences in cross-sectional associations between executive and physical functions among community-dwelling older adults. We did not find longitudinal associations between cognitive and physical functions among middle-aged women either. In addition, based on our findings, participant characteristics may be associated with cognitive and physical intervention-induced change in executive functions. However, the additional benefit of combined cognitive and physical training was uniquely expressed in each of the executive functions investigated in this study. Finally, we found that cognitive performance remained stable or even improved during the transition from the perimenopausal stage to the postmenopausal stage.

6.1 Cross-sectional associations between executive and physical functions

Previous research investigating the cross-sectional associations between executive and physical functions among older adults has reported partially mixed findings. Our results indicate positive cross-sectional associations between updating and faster walking speed among older adults and middle-aged women. In addition, we found that set shifting was positively associated with lower-extremity functioning in older adults and walking distance in late perimenopausal middle-aged women. However, we did not find associations between inhibition and physical functions among older adults. Moreover, we did not find associations between psychomotor speed, set shifting or updating and walking performance among middle-aged women who were in an early perimenopausal stage.

Some of the earlier studies conducted in older adults have shown that better performance in inhibition, set shifting and updating are associated with faster walking speed or better lower-extremity functioning (Berryman et al., 2013; Demnitz et al., 2018; Herman et al., 2011; Morris et al., 2016; Soumare et al., 2009) whereas some studies were not able to find these associations (Hausdorff et al., 2005; Kaye et al., 2012; Valkanova et al., 2018). Previous studies investigating the associations between executive and physical functions in middle-aged populations are limited. Killane et al. (2014) suggest that a positive association between updating, set shifting and walking performance is present in dual-task but not in single-task conditions among adults aged 50 years and over. Furthermore, they did not find an association between updating and walking performance. Gonzales et al. (2016), in turn, did not find a link between set shifting and walking performance in dual-task or single-task conditions.

Our findings showing that especially updating was associated with walking performance are in accordance with systematic review by Heaw et al. (2022), who found that updating, assessed with verbal fluency, has stronger associations with walking speed compared to other cognitive domains. They suggest that this is due to interlinking neural networks between updating and walking in the prefrontal cortex. Furthermore, safe walking and lower-extremity functioning require dynamic reciprocal and fluent sensorimotor performance, and therefore it is logical that they are dependent on updating and mental flexibility but not the ability to inhibit an overlearned stimulus response.

We suggest that the mixed findings of the previous studies (Demnitz et al., 2018; Hausdorff et al., 2005; Morris et al., 2016; Valkanova et al., 2018) may be at least partly explained with differences in the study designs and selected outcomes. Our results showed that the relationship between executive and physical functions is highly dependent on the executive function measured and the nature of the physical task. Thus, it is reasonable to suggest that differences in the study designs and selected outcomes are associated with the inconsistent findings of the previous studies.

We did not find positive associations between executive functions and dual-task cost in walking speed among older adults or among middle-aged women. Instead, we found that better performance in updating was associated with greater dual-task cost (i.e. worse performance in a dual-task walking test) among late perimenopausal middle-aged women. Previous studies have shown that cognitive performance is associated with dual-task walking performance among older (Liu-Ambrose et al., 2009) and middle-aged adults (Killane et al., 2014), at least when the concurrent cognitive task is demanding. We assessed a dual-task performance in older adults with a visuospatial-motor task that is cognitively challenging and shown to induce greater interference while walking, compared to a non-spatial task (Menant et al., 2014). However, it has been shown that the visuospatial cognitive domain is more likely to be associated with postural control of walking than walking speed (Morris et al., 2016), which may explain our findings in older adults. In addition, it has been suggested that the dual-task cost in walking speed is dependent on the nature of the dual-task (Coppin et al., 2006). We assessed dual-task performance among older adults in habitual walking speed that is physically and cognitively easier to perform than, for example, maximal walking speed. We suggest that among relatively healthy and cognitively intact community-dwelling older adults, the association between executive functions and dual-task performance may be present only when cognitive and physical tasks are simultaneously demanding.

We hypothesized that the association between better performance in updating and greater dual-task cost in walking speed in middle-women is due to task prioritization. It has been suggested that individuals with good cognitive and postural reserves might prioritize the cognitive task over the physical task in dual-task conditions, at least when the physical task is simple (Yogev-Seligmann et al., 2010). In the ERMA study, dual-task performance was assessed while walking at maximal walking speed in the safe laboratory environment. Therefore, we suggest that the participants with better executive functioning prioritized the cognitive task over the physical task and therefore their walking speed was reduced below that achieved in single-task conditions.

We are not aware of previous studies investigating sex differences in cross-sectional associations between executive functions and walking or lower-extremity functioning. However, a recent study showed that a cross-sectional association between global cognitive functions, assessed with MMSE and lower habitual walking speed, was present in males but not in females (Wang et al., 2022), indicating sex differences in a cross-sectional association between cognitive functions and walking. In this study, we did not find sex differences in associations between executive functions and walking performance or lower-extremity functioning among older adults. However, it might be that in the present study, the sample size (n=314) was too small to detect these sex differences.

6.2 Longitudinal associations between cognitive functions and walking

In this study, we did not find longitudinal associations between cognitive functions and walking performance among middle-aged women during the transition from the perimenopausal stage to the postmenopausal stage. Instead, we found high stability in both performances during the transition phase. Earlier studies investigating bidirectional associations between cognitive functions and walking with regression models have shown that reduced cognitive functioning predicts slow walking speed (Holtzer et al., 2006) and vice versa (Inzitari et al., 2007). Similar findings are reported in studies utilizing cross-lagged models. These studies have shown that reduced cognitive functioning is associated with declines in walking speed (Stijntjes et al., 2017) and that reduced walking speed is associated with reduced cognitive functions in later life (Best et al., 2016). These findings indicate that the association between cognitive functions and walking performance is bidirectional (Krall et al., 2014). It is noteworthy that studies investigating bidirectional associations between cognitive functions and walking performance have mainly been conducted among older adults. However, Stijntjes et al. (2017) found that poor performance in cognitive functions in earlier adulthood was associated with a stronger decline in walking speed in later life among middle-aged adults (but not vice versa).

We suggest that the rather short follow-up time (on average, 1.5 years in the early perimenopausal and 1.2 years in the late perimenopausal group) and relatively high rank-order stability over the menopausal transition, which we observed in cognitive functions as well as in walking performance, may be associated with our finding showing no significant longitudinal association between cognitive functions and walking performance. For example, previous studies showing positive bidirectional associations between walking performance and cognition had a significantly longer follow-up time compared to the present study (Best et al., 2016; Krall et al., 2014; Stijntjes et al., 2017). However, Stijntjes et al. (2017) did not find a longitudinal association between slow walking speed and cognitive decline in later life among a middle-aged population, despite the rather long follow-up time (from 5 to 12 years). Thus, it may be that among middle-aged women, the bidirectional association between cognitive and physical functions does not occur. In addition, it must be noted that the cross-lagged path model utilized in this study assesses the associations between perimenopausal cognitive functions and walking performance over the transition to the postmenopausal stage and vice versa. However, the model does not assess the association between changes in these variables. Therefore, we suggest that further studies investigating the associations between the changes are needed to clarify longitudinal associations between cognitive functions and walking performance among middle-aged populations.

6.3 Participant characteristics associated with the effects of physical and cognitive training program on executive functions among older adults

Our findings showed that participants with different characteristics may respond differently to cognitive and physical training sessions. We further showed that women receiving cognitive and physical training gained additional benefits from combined training for inhibition, compared to women receiving physical training alone.

We suggest that activation of the neural circuits and the molecular mechanisms that women utilized when solving cognitive tasks (Grissom & Reyes, 2019) may explain women's superior improvement in inhibition, compared to men. However, the combination group improved their performance in inhibition more than physical training alone also among men, but the difference between groups was not statistically significant. It is worth noting that the cognitive training program used in the PASSWORD study presumably fosters goal maintenance, which in turn is a key requirement for inhibition. We suggest, therefore, that our cognitive training program induced greatest improvement for inhibition (Sipilä et al., 2021). It might be that women thus gained additional benefits from cognitive and physical training precisely relating to inhibition.

According to our results, it seems that especially inhibition gains additional benefits from a combination of cognitive and physical training, compared to physical training alone. Our results further indicate that the difference between training methods is present especially when training is low level, as participants who performed less than half of the training gained additional benefits from cognitive and physical training for inhibition and set shifting. To our knowledge, no prior investigations have examined if training compliance is associated with additional benefits of combined physical and cognitive training on executive functions, compared to physical training alone. However, moderator analysis of the previous meta-analysis suggested that a high frequency of physical and cognitive training was inefficient for cognitive functions (Guo et el., 2020; Zhu et al., 2016). In the PASSWORD study, participants especially in the physical and cognitive training group had a rather tight training schedule, and it may be that it caused cognitive fatigue and stress (Fiatarone Singh et al., 2014; Holtzer et al., 2011), which in turn may have had a negative impact on the training response of executive functions. Thus, it may be that participants with lower training compliance were more responsive to physical and cognitive training and therefore gained additional benefits. However, this conclusion is based on subgroup analyses and thus the final conclusion need to be confirmed with other studies. Concerning the set shifting, we found that low-level cognitive and physical training benefit set shifting after the 12-month intervention, whereas low physical training was not sufficient to improve or maintain set shifting. Therefore, we hypothesized that the process underlying the training response in set shifting differs from that underlying inhibition, and further studies are needed to clarify the mechanisms.

According to our analyses, the training responses in executive functions were not associated with age or changes in global cognition. However, to our knowledge there is no prior studies investigating whether participants' characteristics and background factors are associated with greater cognitive and physical training-induced change in executive functions, compared to physical training alone. We suggest that more research is needed to clarify whether some subgroups gained greater benefit from physical and cognitive training than others.

6.4 The effect of the menopausal transition on cognitive functions

We showed subtle but significant improvement in psychomotor speed and working memory during the transition phase from the early perimenopausal stage to the postmenopausal stage. In addition, we found that women who were in the late perimenopausal stage in the beginning of the study improved their performance significantly in psychomotor speed, working memory, set shifting and visual memory during the transition from the late perimenopausal to the postmenopausal stage.

Previous research investigating cognitive performance over the menopausal transition have reported partially inconsistent results. Some studies have hypothesized that at least some of the subdomains of cognitive functioning declines during the transition from the premenopausal stage to the postmenopausal stage (Greendale et al., 2009; Kilpi et al., 2020). On the other hand, some studies, in line with our findings did not find an association between menopausal transition and reduced cognitive functioning (Luetters et al., 2007; Meyer et al., 2003). Moreover, Greendale et al. (2009) have suggested that the decline in cognitive functions due to the menopausal transition is temporary and it is present only in the perimenopausal stage. They further suggest that cognitive performance normalizes in the postmenopausal stage.

Based on the hypothesis by Greendale et al. (2009), our participants were first assessed when their cognitive performance was at its lowest (i.e. in the perimenopausal stage instead of the premenopausal stage). It may be that the same hypothesis may explain our findings concerning the small but significant improvement observed in psychomotor speed, working memory, set shifting and visual memory. In addition to the time of the first assessment, learning may have affected our results. A previous study has shown that middle-aged women are better able to learn from repeated cognitive tests than men and older adults in general (Lamar et al., 2003). In this study, follow-up time (i.e. transition from the early or late perimenopausal stage to the postmenopausal stage) were rather short (1.5 years in the early perimenopausal and 1.2 years in the late perimenopausal group), and therefore we suggest that our participants might be able to utilize their prior experience of the cognitive tests in follow-up measurements.

6.5 Methodological considerations

The present study is based on two larger research projects: the PASSWORD study and the ERMA study. The baseline and follow-up data from both research projects were utilized in this thesis. The strength of this study includes representative sample of 70–85-year-old community-dwelling older adults with intact cognition and 47–55-year-old relatively healthy middle-aged women. Participants for both studies were recruited from the digital and population data services agency.

The preferred sample size in the PASSWORD study was 310 based on power calculations for the main outcome 10-meter maximal walking speed. Finally, 314 participants were recruited to the study. During the recruitment (February 2017–March 2018), it appeared that the amount of older adults who were at most moderately physically active but healthy enough to participate in the multicomponent physical training sessions was limited. Therefore, the recruitment process and the baseline measurements took longer than expected. Overall, the recruitment of the PASSWORD study was successful, and the sample is representative of the community-dwelling older adults who did not meet the physical activity guidelines at the time.

The ERMA cohort was recruited between 2016 and 2018. The invitation letter was sent to 82% of the population; 47% responded to the invitation and participated in at least the first phase of the study. The final distribution of the recruited women was slightly uneven. The proportion of the perimenopausal women was smaller compared to premenopausal and postmenopausal women. This might be due to the longitudinal study conducted among perimenopausal women. The longitudinal design required regular blood testing at the laboratory until postmenopausal status was reached and therefore required additional effort from the participants.

In addition to representative samples, the measurements utilized to assess cognitive and physical functions as well as the background factors can be considered as a strength. Measurements of both studies were conducted in laboratory settings and the measurement protocol was similar at baseline and in the follow-up measurements. The measurements were carefully selected and shown to be suitable for assessing older adults and middle-aged women. Cognitive and physical functions were assessed with a comprehensive battery of tests that assessed physical functions extensively and included a test for several subdomains of cognitive functions. In most cases, the same research assistants conducted measurements for cognitive and physical functions at the baseline and in the follow-up of the studies, which is likely to increase the reliability of our results.

Interventions of the PASSWORD study were carefully planned and were based on previous studies (Fielding et al., 2011; Portegijs et al., 2008) and the physical activity guidelines (Nelson et al., 2007). Safe participation in the physical training was ensured with nurses/physicians' examination at the baseline measurements. Training adherence and adverse events were carefully monitored throughout the interventions. The intensity and difficulty of the exercises increased progressively in both physical training and cognitive training, which probably maintained the motivation of the training. The drop-out rate in the PASSWORD study was low. In the ERMA study, the menopausal status of the participants was carefully classified and closely monitored over the transition from the perimenopausal stage to the postmenopausal stage. Moreover, the follow-up time of each participant was individualized based on hormonal assessments and bleeding diaries instead of using fixed-length follow-up. Overall, the data quality in the PASSWORD and ERMA studies was good. There was some missing data in both studies, but the missing data was considered in the statistical analyses.

This study has also limitations. The cross-sectional study design in papers II and IV did not allow conclusions to be drawn on the basis of causality. However, paper IV also included a longitudinal study design, although the follow-up time in the longitudinal design was rather short. In paper III, a hypothesis-generating exploratory design was utilized. In this study design, it was impossible to apply the power calculations of the PASSWORD study to the subgroup analysis. In addition, the sample size in some subgroups was rather small.

Executive functions were assessed with a single task instead of multiple tasks to target each executive function. Utilizing only single-task measurements makes the measurements of each subdomain of executive functions suboptimal. In addition, despite the fact that the 10-meter maximal walking speed test and 6-minute walking distance test have been shown to be suitable for measuring middle-aged populations (Enright & Sherrill, 1998), it may be that these tests were sub-maximal for well-functioning, rather healthy middle-aged women. Therefore, some other tests, such as bicycle, treadmill or running tests, would maybe have been more suitable for measuring aerobic performance (Löllgen & Leyk, 2018). However, these tests are not as suitable as walking tests are for assessing large study populations. Moreover, in dual-task walking tests we used methods that were either cognitively (PASSWORD) or physically (ERMA) demanding. Based on our findings, utilizing a test method that was simultaneously cognitively and physically demanding would have been better when investigating the associations between executive functions and dual-task cost in walking speed.

Our samples included relatively healthy community-dwelling older adults and middle-aged women. It must be noted that our findings cannot be generalized to older adults in other age groups or persons with a physically active lifestyle, adverse medical condition or reduced cognitive functioning. In addition, our findings concerning the middle-aged women are only representative among women in the menopausal transition.

6.6 Implications and future perspectives

The present study expands previous knowledge about the associations between executive and physical functions, as we were able to examine associations between all the core skills of the executive functions and several aspects of walking performance and lower-extremity functioning in two different age groups. According to our results, the relationship between executive and physical functions is dependent on the executive functions' subdomain and the nature of the physical task. Previous studies have mainly investigated the associations between one or two subdomains of the executive functions and some aspect of walking performance or lower-extremity functioning. Therefore, further studies including measurements for all core skills of the executive functions and several aspects of physical functions are needed to fill this research gap. Furthermore, in addition to older adults, associations between executive functions and physical functions should be investigated among younger age groups to a greater extent. Additionally, sex differences in associations between executive functions and physical functions should be investigated in future studies. In the present study, we did not find statistically significant differences between sexes in the associations between executive functions and physical functions. However, our results suggest that sex differences in these associations could have been found if a larger sample had been utilized. Further knowledge of the role of the executive functions' subdomains and nature of the physical tasks, as well as clarifying mechanisms behind age and sex differences in cross-sectional and longitudinal associations between executive functions and physical functions, can be utilized when developing targeted interventions to promote cognitive and physical health from middle-age to older adulthood.

The present study suggests that the menopausal transition is not a critical period for middle-aged women's cognitive and physical functioning. This information may be used to alleviate stigmatized fears related to menopausal transition. Women in perimenopausal phase can be assured that cognitive decline that they possibly perceived is likely to be transitory. However, due to the short follow-up time and absence of cognitive measurements in the premenopausal phase, further studies with longer follow-up time and careful characterization of the menopausal stage are needed to confirm our findings.

Finally, further studies are needed to investigate whether participants with different background factors respond differently to interventions targeted at improving executive functions. According to the present study, it might be that women and participants with low training compliance might gain additional benefits to their executive functions from interventions combining cognitive and physical training. Our results suggest that combined cognitive and physical training (possibly low intensity) could be more systematically offered to older adults to maintain their functioning. However, our study design, a hypothesis generating sub-group analysis of a randomized controlled trial, was suboptimal in investigating the role of the background factors in intervention-induced change in executive functions. Moreover, we were only able to investigate how participants' characteristics were associated with a yearlong separately performed computer-based cognitive training and multicomponent physical training intervention-induced change in executive functions. More research with more optimal study designs and different intervention procedures is needed to develop optimal intervention to promote older adults' executive functions.

7 MAIN FINDINGS AND CONCLUSIONS

The main findings and conclusions of the present study can be summarized as follows:

1. Executive functions and physical functions are positively associated in older adults and middle-aged women. However, the association depends on the nature of the physical task and the executive subdomain measured.

2. Cognitive performance in the perimenopausal stage is not associated with postmenopausal walking performance or vice versa. It seems that the transition from the perimenopausal to the postmenopausal stage is not a critical period for cognition and walking in middle-aged women.

3. Cognitive performance remains stable or even improves during the transition from the perimenopausal stage to the postmenopausal stage. Menopause-related declines in estrogens production may not be associated with cognitive decline among middle-aged women.

4. Physical and cognitive training improves older adults' executive functions. Women and those who only occasionally comply with a training regimen may gain additional benefits from physical and cognitive training compared to physical training alone. The additional benefit of physical and cognitive training is dependent on the executive function subdomain that is measured.

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ORIGINAL PUBLICATIONS

I

PROMOTING SAFE WALKING AMONG OLDER PEOPLE: THE EFFECTS OF A PHYSICAL AND COGNITIVE TRAINING INTERVENTION VS. PHYSICAL TRAINING ALONE ON MOBILITY AND FALLS AMONG OLDER COMMUNITY-DWELLING MEN AND WOMEN (THE PASSWORD STUDY): DESIGN AND METHODS OF A RANDOMIZED CONTROLLED TRIAL

by

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Promoting safe walking among older people: the effects of a physical and cognitive training intervention vs. physical training alone on mobility and falls among older community-dwelling men and women (the PASSWORD study): design and methods of a randomized controlled trial

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Abstract

Background: Safe and stable walking is a complex process involving the interaction of neuromuscular, sensory and cognitive functions. As physical and cognitive functions deteriorate with ageing, training of both functions may have more beneficial effects on walking and falls prevention than either alone. This article describes the study design, recruitment strategies and interventions of the PASSWORD study investigating whether a combination of physical and cognitive training (PTCT) has greater effects on walking speed, dual-task cost in walking speed, fall incidence and executive functions compared to physical training (PT) alone among 70–85-year-old community-dwelling sedentary or at most moderately physically active men and women.

Methods: Community-dwelling sedentary or at most moderately physically active, men and women living in the city of Jyväskylä will be recruited and randomized into physical training (PT) and physical and cognitive training (PTCT). The 12-month interventions include supervised training sessions and home exercises. Both groups attend physical training intervention, which follows the current physical activity guidelines. The PTCT group performes also a web-based computer program targeting executive functions. Outcomes will be assessed at baseline and at 6 and 12 months thereafter. Falls data are collected during the interventions and the subsequent one-year follow-up. The primary outcome is 10-m walking speed. Secondary outcomes include 6-min walking distance, dual-task cost in walking speed, fall incidence and executive function assessed with color Stroop and Trail Making A and B tests. Explanatory outcomes include e.g. body composition and bone characteristics, physical performance, physical activity, life-space mobility, fall-related self-efficacy, emotional well-being and personality characteristics.

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Discussion: The study is designed to capture the additive and possible synergistic effects of physical and cognitive training. When completed, the study will provide new knowledge on the effects of physical and cognitive training on the prevention of walking limitations and rate of falls in older people. The expected results will be of value in informing strategies designed to promote safe walking among older people and may have a significant health and socio-economic impact.

Trial registration: ISRCTN52388040.

Keywords: Aging, Executive function, Physical activity, Prevention, Sedentary

Background

A major task facing aging societies is to develop effective strategies to promote and improve older people's functional capacity and engagement in society. Among the most important factors is the ability to walk safely and independently in one's environment. Safe walking facilitates a physically and socially active life and access to goods and services [1].

Safe and stable walking is a complex process involving the interaction of neuromuscular, sensory and cognitive functions [2, 3]. The physiological prerequisites for walking are lower body muscle strength and power, postural balance and endurance [4]. Of the higher-order cognitive functions, better executive functions correlate with better walking ability and less falls among community-dwelling older people [2, 5, 6]. Executive functions control processes that support effective, flexible and goal directed behavior relying on a network of brain regions including prefrontal and parietal cortices and striatum [7, 8]. As physical and cognitive functions deteriorate with ageing, promoting these functions may help maintain safe walking among older people.

Physical activity is most likely a key factor in promoting safe walking in older people; however, the current scientific evidence is partially conflicting. A recently published large-scale trial showed that supervised moderate intensity training reduced disability risk, improved walking speed and physical performance but not cognitive functions among 70- to 89-year-old participants at risk for disability [9–11]. In another study, a resistance-training intervention resulted in significant improvements in muscle power but not in walking speed among 65- to 75-year-old women compared to a balance and toning control group [12]. Interestingly, in the latter study improvements in muscle power were accompanied by improvements in executive functions. Greater improvements in executive functions were also associated with better maintenance of physical activity over the one-year follow-up. Moreover, a falls prevention program including supervised strengthening, balance and functional exercises improved muscle strength and mobility in 70- to 80-year-old women with a history of falls, but had no effects on the overall rate of falls [13].

The interplay between higher cognitive functions and walking suggest that not only physical but also cognitive training has potential benefits for the prevention of mobility limitation and falls in older people. It may be that physical training and cognitive training induce additive or synergistic effects when combined in the same intervention. Physical training increases neurogenesis, angiogenesis and upregulates neurotrophic factors [14], while cognitive training increases recruitment of neurons and neuronal networks [15].

Research on the effects of cognitive training on walking among older people is scarce. Two pilot studies suggest that a computer-based program targeting executive functions may have effects on an untrained task with a large neuromuscular component [16, 17]. The precise underlying mechanisms remain unclear, but evidence from elsewhere shows that transfer may occur if the training and the transfer tasks share common processes and involve the same brain areas [18]. Earlier studies show that the frontal lobe, especially the dorsolateral prefrontal cortex is activated by both walking and executive functioning [2, 19] and that both cognitive and physical training increases dopamine release and hence may be one mechanism by which they interact [20].

This article describes the study design, recruitment protocol and interventions of a parallel group randomized controlled trial (RCT) among 70–85-year-old community-dwelling sedentary or moderately physically active men and women. The goal is to determine whether a combination of physical and cognitive training (PTCT) has greater effects on walking speed, dual-task cost in walking speed and executive functions compared to physical training (PT) alone. The effects of the PTCT intervention, compared to PT alone, on rate of falls during the 12-month intervention and subsequent one-year follow-up will also be investigated.

Methods/design

Study design

The PASSWORD study is a single site RCT with two research arms; Physical Training (PT, control) and a combination of Physical and Cognitive Training (PTCT) and conducted at the university laboratory. The interventions last for 12 months. Outcomes will be assessed at baseline and at 6 and 12 months thereafter. Falls data are collected during the 12-month interventions and during the subsequent one-year follow-up. Participants will be randomized into groups of equal size after the baseline assessments by a senior researcher who is not involved in the data collection or conducting the interventions of this study. A computer-#generated random allocation sequence of two-fold stratification by gender and age (70–74, 75–79, 80–85) with randomly varying blocks of two and four will be utilized. Investigators collecting outcome data are blinded to the study group allocation. The participants are instructed not to talk about the group assignment with the personnel collecting the data. The study protocol has been designed according to CONSORT guidelines and it has been registered in the International Standard Randomized Controlled Trial Number Register (http://www.isrctn.com/ISRCTN52388040). Ethics approval for the study was received from the review board at the Ethical Committee of Central Finland Health Care District (14/12/2016, ref.: 11/2016). We give an information letter, explaining the details of the study, possible risks, and permission to use the data for research purposes, participants' right to decline to participate at any point, anonymity and confidentially of the data to all potential participants. Before the baseline measurements and before signing the informed consent, each participant has opportunity to ask questions related to the study protocol from a trained research assistant, research nurse or the Principal Investigator.

Participants and recruitment

Community-dwelling sedentary or at most moderately physically active, 70- to 85-year-old men and women living in the city of Jyväskylä, Finland will be recruited. The current level of physical activity is assessed by structured questions during the telephone interview. The acceptable level is less than 150 min per week of moderate physical activity and no regular resistance training during the past year. The inclusion and exclusion criteria are presented in Table 1.

Participants are randomly selected from the Finnish National Registry. Recruitment starts with a letter containing information about the study and an announcement to expect a phone call during the following week. Phone numbers are collected from a nationwide database. Repeat phone calls are made if necessary. The purpose of the phone interview, using standardized questions, is to screen for inclusion and exclusion criteria related to mobility, physical activity and major chronic diseases. In addition, the Short Nutritional Assessment Questionnaire (SNAQ) is used to assess the risk for malnutrition. Those who score two or more points in the SNAQ, will

Table 1 Inclusion and exclusion criteria of the PASSWORD study

Inclusion criteria	Exclusion criteria
Age 70 to 85	Severe chronic condition or medication affecting cognitive and/or physical function:
Community-dwelling	-cancer requiring treatment in the past year (except for basalioma, cancers that have been cured or carry an excellent prognosis)
Able to walk 500 m without assistance (cane is allowed)	-severe musculoskeletal (e.g. osteoarthritis, osteoporosis with fragility fracture) disease
	-severe lung, renal or cardio-vascular disease, diabetes with insulin medication
Sedentary or at most moderately physically active (less than 150 min of walking/week and no regular attendance in resistance training)	-severe psychotic disorder, cognitive impairment or disease affecting cognition (e.g. Alzheimer's disease, dementia, abnormal CERAD score),
	-serious neurological disease or disorder (e.g. Parkinson's disease), stroke or cerebral hemorrhage with complications
MMSE ≥24 Informed consent to participation	Underlying diseases likely to limit lifespan and/or intervention safety. Contraindication for physical exercise or walking tests based on ACSM[41]
	Other medical, psychiatric, or behavioral factor that in the judgment of the PI and study physician may interfere with study participation or the ability to follow the intervention protocol
	Excessive and regular use of alcohol (more than 7 units per week for women and 14 for men)
	Difficulty in communication due to severe vision or hearing problems
	Unable or unwilling to give informed consent or accept randomization into either study group
	Another member of the household is a participant in PASSWORD

MMSE Mini mental state examination test, *MCI* Mild cognitive impairment, *ACSM* American college of sports medicine respond to the Mini Nutritional Assessment (MNA-SF) to ensure safe participation in the training intervention. Depression (Geriatric Depression Scale) and cognitive impairment (Mini Mental State Examination, MMSE, and Consortium to Establish a Registry for Alzheimer's Disease, CERAD) will be assessed and health status confirmed by a nurse and, if necessary, a physician and clinical psychologist before the baseline assessments. Flow chart in shown in Fig. 1.

Description of measurements

Primary outcome

The primary outcome is 10-m walking speed. Participants are asked to walk as fast as possible over the 10-m course. The time to complete the walk is measured by photocells. The test will be done twice and the best performance documented as the result. For the analysis, maximal walking speed (m/s) will be calculated. The test-retest precision with a 1- to 2-week interval in our laboratory is 5% [21]. Low walking speed is associated with e.g. increased risk for disability, cognitive impairment, institutionalization and falls [22].

Secondary outcomes

Secondary outcomes are 6-min walking distance, dual-task cost in walking speed, fall incidence and executive function. In *the 6-min walking test*, participants are encouraged to walk up and down a 20-m circuit for

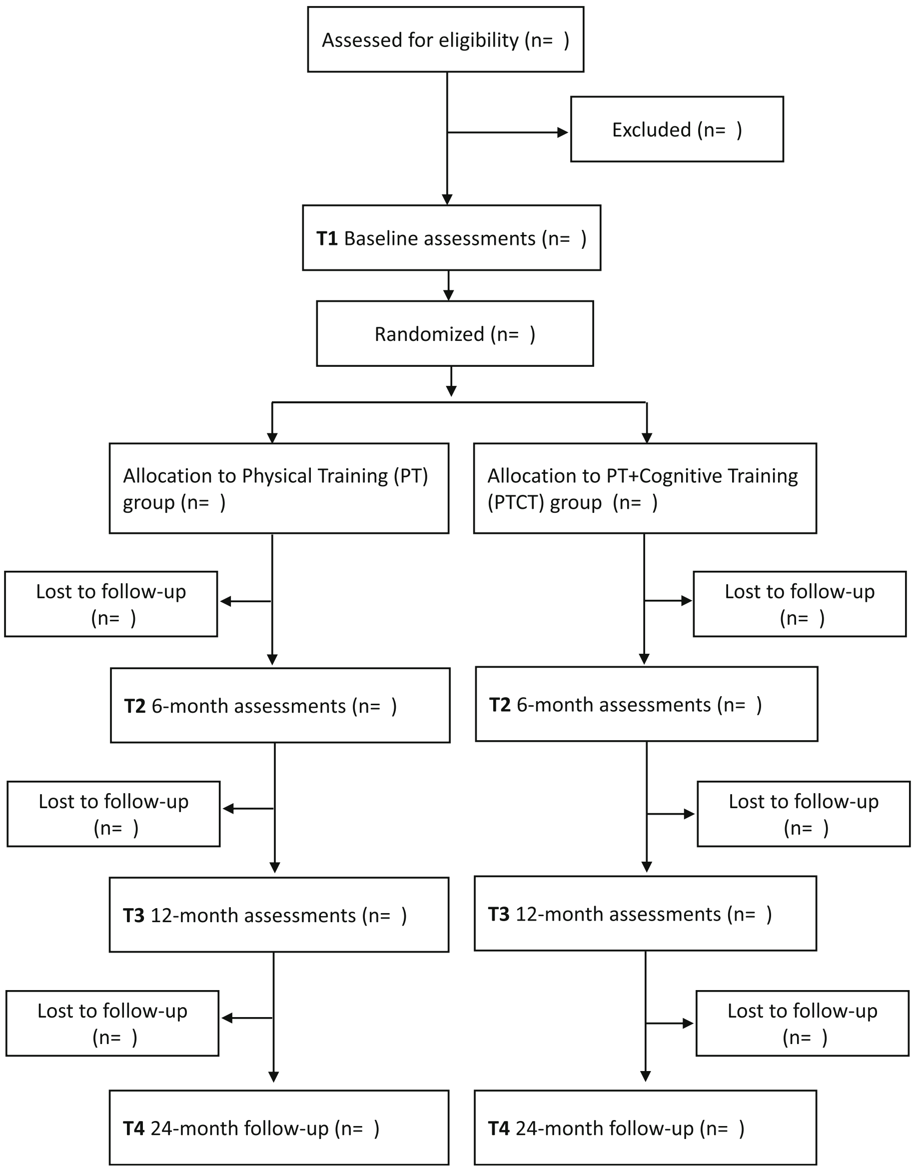

Fig. 1 Flow chart of the PASSWORD study

6 min at a comfortable speed and without resting [23]. Rate of perceived exertion (RPE; [24]) will be assessed before the walk and at three and 6 min thereafter. The 6-min walking test serves as a measure for community walking and is associated with, e.g., mobility limitation and disability [25].

The dual-task walking test is adopted from that used by Menant et al. [26]. Participants are first asked to walk at a self-selected speed along a 20-m long walkway. They are then asked to repeat the walk while performing a visuospatial cognitive task. We measure walking times by photocells and then calculate the difference between the two walks (dual-task cost). The visuospatial task involves a display with three boxes side by side labelled A, B and C. Participants are asked to visualize a star located in one of the boxes making three movements. Prerecorded instructions deliver the random starting position and the direction of the three movements, i.e. left or right. The cognitive task instructions are delivered continuously throughout the walking trial through headphones. A new instruction will be delivered within 1 s of the participant answering the previous question. Participants practice the visuospatial task carefully before the dual-task walking test.

We monitor *fall incidence* by monthly diaries throughout the study. We define a fall as an unexpected event in which the participant comes to rest on the ground, floor or lower level without overwhelming extrinsic cause. For each fall, detailed information on its location and need for care due to the fall is reported. The participant will send the monthly calendar back to the study coordinator during the first week of the following month.

Executive functions are assessed by the color Stroop Test [27] and Trail Making A and B [28]. The Stroop Test is a test for inhibition and it includes three test conditions. First, participants are instructed to read out 72 words printed in black ink. Second, they are instructed to read out the color of 72 colored letter X's. Finally, they are shown a page with 72 color words printed in incongruent colored inks (e.g., the word "RED" printed in blue ink). Participants are asked to name the color in which the words are printed and ignore the word itself. Participants are asked to do the test as quickly and as accurately as possible. The time taken to read each condition is recorded and the time difference between the third and the second condition calculated. Smaller time differences indicate better performance.

Trail Making Tests Parts A and B are used to assess set shifting. We instruct the participants to perform both parts as quickly and as correctly as possible. Part A assesses psychomotor speed. Participants are instructed to draw a line connecting circles with numbers 1 to 25 sequentially. Part B consists of circles with numbers and letters; participants are instructed to draw a line from 1 to A, A to 2, 2 to B, B to 3 etc., until they reach letter L. The time to complete each task is recorded and the time difference between Part B and A calculated. The smaller the difference, the better the performance.

Exploratory outcomes

Overall health including chronic diseases, medication, vision, blood pressure at resting and during orthostatic test, and resting EKG is assessed during a nurse's examination. Information on chronic conditions and medication is collected by self-report and from the integrated patient information system utilized by the national health services (Effica database) by the study physician at baseline. If considered necessary, an examination by a study physician will be arranged after the nurse's examination. Blood count, C reactive protein, and hemoglobin are measured to ascertain safe participation in the laboratory assessments and the intervention. Serum samples are stored for further analysis of inflammatory and growth factors.

Anthropometrics and body composition is measured by standard procedures and dual-energy x-ray absorptiometry (DXA, LUNAR Prodigy, GE Healthcare). Body height and weight are measured and a body mass index calculated. Total body composition and proximal femoral neck bone characteristics are measured by DXA. Subjects are scanned in supine position in the center of the table using the default-scanning mode for total body and proximal femoral region automatically selected by the Prodigy software (Lunar Prodigy Advance Encore v. 14.10.022).

Perceived difficulty in walking outdoors, 500 m and two kilometers is assessed with standard questions. The response options are: Able to manage without difficulty, Able to manage with some difficulty, Able to manage with a great deal of difficulty, Able to manage only with the help of another person, Unable to manage even with help [29].

Life-space mobility is assessed with the Finnish version of the University of Alabama at Birmingham Study of Aging Life-Space Assessment (LSA) [30, 31]. The LSA comprises 15 items and assesses mobility through the different life-space levels (bedroom, other rooms, outside home, neighborhood, town, beyond town) during the preceding 4 weeks. For each level, participants report how many days a week they attained that level and if they needed help from another person or assistive devices. Four indicators, with higher scores indicating a larger life-space, are calculated. 1) Independent life-space indicates the highest level of life-space attained without help from any devices or persons. 2) Assisted life-space indicates the highest level of life-space attained using the help of assistive devices if needed but not the help of another person. 3) Maximal life-space indicates the greatest distance attained with the help of devices and/or persons if needed. 4) A composite score reflects the distance, frequency and level of independence travelled (range 0–120).

Physical performance assessments include the Short Physical Performance Battery (SPPB), isometric knee extension and grip force and lower body extension power [32]. The SPPB includes habitual walking speed over four meters, five-time chair rise, and standing balance tests. The maximum score is 12, with higher scores indicating better performance. Those who score the maximum in the original SPPB balance test will repeat the test on a soft platform.

Maximal isometric knee extension force on the side on the dominant hand is measured using an adjustable dynamometer chair (Good Strength, Metitur Ltd., Palokka, Finland). The ankle is attached to a strain-gauge with the knee angle fixed at 60 degrees from full extension. The leg is extended as forcefully as possible and participants are encouraged to make a maximal effort during each trial [33]. Dominant handgrip force is measured with the dynamometer fixed to the arm of the chair with the elbow flexed at 90°. Participants are encouraged to squeeze the handle as hard as possible. Both force measurements are repeated three time or until no further improvement occurs. The highest force is used for analysis [33].

Leg extension muscle power is measured with the Nottingham Leg Extensor Power Rig from both legs [34]. Muscle power is a product of force and velocity, and it refers to the ability to produce force quickly. The measurement is repeated until no further improvement occurs and the best performance is used for analysis.

Physical disability is assessed by a validated questionnaire estimating perceived difficulties in six basic activities of daily living (ADL) which are eating, transferring from/to bed, dressing, bathing, cutting toe nails, and toileting [35, 36]. We also assess difficulties in eight instrumental activities of daily living (IADL), which are preparing meals, doing laundry, coping with light housework, coping with heavy housework, handling medication, using the telephone, using public transportation, and handling finances [36, 37]. Each ADL and IADL item includes five response categories: able to manage without difficulty, able to manage with some difficulty, able to manage with major difficulty, able to manage only with the help of another person, and unable to manage even with help.

Fall-related self-efficacy is assessed by the Falls Efficacy Scale International (FES-I; [38]). The questionnaire comprises 16 items assessing, e.g., walking on slippery, uneven or sloping surfaces, and visiting friends or relatives or going to a social event. Concern about falling when carrying out each activity is assessed on a four-point scale (range 1 = not at all concerned to 4 = very concerned). The total FES-I score ranges from 16 to 64. Fall-related self-efficacy describes perceived self-confidence in avoiding falls during every day activities [39].

Neuropsychological tests include global cognitive function as assessed by CERAD total score [40], and verbal fluency (Letter Verbal Fluency Test, [41]). The CERAD is composed of five subtests: Category Verbal Fluency, Modified Boston Naming Test (BNT), Mini Mental State Examination (MMSE), Word List Memory, and Constructional Praxis. The total score (range 0–100) is calculated according to the original procedure developed by Chandler et al. [42]. For the letter fluency task, participants are instructed to verbally generate as many words as possible that began with the letters P, A, and S in three separate 1-min trials.

Psychological function include tests for emotional well-being and personality characteristics. Emotional well-being is assessed using the Satisfaction with Life Scale [43] and Internationally Reliable Short Form of the Positive and Negative Affect Schedule (I-PANAS-SF, [44]). The Satisfaction with Life Scale consists of five items (e.g., "In most ways my life is close to my ideal"; response scale from 1 = strongly disagree to 7 = strongly agree), of which a sum score will be calculated. The I-PANAS-SF consists of ten adjectives (five for positive affectivity, e.g., "enthusiastic" and five for negative affectivity, e.g., "hostile"; response scale from 1 = does not describe my mood at all to 5 = describes me very well). Separate sum scores for positive and negative affectivity will be calculated. Personality traits are assessed using a short form of the Eysenck Personality Inventory modified by Floderus [45, 46] with 19 items with response scale 1 = no, 2 = yes (ten for extraversion, e.g., "Are you lively and talkative?" and nine for neuroticism, e.g. "Do you often feel apathetic and tired without any special reason?"). Separate sum scores for extraversion and neuroticism will be computed. The NEO-Personality Inventory-3 is also used (NEO-PI-3; [47]) for investigating personality traits. It has 240 items (response scale from 1 = strongly disagree to 5 = strongly agree), 48 for each personality trait (neuroticism, extraversion, openness to new experiences, conscientiousness, and agreeableness). Each of these five traits have six facets. Sum scores for each trait and their facets will be computed. Sense of coherence was measured using the 13-item version of Antonovsky's [48] scale (e.g., "You anticipate that your personal life in the future will be…1 = totally without meaning or purpose to 7 = full of meaning and purpose").A sum score of the items will be computed.

The level of physical activity and sedentary behavior is assessed by validated questions [49] and an accelerometer. Accelerometer recording is performed over seven consecutive days with a hip worn device (UKK, Tampere, Finland). The UKK device measures and stores acceleration in three orthogonal (x, y and z) directions at a sampling rate of 100 Hz. The accelerometers are returned by mail to the research institute where the stored data is copied to a hard disk for later analysis.

Interventions

Interventions start with a 60–90-min introductory seminar, including a motivational lecture on the benefits of physical activity in older people. In addition, a description of the physical activity intervention and an individual time schedule for the supervised sessions are given. Participants have also an opportunity to ask questions and to communicate their expectations and possible challenges they face regarding participation in the study. The PTCT participants also attend the introductory seminar during which detailed information on cognitive training is given.

The interventions include supervised training sessions and home exercises. Supervised sessions are organized weekly in groups of 10–15 participants. Training adherence is carefully monitored and a daily diary recording all home exercises is kept. During the first 2 months, physical training only is organized. This arrangement facilitates participants' adaptation to the training. The acceptability of the interventions is assessed by a questionnaire after the intervention. For the post-intervention follow-up, encouragement to continue physical and cognitive training, but no support, is given.

The multicomponent physical training (PT) intervention

PT intervention will be adapted from the physical activity guidelines for older adults, our earlier studies [33, 50] and the Lifestyle Interventions and Independence for Elders (LIFE) study [51]. The PT intervention will include aerobic physical exercises (mostly walking) and progressive resistance and balance training. Five to six different training periods with variation in training specificity, volume and intensity [52] are designed to maintain physiological responses to training and to prevent overtraining and fatigue during the 1-year training intervention. Detailed descriptions of the periods are shown in Table 2.

Supervised walking sessions are organized once a week outdoors on a 400-m circular walking lane and, during the wintertime, indoors in a sports hall with a 200-m oval track. Throughout the study, walking sessions begin with a 10–15 min warm-up, including a short walk at self-selected speed and dynamic balance exercises of increasing difficulty to be performed while walking. After the warm-up, continuous walking for 10–20 min, at a target intensity of 13–15 (somewhat hard to hard) on the Borg scale [24], is performed.

Resistance training takes place in three senior gyms equipped with HUR senior line resistance training machines utilizing air pressure technology and Smart Card/Smart Touch Software (http://www.hur.fi/en). During the 12-month intervention, six different training periods, aimed at increasing muscle strength and power, are performed. Each training session includes 8–9 exercises for the lower body, trunk and upper body muscles. Leg press, leg curl and leg extension exercises form the core of the training program. Six-repetition maximum (6RM) tests for these exercises are performed during the first training session and after the 3rd and 5th training periods to determine training load. In addition, hip adduction and abduction, hip extension and heel rise as well as rowing, chest press or elbow extension are performed interchangeably during the training sessions. The training load for these exercises is self-selected by the participants with the aim of performing the same number of sets and repetitions as for the core exercises. Each resistance training session starts with a 10-min warm-up, including balance exercises, which increase in difficulty during the study.

The progressive home exercise program includes a structured gymnastic program with strengthening exercises for the lower limb muscles, postural balance exercise and stretching for major muscle groups. In the strengthening exercises, workload is increased with resistance bands of three different strengths. The standing balance exercises include heel and toe rise, semi- and tandem standing, standing on one leg, line walking and figure-of-eight walking. The level of challenge is increased by reducing hand, base and vision support. Participants are also advised to accumulate moderate aerobic activity amounting to a total of 150 min per week in bouts of at least 10 min duration. Recommended activities include walking, Nordic walking, biking and cross-country skiing.

Cognitive computer-based training (CT)

CT targets executive functions, namely inhibition, shifting and updating of working memory, and is built on the unity/diversity model of executive functions proposed by Miyake et al. [8]. The CT program is a web-based in-house developed computer program (iPASS) modified from that used in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (the FINGER) study [18, 53]. The target training frequency is 3–4 times a week. CT starts with supervised group sessions organized in the University computer classroom and supervised by a student with, at least, psychology as a minor subject. During the first weeks of CT, peer support for the requisite computer skills is organized in collaboration with the GeroNet tutors of the local University of the Third Age. Participants who have the necessary computer skills and a computer at home, are allowed to start CT at home after 2–3 group sessions. Those who lack access to a computer at home can attend supervised sessions at least once

Table 2 Description of the multicomponent physical training intervention of the PASSWORD –study

Time, months	Programs/ RM tests	Supervised resistance/balance exercise program	Supervised walking/balance exercise program	Home gymnastic program
1–2	6RM tests	Familiarization with equipment; RM for Leg press, Leg curl, Leg extension	150 min of aerobic exercise/week. Outdoors activities are encouraged throughout the intervention	
	Period 1 (adoption phase)	Warm-up with balance exercises; Resistance training at 50% of 1RM, 2 × 20 reps (adoption phase)	Warm-up (walk at habitualspeed and dynamic balance exercises while walking); 10-min continuous walk with RPE 13	Strength exercises for lower limb muscles; Postural balance exercise; Stretching exercises for major muscle groups
3–4	Period 2	Warm-up with balance exercises; *Resistance training*: resistance at 60% 1RM, 2 × 15 reps	Warm-up (at habitual speed, dynamic balance exercises of increasing difficulty over time while walking); 10–15 min continuous walking with RPE 13	Strength exercises for lower limb muscles; Postural balance exercise; Stretching exercises for major muscle groups
5–6	Period 3	Warm-up with balance exercises; *Power training:* Resistance 50% 1RM, 3 × 5 reps (fast contractions) *Hypertrophy:* Resistance 70% 1RM, 2 × 10 reps (resistance is increased by 1–2 kg if predefined number of reps is exceeded)	Warm-up (as in periods 3–4); 15–20-min continuous walk with RPE 13	Strength exercises for lower limb muscles with *red TheraBand CLX*; Postural balance exercise; Stretching exercises for major muscle groups
	6RM tests	Leg press, Leg curl, Leg extension Agility training for two weeks	1 month break during summertime	
7–8	Period 4	Warm-up with balance exercises; *Hypertrophy:* Resistance training at 70% 1RM, 3 × 10 reps (resistance is increased by 1–2 kg if predefined number of reps is exceeded)	Warm-up (as in periods 3–4) 20-min continuous walk with RPE 13	Strength exercises for lower limb muscles with *green/blue Thera Band CLX*; Postural balance exercise; Stretching exercises for major muscle groups
9–10	Period 5	Warm-up with balance exercises; *Hypertrophy:* Resistance 80%, 1–2 × 10 reps (resistance is increased by 1–2 kg if predefined number of reps is exceeded) *Power:* Resistance 60%, 1–2 × 6–8 (fast contractions)	Warm-up (as in periods 3–4); 20-min continuous walk with RPE 13 or 20-min walk with < 1 min intervals with RPE 15	Strength exercises for lower limb muscles with *blue TheraBand CLX*; Postural balance exercise; Stretching exercises for major muscle groups
	6RM tests	Leg press, Leg curl, Leg extension		
11–12	Period 6	Warm-up with balance exercises; *Power:* Resistance 60%, 3 × 6 reps (fast contractions) *Hypertrophy:* Resistance 80%, 2 × 10 reps (resistance is increased by 1–2 kg if predefined number of reps is exceeded)	Warm-up (as in periods 3–4); 20-min walk with < 1 min intervals with RPE 15	Strength exercises for lower limb muscles with *blue TheraBand CLX*; Postural balance exercise; Stretching exercises for major muscle groups

a week and will also have the possibility to train in one of ten locations provided by the City of Jyväskylä (libraries, sheltered accommodation, etc.). In each location, a GeroNet tutor will be present each week for 2–3 h at a time.

During each training session, four different tasks are practiced. The tasks are organized in two blocks, which alternate between sessions. Task difficulty increases during the intervention period. Block 1 includes letter updating, predictable set-shifting, spatial working memory maintenance, and stroop color tasks (inhibition). Block 2 includes spatial updating, unpredictable set-shifting, spatial working memory maintenance, and stroop number tasks (inhibition). Participants are instructed to do the tasks as quickly and as accurately as possible. One training session lasts approximately 20 min.

Participant safety and data quality assurance

Participant safety is a priority in this study. The screening process ensures safe participation in the assessments and interventions. Supervisors and the personnel will be carefully trained for collecting the data and participants safety (including e.g. first aid course). Adverse events and falls will be tracked throughout the 12-month intervention, with special emphasis on events that could be associated with the study. Diseases, symptoms, and medication arising during the intervention are self-reported every 3 months. The study physician, study nurse and principal investigator will review these reports and make the decision on modification of the intervention and, if necessary, the decision to terminate the trial. All participants and personnel will be covered by insurance taken out by the University.

Our research center has a long tradition in administering physical activity interventions and mobility, physical and cognitive function measures among older populations. A Standard Operation Procedure document will be carefully followed throughout the study. Periodical meetings of the study group and checks will be set up to monitor data collection quality. During participants' laboratory visits, all questionnaires are reviewed by the staff. Where information is missing, participants are asked to complete the questionnaire. Information collected on paper will be saved as data files as soon as possible. Each participant will be assigned an identification number. The identification -key will be in the possession of the research coordinator, research nurse and principal investigator (PI) during the data collection and thereafter in the possession of the PI only. All collected data will be stored on the University server and protected by passwords. Data collection form are available at https://www.jyu.fi/sport/fi/tutkimus/hankkeet/password

Statistical analysis and sample size

The effects of the intervention will be assessed on the intention-to-treat principle. Maximum likelihood methodology will be used to account for missing data. The primary outcome will be tested for group-interaction over time using an interaction contrast in a linear model for longitudinal data accounting for within-person correlation and different variances at the two time-points. Negative binomial regression will be used to estimate the incident rate ratio for falls. The Cox proportional hazard regression model will be used to calculate hazard rates up to the first fall for fallers in both groups with PT as a reference. In addition, individual changes in the main and secondary outcomes observed during the study will be calculated and a reliable change index computed. The effects of the intervention on primary and secondary outcomes will also be evaluated in sub-analyses stratified by age, gender, baseline cognition, and level of compliance to the intervention.

A priori sample size calculations were based on previously published data [13, 16, 17] and on our own data on 10-m walking speed. We expect a baseline mean level of 1.3 m/s (standard deviation of 0.36 m/s) in both groups [53, 54]. The PT intervention is expected to induce a four-percentage point mean increase in both groups and a six-percentage point higher mean in the PTCT group than PT group with no change in standard deviation (SD). The follow-up within-person correlation for the two measurements is estimated to be $r = 0.80$ [49], yielding 0.23 m/s as an estimate of the SD for change. Setting the significance level at 0.05 and power at 80% for the group-time interaction favoring the PTCT vs. the PT group indicated that a sample size of 135 participants per group is required. Given an anticipated dropout level of 15%, we decided to recruit 155 participants per group. An additional power analysis, based on recently published data [13] was calculated for the secondary outcome of the falls rate. At 80% power and with a total sample size of 270–310, it would be possible to detect a difference of 27–29% in falls rate significant ($\alpha = 0.05$) between the PT and PTCT groups.

Current status

As of April 1st 2018, 314 participants have been recruited and randomized to study groups.

Discussion

The purpose of the PASSWORD study, conducted among 70–85-year-old community-dwelling sedentary or at most moderately physically active men and women, is to investigate whether physical and cognitive training combined has greater effects on walking speed, dual task cost in walking speed, executive function and fall incidence than physical training alone. The study is designed to capture the additive and possible synergistic effects of physical and cognitive training by using evidence-based guidelines, training regimens, and a comprehensive battery of validated tests. When completed, the study will provide new knowledge on the additive effects of physical and cognitive training on the prevention of walking limitations and rate of falls in older people. The expected results will be of value in informing strategies designed to promote safe walking among older people. The results may also have a significant health and socio-economic impact.

The current scientific evidence on the effects of physical training on safe walking and falls prevention is encouraging but partially conflicting. Some have shown benefits for walking but not for cognition [9–11], while others have yielded the opposite results [12]. Moreover, mixed results have been reported on the role of physical activity on fall incidence [13]. Observational data indicate, that cognitive training has potential for the prevention of mobility limitation and falls in older people [2, 6]. Data on experimental designs is, however, scarce. A few earlier studies have investigated the effects of physical and cognitive training interventions on walking speed or the rate of falls compared with physical activity alone [55]. However, the training regimens used did not follow any existing guidelines or evidence-based regimens and the studies themselves were small-scale.

The PASSWORD study utilizes interventions which rely on evidence-based findings and which have been tested in large scale trials with good compliance and results [9, 53].

Supervised sessions aim at maximal training effects whereas home exercises facilitate adaptation to an active lifestyle. The PASSWORD physical training intervention is based on current guidelines for older adults. To benefit health and well-being across a broad spectrum, muscle strengthening and balance training as well as moderate intensity aerobic activities are performed regularly on a weekly basis.

The cognitive training program is a modification of that already used in a large multicenter study, the FINGER study [53]. Multidomain cognitive training activates larger neuronal networks and is more likely to elicit transfer effects than single domain training. It also enables variation in training sessions, which may increase training compliance. Moreover, computer-based exercises enable individually adjusted progression by increasing the level of difficulty over time.

In long-term trials, participant commitment to the study protocol may be challenging and may change over the trial. Travelling to organized, supervised sessions on a weekly basis over a lengthy trial may, for several reasons, most typically diseases, lack of time and loss of interest, be too demanding for many older people. Hinrichs et al. [56] found that in a physical activity intervention study of only 12 weeks duration involving community-dwelling mobility-limited older people, 47% of the participants reported 151 adverse events. Only two of the events were related to the intervention. This indicates that although a training program has been carefully designed and is safe, high morbidity unrelated to the intervention can constitute a critical challenge for sustained participation.

To foster adherence to the planned interventions and measurements, we carefully review participants' health and cognition, fully inform them about the procedures and interventions and give them opportunities to ask questions concerning the study before randomization. Moreover, we add the different components of the intervention gradually, over a period of 6–8 weeks, to the training program. This gives the participants time to adapt to the intervention routines. Regular supervised group sessions may help to engage participants in the group activity and thus in the training protocol. As not all participants are expected to have computer skills or a computer at home, peer support and possibility to train out of home is provided throughout the study.

In conclusion, the evidence on the effects of physical training interventions on walking speed, falls prevention and cognition among community-dwelling at most moderately physically active older people is contradictory. Therefore, research investigating new strategies to promote safe walking in older populations is needed. The PASSWORD study is a randomized controlled trial designed to capture the synergistic effects of a combination of physical and cognitive training on safe walking compared to physical training alone. The physical training intervention chosen for the control condition follows the current guidelines ("standard care") for older adults. A unique feature of PASSWORD is that it uses proven interventions in a novel combination and a robust set of mobility, falls and executive function measurements. The results of the PASSWORD study are expected to influence guidelines on the prevention and treatment of mobility limitations and disabilities among older people and thus inform future health care practices and policies.

Abbreviations

ADL: Activities of daily living; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CT: Cognitive training; DXA: Dual-energy x-ray absorptiometry; EKG: Electrocardiography; FES-I: The Falls Efficacy Scale International; GDS: Geriatric Depression Scale; IADL: Instrumental activities of daily living; LSA: Life-Space Assessment; MMSE: Mini-Mental State Examination; MNA-SF: Mini Nutritional Assessment- Short Form; NEO-PI: NEO Personality Inventory-3; PT: Physical training; PTCT: Combination of physical training and cognitive training; RCT: Randomized controlled trial; Reps: Repetitions; RM: Repetition maximum; RPE: Rate of perceived exertion; SD: Standart deviation; SNAQ: Short Nutritional Assessment Questionnaire; SPPB: Short Physical Performance Battery; the FINGER-study: The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; the LIFE-study: The Lifestyle Interventions and Independence for Elders

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Availability of data and materials

The main results will be published by the research group. Data will be available to other investigators for additional analysis, as individually agreed with the research group.

Date and version identifier

08/03/2018:

- The recruitment end date was changed from 01/03/2018 to 01/04/2018.
- The overall trial end date was changed from 31/12/2018 to 01/04/2019.

08/11/2017:

- The recruitment end date was changed from 31/12/2017 to 01/03/2018.

– The following measurements were added:
  1. Isometric knee extension and grip strength are measured at baseline and 12 months.
  2. Lower body extension power is measured using the Nottingham power rig at baseline and 12 months.
  3. Level of sedentary behavior is assessed through self-reporting and use of an accelerometer at baseline, 6 and 12 months.
  4. ADL and IADL are measured with a standardized questionnaire at baseline, 6 and 12 months.
  5. Emotional well-being is measured with the satisfaction with life scale, Diener 1989; Internationally reliable short form of the Positive and Negative Affect Schedule at baseline, 6 and 12 months, and personality is assessed with the Eysenck Personality Inventory, Floderus B. 1974, at baseline and 12 months and the NEO-Personality Inventory-3 (NEO-PI) at 12 months.

Authors' contributions
All authors have read and agree with the content of the final manuscript. All authors have made substantial contributions to the design of the study and the manuscript. SS, TH, RF, MK, JK, TR, SES, AS-N, TT were responsible for the study conception and design. PL and MA were responsible for designing the medical screening and follow-up during the intervention. AT and SS were responsible for designing and implementing the recruitment of participants. SS, ES and TT were responsible for designing and implementing the randomization protocol. KK was responsible for designing the protocol for measuring emotional well-being and personality. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethics approval for the study was received from the review board of the Ethical Committee of Central Finland Health Care District on December 2016 (14/12/2016, ref.: 11/2016).
Written informed consent will be requested from subjects before the study start.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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II

ASSOCIATIONS BETWEEN PHYSICAL AND EXECUTIVE FUNCTIONS AMONG COMMUNITY-DWELLING OLDER MEN AND WOMEN

by

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Associations Between Physical and Executive Functions Among Community-Dwelling Older Men and Women

Anna Tirkkonen, Jenni Kulmala, Tuomo Hänninen, Timo Törmäkangas, Anna Stigsdotter Neely, and Sarianna Sipilä

Walking is a complex task requiring the interplay of neuromuscular, sensory, and cognitive functions. Owing to the age-related decline in cognitive and physical functions, walking may be compromised in older adults, for cognitive functions, especially poor performance in executive functions, is associated with slow walking speed. Hence, the aim of this study was to investigate the associations between different subdomains of executive functions and physical functions and whether the associations found differ between men and women. Multiple linear regression analysis was performed on data collected from 314 community-dwelling older adults who did not meet physical activity guidelines but had intact cognition. Our results showed that, while executive functions were associated with gait and lower extremity functioning, the associations depended partly on the executive process measured and the nature of the physical task. Moreover, the associations did not differ between the sexes.

Keywords: cognition, dual-task cost, gait, sex differences

Walking is a complex task, which is based on the interplay of neuromuscular, sensory, and cognitive functions (Holtzer, Verghese, Xue, & Lipton, 2006; Yogev-Seligmann, Hausdorff, & Giladi, 2008). As physical and cognitive functions decline with aging, walking, especially in more challenging conditions, may be compromised in older adults (Shumway-Cook et al., 2007). Reduced gait speed and cognitive functioning are both important determinants of health that are associated with poor health outcomes, disability, and mortality. A recent study suggests that the relationship between these determinants is bidirectional and that they are mutually capable of accelerating each other's development (Basile & Sardella, 2021). It has also been indicated that the presence of both reduced gait speed and cognitive impairment is more predictive of future disability and mortality than either of these determinants alone (Grande et al., 2020).

Poor cognition, especially poor performance in executive functions, that is, higher level functions that allow flexible goal-directed action and problem solving, has been found to be associated with slow gait speed (Morris, Lord, Bunce, Burn, & Rochester, 2016). According to Miyake et al. (2000), executive functions include cognitive processes, such as the ability to update and monitor working memory representation (updating), the ability to shift attention between tasks (set shifting), and the ability to inhibit an overlearned stimulus response (inhibition).

Several brain regions are involved in regulating gait end executive functions. According to Grande et al. (2019), gait relies on the interplay between prefrontal, motor, and posterior parietal cortices, subcortical areas, and more peripheral structures. From the executive functions, updating, set shifting, and inhibition have been shown to increase activation in the frontoparietal network (including, e.g., dorsolateral prefrontal cortex), the cingulo-opercular network, and the striatum (Wu et al., 2020). It has been hypothesized that the partially overlapping anatomical locations and neuronal networks, mainly in the prefrontal (Morris et al., 2016) and parietal areas, may be underlying causes of the association between executive function and gait parameters (Poole et al., 2019).

Previous research investigating the associations between different subdomains of executive functions and gait have reported partially conflicting results. Associations between better performance in updating, set shifting or inhibition, and faster gait speed or better lower extremity functioning have been reported in some (Berryman et al., 2013; Coppin et al., 2006; Demnitz et al., 2018; Herman, Giladi, & Hausdorff, 2011; Morris et al., 2016; Soumare, Tavernier, Alperovitch, Tzourio, & Elbaz, 2009), but not all, studies (Hausdorff, Yogev, Springer, Simon, & Giladi, 2005; Valkanova et al., 2018). Thus, there is no consistent knowledge regarding if some subdomain of executive function is more strongly associated with different types of walking or physical performance than others.

Performing a cognitive task simultaneously with a physical task, such as walking, requires the allocation of limited cognitive processing resources. Walking-related dual tasking thus affects walking parameters, slows down gait speed, and negatively impacts cognition (Menant, Sturnieks, Brodie, Smith, & Lord, 2014). Due to the anatomical overlap regulating gait speed and executive functions, decrements in dual-task performance may be due to competition for the same resources.

Earlier studies that have investigated sex differences in executive functions have shown mixed results. One study found sex differences to be subdomain-specific: women outperformed men in fluent language production and in a task requiring working memory updating, whereas, no sex differences were observed in set shifting (McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016). Grissom and Reyes (2019), in turn, suggested that sex is not the primary factor influencing performance in executive functions and that the differences between the sexes may be more dependent on

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differences in the strategies used to complete a task than in the ability to perform it. In physical functions, men have higher performance compared with women in tasks requiring maximal performance, such as muscle strength and power (Sialino et al., 2019). Despite these differences, sex differences in the associations between cognitive and physical functions have been little studied. Best et al. (2016) found no differences between women and men in the longitudinal association between habitual gait speed and executive functions. Thibeau, McFall, Camicioli, and Dixon (2019), in turn, found a moderating effect of sex on the longitudinal association between mobility (including habitual gait speed and dynamic balance) and executive functions. As performance in physical and executive tasks between the sexes differs depending on the nature of the task, we suggest that the potential sex differences in the associations between executive functions and physical functions may also depend on the executive function assessed or the nature of the physical task.

The aim of this study was to investigate if better performance in executive functions is associated with better performance in physical functions, especially walking-related functions, in community-dwelling older people and whether the associations differ between men and women. We applied the model of Miyake et al. (2000), which "categorizes" executive functions into three subdomains—mental set shifting, updating, and inhibition—and included tests for each. We assessed physical functioning with tests that have been extensively used in studies among older people, have predictive value for physical limitation and disabilities, and require cognitive demand from low to high.

Methods

Participants

This cross-sectional study utilized baseline data gathered for a randomized controlled trial (The PASSWORD study, ISRCTN52 388040). A detailed description of the study design and recruitment was published earlier (Sipila et al., 2018). The participants were randomly selected from the Finnish National Registry. They were 70- to 85-year-old community-dwelling men and women living in the city of Jyväskylä, Finland, who did not meet physical activity guidelines (<150 min of moderate physical activity/week and no regular resistance training; Nelson et al., 2007) but were able to walk 500 m without assistance. Participants suffering from severe chronic or progressive diseases, severe musculoskeletal problems, depressive mood (Geriatric Depression Scale-15 > 5 points and who, according to the participants themselves and assessments by physicians and primary investigators, would not have the resources to commit to the study), excessive (risk level) use of alcohol (more than seven units per week for women and 14 for men) or any other contraindications for physical training, or a Mini-Mental State Examination (MMSE) score below 24 points were excluded.

Finally, 314 individuals were recruited for the study. The study was implemented according to the Declaration of Helsinki and approved by the ethical committee of the Central Finland Health Care District (K-S shp Dnro 11U/2016). All participants signed an informed consent before the baseline measurements.

Measurements

Physical functions. In the *10-m maximal gait speed* test (maximal gait speed), the participants were asked to walk as fast as possible over the 10-m course, with 2–3 m allowed for acceleration. The time taken (in seconds) to complete the walk was measured by photocells and the gait speed (in meters per second) calculated. This test requires additional physical effort and is more sensitive to different levels of cognition than habitual gait speed (Fitzpatrick et al., 2007). In the *20-m habitual gait speed test* (habitual gait speed), participants were asked to walk 20 m at their habitual speed. The time (in seconds) taken to complete the walk was measured by photocells and the gait speed (in meters per second) calculated. Reduced habitual gait speed is associated with risk for disability and cognitive impairment (Abellan van Kan et al., 2009). After the habitual gait speed test, the participants were asked to repeat the walk again while performing a visuospatial cognitive task (Menant et al., 2014). The visuospatial task involved a display with three boxes set side by side and labeled A, B, and C. The participants were asked to visualize a star that randomly moved to the left or right from one box to another. After three imagined movements, the participants were asked to name the box containing the star. The participants were informed about the random starting position of the star and the direction of its movements through headphones continuously throughout the walking trial. Each new set of three movements was announced within 1 second of the participant answering the previous question. The difference between the two trials, that is, *dual-task cost,* was calculated. Dual-task cost shows how the need to divide attention affects gait speed (Yogev-Seligmann et al., 2008). In the *6-min walking distance* test (6-min walking distance), the participants were asked to walk around a 20-m indoor track for 6 min, their aim being to walk the longest possible distance without risking their health. This test serves as a measure for community walking and walking endurance (Manttari et al., 2018). Lower extremity function, which is essential for walking, was measured with the *Short Physical Performance Battery* (SPPB), which is composed of three subtests: the standing balance test, habitual gait speed test, and repeated chair rise test (Guralnik et al., 1994). A sum score (0–12) was calculated, with higher scores indicating better performance.

Executive functions. *In the Color-Word Stroop test* (Stroop), the participants were asked to name colors under different conditions (Graf, Uttl, & Tuokko, 1995). First, they were asked to name a set of red-, blue-, or green-colored letter x's as quickly as possible. They were then asked to read words naming colors (e.g., red, blue) printed in black. Finally, they were required to state the color named by a word printed in an incongruent color, for example, the word "blue" printed in red ink. The inhibition cost, that is, the difference between the time taken to name the colors and the time taken to complete the incongruent word–color trial was calculated. The Stroop test assesses the ability to inhibit a practiced and overlearned stimulus response (word reading), and to react to the less trained task of color naming. In the *Trail Making Test* (TMT) A, which assesses psychomotor speed, the participants were instructed to draw a line from Number 1 to Number 2 and so on up to Number 25 (Reitan, 1958). In TMT B, which assesses mental flexibility and set shifting, the participants were instructed to draw a line from Number 1 to the Letter A and then from Number 2 to the Letter B and so on. The difference in the time taken to complete the two tests (TMT B–A) was calculated and used as an outcome. Updating and lexical access speed were assessed with the *Verbal Fluency test* (VF; Koivisto et al., 1992). In this test, the participants were asked to name as many words beginning with P, A, and S as possible in 1 min, and the number of words was summed.

Background variables. Information on *age and sex* was drawn from the Finnish National Population register. Body height and weight were measured, and body mass index was calculated. *Chronic diseases and medication* were self-reported and verified by the study physician through Finland's integrated patient information system. *Cognitive status* was assessed with the MMSE, which is a tool commonly used for screening cognitive functions among older adults (Folstein, Folstein, & McHugh, 1975). The MMSE provides information about registration, attention, calculation, recall, and language. The maximum MMSE test score is 30, and scores above 24 indicate normal cognitive function. Information on falls during the previous year, physical activity, education, and smoking were self-reported and assessed by validated questions. *Indoor and outdoor falls* during the previous year were reported separately, as follows: 1 = *none*, 2 = *once*, 3 = *2–4 times*, 4 = *5–7 times*, 5 = *8 times or more*. On the basis of the information received on these questions, the participants were characterized as fallers (Categories 2–5) and nonfallers (Category 1). Self-reported physical activity was assessed on a 7-point scale. The response options were 1 = *I do not move more than is necessary in my daily routines/chores*; 2 = *I go for casual walks and engage in light outdoor recreation 1–2 times a week*; 3 = *I go for casual walks and engage in light outdoor recreation several times a week*; 4 = *I engage 1–2 times a week in brisk physical activity (e.g., yard work, walking, cycling) to the point of perspiring and some degree of breathlessness*; 5 = *several times a week (3–5) I engage in brisk physical activity (e.g., yard work, walking, cycling) to the point of perspiring and some degree of breathlessness*; 6 = *I do keep fit exercises several times a week in a way that causes rather strong shortness of breath and sweating during the activity*; and 7 = *I participate in competitive sports and maintain my fitness through regular training* (Hirvensalo, Rantanen, & Heikkinen, 2000). For the regression analysis, physical activity was recategorized as high (Categories 5–7), medium (Categories 3–4), and low (Categories 1 and 2). Except for one participant who had reported Category 6, all the participants in the high physical activity category ($n = 40$) had reported Category 5. No participant had reported Category 7. Education was categorized as low (primary school or less), medium (middle school, folk high school, vocational school, or secondary school), or high (high school diploma or university degree). Smoking categories were never, former, and current. For the analysis, smoking status was recoded as smokers (former and current) and nonsmokers.

Statistical Analyses

The sample size of this study, calculated for the primary outcome of the randomized controlled trial design, that is, 10-m maximal gait speed, was 314. The participants' characteristics were expressed as means (*SD*s) for continuous variables and as *n* (%) for categorical variables. The differences between men and women were tested with the Mann–Whitney *U* test for nonnormally distributed continuous variables, with a chi-square test for categorical variables and independent samples *t* test for normally distributed continuous variables. To correct for the abnormal distribution of the dual-task cost, we added a constant of 1 + the absolute value of the minimum of the variable (–1.724) before using the Box–Cox transformation with $\lambda = -0.39$.

Associations between executive, and physical functions and their interaction with sex were assessed with multiple linear regression analyses. For the analysis, three model sets were constructed to explain each physical function measurement. In the executive functions main effect models, the main predictors were executive function and sex. In the executive functions–sex interaction models, the main predictors were executive function, sex, and the executive function–sex interaction. In the sex-stratified models, the analyses were carried out separately for women and men and the main predictor was executive function. Finally, we adjusted the main effect models and sex interaction models for multiple testing using the Bonferroni correction. When the sex interaction *p* value was nonsignificant, the parameters of the main effects model produced the most parsimonious description of the associations between executive functions and physical functions, and the results were interpreted from the main effects model.

Education, age, MMSE scores and smoking, which were theoretically meaningful and available control variables were included in the models. Relationships between physical and executive functions and the control variables were tested with the Pearson correlation coefficient and Spearman's rank correlation coefficient.

For regression models, two dummy variables were created from education and physical activity. The normality of residuals was checked using quantile–quantile plots and skewness and kurtosis statistics. The heteroskedasticity of residuals was assessed by regressing squared residuals on the predictor variables. The degree of multicollinearity was assessed using variance-inflating factors. Residual diagnostics suggested that two outliers remained for the outcome, dual-task cost, even after the Box–Cox transformation. However, the sensitivity analysis indicated that removing these subjects from the analysis would not lead to substantial modification of the results, and hence, we decided to retain the subjects in the analysis. Analyses were performed using SPSS statistics (version 26.0; IBM Corp., Armonk, NY). The descriptive and bivariate correlation analyses were considered explorative, and we set alpha to the nominal .05 level. For the model-based tests of effects, we used the Bonferroni-corrected alpha level set at .05.

Results

The participant characteristics are shown in Table 1. The mean age was 75 years, and 60% of the subjects were women. Significant anthropometric differences were observed between men and women. Women were more likely to have a higher education status and slightly higher MMSE scores than men. Men were likely to smoke more than women and perform better in the physical function and dual-task tests, except for habitual gait speed. No significant differences between men and women were found in the Stroop or TMT B−A. Women significantly outperformed men in VF (Table 1).

Of the selected control variables, age and education correlated with the physical function measurements, with the exception of dual-task cost, which did not correlate with age or education. Age correlated with all executive functions, except VF. Education and MMSE scores correlated with all executive functions. Physical activity correlated with all the physical function measurements, except maximal gait speed and dual-task cost. Physical activity showed no significant association with executive functions, and MMSE showed no significant association with physical functions. Smoking did not show a statistically significant association with physical or executive functions. However, as smoking is a known risk factor for poor physical and cognitive functioning, we decided to retain it in the models (Table 3).

In the multiple linear regression analysis (Table 2), we first examined only associations involving the main effects of executive function (significant main effect and nonsignificant sex interaction). After adjusting the models for multiple comparisons, we

Table 1 Participant Characteristics

Variable	All ($n = 314$)	Women ($n = 188$)	Men ($n = 126$)	p
Age (years)	74.5 ± 3.8	74.5 ± 3.8	74.4 ± 3.9	.568[a]
Height (m)	1.66 ± 0.09	1.61 ± 0.06	1.74 ± 0.06	<.001[c]
Weight (kg)	76.9 ± 14.2	71.9 ± 13.1	84.3 ± 12.5	<.001[a]
BMI	27.9 ± 4.7	28.0 ± 5.3	27.9 ± 3.6	.394[a]
Education (%)				.027[b]
Low	48 (15)	21 (11)	27 (21)	
Medium	200 (64)	122 (65)	78 (62)	
High	66 (21)	45 (24)	21 (17)	
Current physical activity (%)				.227[b]
Low	126 (40)	73 (39)	53 (42)	
Medium	148 (47)	95 (51)	53 (42)	
High	40 (13)	20 (11)	20 (16)	
Fall in the previous year (%)				.231[b]
Yes	164 (52)	93 (50)	71 (56)	
No	150 (48)	95 (51)	55 (44)	
Smoking status (%)				<.001[b]
Never smoker	191 (61)	135 (72)	56 (44)	
Former smoker	109 (35)	48 (26)	61 (48)	
Current smoker	14 (4)	5 (3)	9 (7)	
Number of the chronic diseases	2.4 ± 1.5	2.5 ± 1.5	2.6 ± 1.5	.312[a]
MMSE (score)	27.6 ± 1.5	27.8 ± 1.5	27.5 ± 1.4	.049[a]
SPPB (score)	10.1 ± 1.5	9.8 ± 1.5	10.6 ± 1.4	<.001[a]
10-m gait speed (m/s)	2.0 ± 0.4	1.9 ± 0.3	2.1 ± 0.4	<.001[c]
20-m gait speed (m/s)	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	.148[c]
6-min walking distance (m)	475.4 ± 81.7	457.3 ± 70.3	502.4 ± 89.9	<.001[c]
Dual-task cost (s)[d]	1.25 ± 0.25	1.29 ± 0.24	1.20 ± 0.25	.004[a]
Stroop difference (s)	46.7 ± 25.0	46.5 ± 22.4	46.9 ± 28.6	.770[a]
TMT B–A (s)	88.0 ± 52.2 ($n = 313$)	83.8 ± 50.8 ($n = 187$)	94.4 ± 53.8	.051[a]
Verbal fluency test (words)	41.6 ± 13.0	44.4 ± 12.1	37.5 ± 13.2	<.001[c]

Note. One participant was unable to perform TMT test due to hand pain. Values are presented as mean ± *SD* or *n* (%). BMI = body mass index; MMSE = Mini-Mental State Examination; SPPB = Short Physical Performance Battery; TMT = trail making test.
[a]Mann–Whitney *U* test. [b]Chi-square. [c]Independent samples *t* test. [d]Distribution shifted by adding a constant of 2.724 and Box–Cox transformed with $\lambda = -0.39$.

found that VF was associated with higher maximal and habitual gait speed ($\beta = 0.273$ $p < .001$, $\beta = 0.184$ $p = .009$, respectively), longer 6-min walking distance ($\beta = 0.242$, $p < .001$), and higher SPPB scores ($\beta = 0.234$, $p < .001$). TMT B–A was associated with higher SPPB scores ($\beta = -0.236$, $p < .001$). Stroop was not associated with any of the physical function tests. In addition, all sex interactions were nonsignificant. The sex-stratified models are shown in Supplementary Table S1 (available online).

Discussion

In this study conducted among community-dwelling older adults who did not meet physical activity guidelines, we found that better performance in executive functions related to updating, and set shifting was associated with better walking performance and lower extremity functioning. However, the ability to inhibit an overlearned stimulus response was not associated with any of the physical function tests. In addition, we found nonsignificant sex interactions in the associations between physical and executive functions.

Earlier studies that have investigated the associations between executive functioning and walking performance have reported partially conflicting results. Associations between better performance in set shifting, updating, and inhibition and faster gait speed or better lower extremity functioning have been reported in some studies (Berryman et al., 2013; Coppin et al., 2006; Demnitz et al., 2018; Herman et al., 2011; Soumare et al., 2009), while other studies did not find these associations (Hausdorff et al., 2005; Kaye et al., 2012; Valkanova et al., 2018). Our results suggest that, among community-dwelling and relatively healthy older people, executive functions related in particular to updating, but also to set shifting, are associated with physical functions.

We found that updating and set shifting were associated with faster maximal and habitual gait speed, longer distance traveled (updating), and better lower extremity functioning (updating and set shifting), whereas, no significant association was observed between executive functions and dual-task cost in gait speed. These results suggest that safe and stable walking and lower extremity functions requiring dynamic, reciprocal, rhythmic, and fluent sensorimotor performance may depend more on updating/

Table 2 Associations Between Physical Functions and Executive Functions Among 70-to 85- Year-Old Men and Women

	Maximal gait speed			Habitual gait speed			Dual-task cost[a]			6-min walking distance			SPPB		
Variable	β	R^2	*p*	β	R^2	*p*	β	R^2	*p*	β	R^2	*p*	β	R^2	*p*
Main effects models															
VF	0.273	.272	<.001	0.184	.127	.009	−0.050	.032	1.000	0.242	.291	<.001	0.234	.184	<.001
TMT B−A	−0.100	.214	.409	−0.111	.108	.360	0.144	.046	.121	−0.130	.253	.107	−0.236	.178	<.001
Stroop	−0.063	.213	1.000	−0.052	.101	1.000	0.110	.042	.267	−0.057	.245	1.000	−0.058	.142	1.000
Interaction effect models															
VF × Sex			.120			.799			.357			.110			1.000
TMT B−A × Sex			1.000			1.000			.109			1.000			1.000
Stroop × Sex			.788			1.000			1.000			.544			1.000

Note. Main effect coefficients are from main effects models for each executive function, and sex interaction *p* values are from the sex executive function interaction models. Bonferroni corrected *p* value for five outcome variables. In sex interaction models, reference was male. Control variables in models were age, education, level of physical activity, smoking, and MMSE scores. TMT = trail making test; VF = verbal fluency test; SPPB = Short Physical Performance Battery; MMSE = Mini-Mental State Examination.

[a]Distribution shifted by adding a constant of 2.724 and Box–Cox transformed with $\lambda = -0.39$.

Table 3 Bivariate Correlations Between Physical and Executive Function Variables (Columns) and Background Variables (Rows)

Variable		Maximal gait speed	Dual-task cost	Habitual gait speed	Walking distance	SPPB	Verbal fluency	TMT B−A	Stroop
Age (years)[a]	*r*	−.29	.07	−.26	−.33	−.18	−.05	.28	.15
	p	<.001	.222	<.001	<.001	.002	.427	<.001	.010
Education[b]	r_S	.14	−.07	.12	.14	.17	.33	−.35	−.15
	p	.011	.188	.036	.013	.016	<.001	<.001	.008
Physical activity[b]	r_S	.07	.05	.18	.20	.18	−.05	−.03	.03
	p	.204	.368	.002	<.001	.002	.394	.576	.647
MMSE[a]	*r*	.05	−.05	.05	.04	.05	.19	−.25	−.11
	p	.378	.407	.421	.502	.341	.001	<.001	.043
Smoking[b]	r_S	−.02	−.06	−.07	−.10	<.01	−.01	<.01	.02
	p	.693	.336	.194	.102	.951	.836	.997	.768

Note. Correlation coefficients and *p* values are presented. TMT = trail making test; SPPB = Short Physical Performance Battery; MMSE = Mini-Mental State Examination. [a]Pearson correlation coefficient. [b]Spearman's rank correlation coefficient.

lexical access speed and mental flexibility than the ability to inhibit an overlearned stimulus response. As indicated above, our findings highlight the dependency of the associations between physical and executive functions on the type of executive processes and physical tasks measured and thus may partly explain the conflicting results of prior studies (Berryman et al., 2013; Coppin et al., 2006; Demnitz et al., 2018; Hausdorff et al., 2005; Herman et al., 2011; Kaye et al., 2012; Valkanova et al., 2018).

Surprisingly, unlike previous studies that have reported associations between executive functions and dual-task gait performance, at least when the concurrent cognitive task is demanding (Liu-Ambrose, Katarynych, Ashe, Nagamatsu, & Hsu, 2009; Menant et al., 2014), we found no association between executive functions and smaller dual-task cost in gait speed. We assessed the dual-task condition with a cognitively challenging visuospatial–motor task that has been found to induce greater interference while walking than nonspatial tasks (Menant et al., 2014) and were therefore surprised to find that the association between executive functions and dual-task cost in gait speed was nonsignificant. However, a systematic review showed that the visuospatial cognitive domain is associated with the postural control domain of gait rather than pace, that is, speed of gait (Morris et al., 2016). Moreover, Coppin et al. (2006) have suggested that the cost associated with increased executive load during basic walking differs by the nature of the dual task. We assessed dual-task gait performance in habitual gait speed, which is not a physically challenging task, and this may have affected our results. It may be that, among well-functioning, relatively healthy older adults, the association between executive functions and dual-task performance is more prominent when both the cognitive and physical task are simultaneously demanding.

The associations of sex differences with executive and physical functions were nonsignificant. Prior research on this topic is limited. Best et al. (2016) found no sex differences in the longitudinal associations between executive functions and habitual gait speed, whereas, Thibeau et al. (2019) reported that sex moderated the longitudinal associations of executive functions with walking and balance. They suggested that the sex-dependent association of physical activity and walking or balance with executive functions is multifactorial, due to, for example, age-related changes in neural networks and brain structure in the frontal cortex that differ between the sexes (Crivello, Tzourio-Mazoyer, Tzourio, & Mazoyer, 2014; Scheinost et al., 2015). In addition, muscle and metabolic biomarkers affecting gait speed and cognition differ between men and women. For example, sex-specific muscle and metabolic biomarkers have been shown to be associated with changes in gait speed in both sexes, whereas metabolic biomarkers were shown to be associated with changes in cognitive functions only among men (Waters, Vlietstra, Qualls, Morley, & Vellas, 2020). It should be noted that the earlier studies only measured habitual gait speed, which does not necessarily reveal the known sex differences underlying gait speed, such as body height and lower body muscle strength. Our results showing no sex differences in the associations between gait speed and executive functions extend those reported by Best et al. (2016) by showing no sex differences in the associations of gait speed tests differing in difficulty and length with executive functioning among a sample of older adults who did not meet physical activity guidelines. However, further studies are needed to confirm this result.

To further knowledge on the associations between cognitive and physical functions among relatively healthy older people, we designed a measurement protocol with a comprehensive array of executive and physical function measures. We included tests for three subdomains of executive functioning that have been extensively used in studies among older people. The measures of physical function traits used here are commonly used in clinical settings and in aging research and known to predict adverse outcomes, for example, disability, cognitive impairment, falls, and even mortality in older populations (Abellan van Kan et al., 2009). These included a relatively simple measure, habitual gait speed over a short distance, along with more physically and cognitively challenging tests, such as walking over a longer distance either at maximal gait speed or under dual-task conditions, and a more complex measure (SPPB) in which walking, balance, and lower body muscle power scores are merged into a composite score.

In addition to assessing gait and executive function with an extensive measurement protocol, the strengths of this study include a representative sample of community-dwelling older people who did not meet the physical activity guidelines and measurements that are widely used and considered to be suitable for assessing older adults. Moreover, the fact that the measurements were conducted by the same investigators is likely to enhance the reliability of the results.

The main limitation of this study is the cross-sectional design, which does not allow conclusions to be drawn on causality. We only used a single task to target each executive function, instead of multiple tasks, which makes the measurement of each executive function suboptimal. Hence, caution in interpreting the results is warranted. In addition, our results cannot be generalized to groups who do not meet our eligibility criteria. However, the sample was drawn from the Finnish National Register, and as few potential participants as possible were excluded from the study. Our participants were relatively healthy, with intact cognition. This characteristic may even have attenuated the results and could explain why, among the control variables, the MMSE did not correlate with physical functions and physical activity did not correlate with executive functions.

Conclusions

We found that, while executive functions are associated with walking and lower extremity functioning among older adults, the associations were partly dependent on the specific executive process measured and the nature of the physical task. Longitudinal studies are needed to confirm the associations found and ascertain possible causality.

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III

PARTICIPANT CHARACTERISTICS ASSOCIATED WITH THE EFFECTS OF A PHYSICAL AND COGNITIVE TRAINING PROGRAM ON EXECUTIVE FUNCTIONS

by

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Participant characteristics associated with the effects of a physical and cognitive training program on executive functions

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Background: Physical and cognitive interventions have been shown to induce positive effects on older adults' executive functioning. However, since participants with different background characteristics may respond differently to such interventions, we investigated whether training effects on executive functions were associated with sex, training compliance, and age. We also investigated if change in global cognition was associated with physical and cognitive training intervention-induced changes in executive functions.

Methods: Exploratory data from a randomized controlled trial were analyzed. Participants were 70–85-year-old men and women who received a 12-month physical (PT) or physical and cognitive training (PTCT) intervention. Measurements of executive functions related to inhibition (Stroop), set shifting (Trail Making Test B) and updating (Verbal Fluency) were performed at baseline and 12 months. Data were analyzed using a longitudinal linear path model for the two measurements occasion.

Results: Stroop improved significantly more in women and participants in the low compliance subgroup who received PTCT than in counterparts in the PT subgroup (difference −8.758, p = 0.001 and difference −8.405, p = 0.010, respectively). In addition, TMT B improved after the intervention in the low compliance PTCT subgroup and worsened in the corresponding PT subgroup (difference −15.034, p = 0.032). No other significant associations were observed.

Conclusion: Executive functions in women and in the participants, who only occasionally engaged in training showed greater improvement after the PTCT than PT intervention. However, the additional extra benefit gained from the PTCT intervention was uniquely expressed in each executive function measured in this study.

KEYWORDS

older adults, executive functions, training response, physical training, physical and cognitive training

Introduction

Executive functions are high-order cognitive functions that enables independent, appropriate and self-serving behavior (Harada et al., 2013). It is generally agreed that executive functions are consist of three sub-domains, inhibition, set shifting and updating that are united but show also diversity and serve as a base, for example, for problem solving, reasoning and planning (Miyake et al., 2000; Diamond, 2013). Executive functions has been shown to be prone age-related decline (Harada et al., 2013), however this decline can be attenuated with training (Diamond, 2013).

Physical and cognitive interventions have been shown to induce positive effects on older adults' executive functioning (Ten Brinke et al., 2020; Sipilä et al., 2021; Han et al., 2022). However, participants with different baseline characteristics may respond differently to different training interventions. To develop optimized interventions and guidelines for executive functioning among older people, the factors that may influence training responses need to be identified. The results of PASSWORD, our earlier randomized controlled study (Sipilä et al., 2021), showed that a 12-month multicomponent physical training program combined with computer-based cognitive training improved executive functions related to inhibition more compared to physical training alone among older adults who did not meet physical activity guidelines at baseline. However, no significant intervention-induced changes between the study groups were observed in other domains of executive functions namely set shifting or updating.

Previous research findings suggest that the training response of physical and cognitive training (PTCT) interventions are depended on sex, training frequency and age, although of the previous studies are somewhat inconsistent. For example, meta-analysis by Barha et al. (2017) found that women executive functioning gained greater benefit from physical training interventions compared to men. However, recent randomized controlled trial (Roig-Coll et al., 2020) did not found sex differences in exercise efficacy after combined PTCT. Additionally, previous meta-analysis has suggested that high frequency of combined PTCT (5 times a week or more) is inefficient for executive functions (Zhu et al., 2016). Physical training, in turn, has been suggested to be most beneficial for executive functions when training frequency is rather frequent (3–5 times a week) in meta-analysis by Karr et al. (2014). Moreover, previous meta-analyses have been shown that, among older adults, older age was associated with greater positive intervention induced change in executive functions after combined PTCT (Zhu et al., 2016; Han et al., 2022). Concerning the physical training it might be that age does not have a similar role (Karr et al., 2014). Finally, better global cognition has been show to correlate with better performance in executive functions (Shao et al., 2020).

In this hypothesis-generating analysis, we investigated whether the training responses observed in different domains of executive functioning, inhibition, set shifting and updating were dependent on sex, training compliance or age. We further investigated if change in global cognition was associated with intervention-induced change in executive functions sub-domains.

Methods

Study design

This study utilized data from our earlier assessor-blinded randomized controlled trial.[1] The study design and the results have been published previously (Sipilä et al., 2018, 2021). Ethical approval of the study was obtained from the Ethical Committee of Central Finland Health Care District (14/12/2016, ref: 11/2016). All participants gave a written consent before the baseline measurements.

Participants

Participants were 70–85-year-old community-dwelling men and women living in Jyväskylä, Finland and were randomly

1 http://www.isrctn.com/ISRCTN52388040

extracted from Finland's Population Information System administered by the Population Register Center. The inclusion criteria were willingness to participate, not meeting physical activity guidelines (less than 150 min of moderate activity/week and no regular resistance training), ability to walk 500 meters without assistance, and a Mini-Mental State Examination (MMSE) score $\geq$ 24. The exclusion criteria were a severe chronic condition and/or medication affecting cognitive and/or physical performance, any contraindication for walking for physical training or walking tests, depressive mood (GDS-15 > 5 points and not having the self-reported or physician and primary investigator-assessed resources to commit to the study), risk-level use of alcohol (> 7 units per week for women and 14 for men), or any other contraindications for physical training or another member of the household participating in the PASSWORD-study. After exclusions, 314 participants were recruited to the study.

Randomization and blinding

Participants were randomized in a 1:1 ratio and stratified by age (70–74, 75–79, 80–85) and sex into the PTCT (n = 155) or Physical Training alone (PT) (n = 159) groups.

Interventions

The interventions have been described previously (Sipilä et al., 2021). In brief, both groups received a 12-month multicomponent progressive physical training intervention which was designed on the basis of physical activity guidelines and earlier studies (Sihvonen et al., 2004; Portegijs et al., 2008; Fielding et al., 2011). The PT intervention included two supervised training sessions a week, one for resistance and balance exercises and the other for walking and dynamic balance exercises. Resistance and balance exercises included short warm-up, balance exercises and strengthening resistance exercises for lower limbs, trunk, and upper body. Walking and dynamic balance sessions included 10-min warm-up and dynamic balance training, following 10–20 min continuously walk with target intensity of somewhat hard to hard. Supervised resistance training session took place in senior gyms equipped with machines utilizing air pressure technology.[2] Supervised walking and dynamic balance training sessions took place outdoors except during winter months indoor sports hall. In addition, participants received a progressive home exercise program which was instructed to perform 2–3 times a week. Home exercise program included strength exercises for lower limbs, balance exercises and stretching. The PTCT group received also 12-month progressive computer-based cognitive training intervention targeted at improving executive functions. Participants were instructed to perform cognitive training 3–4 times a week.

2 http://www.hur.fi/en

Measurements

Executive functions were assessed at baseline, 6 and 12 months. Other outcomes were assessed at baseline and 12 months. This study utilized data from the baseline and 12 months measurements for all outcomes.

Executive functions

Inhibition was assessed with the Color-Word Stroop test. In this test participants were requested to name colors in incongruent and congruent conditions. Finally, the time difference between two conditions was calculated and used as the outcome (Graf et al., 1995). *Set shifting* was assessed with the Trail Making Test Part B. This test requires participants to alternately combine numbers and letters as quickly as possible (Reitan, 1958). *Updating* was assessed with the Verbal Fluency Test. This test requires participants to name as many words beginning with P, A or S as they can in three separate 1-min trials (Koivisto et al., 1992). The total score is the summed number of the named words.

Participant characteristics

Subgroup analyses on age, sex, global cognition, and training compliance were pre-specified for walking speed, the main outcome, of PASSWORD (Sipilä et al., 2021). Participant *sex* and *age* were drawn from Finland's Population Information System administered by the Population Register Center. *Global cognition* was assessed at baseline and after the interventions with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Chandler et al., 2005; Paajanen et al., 2010). Compliance was based on participation in supervised training sessions. The high-compliance PT subgroup participated in at least 50% and the low-compliance PT subgroup in less than 50% of the supervised PT sessions. The high-compliance PTCT subgroup participated in at least 50% of the supervised PT sessions and performed Cognitive training (CT) at least twice a week. The low compliance PTCT subgroup participated in less than 50% of the supervised PT sessions and/or performed CT less than twice a week. The mean compliance for each program (walking and dynamic balance sessions: 59% in the PT group and 62% in the PTCT group. Resistance and balance sessions: 72% in PT group and 77% in PTCT group. Cognitive training: on average 1.9 times a week) has been published previously (Sipilä et al., 2021).

Descriptive variables

Body *height* and *weight* were measured at baseline, and BMI was calculated. *Education, current physical activity, smoking* *status*, and *self-rated health* were self- reported. *Education* was categorized as low (primary school or less) medium (middle school, folk high school, vocational school, or secondary school) or high (high school or university). Current physical activity was assessed with a seven-point scale (Hirvensalo et al., 2000) and re-categorized as high (categories 5–7) medium (categories 3 and 4) or low (categories 1 and 2). S*moking status* was categorized as never smokers (never smoker/less than 100 times), former smokers (never smoked regularly but smoked over 100 times) or current smoker (current smoker, regularly or occasionally). *Self-rated health* was reported as very good/good or average/poor.

Statistical analyses

As descriptive statics we report the means and standard deviations for continuous variables and frequencies and percentages for categorical variables separately for PT and PTCT groups.

To identify potential outliers for the outcome variables of the main analyses, the outcome distributions were inspected graphically using univariate histograms and quantile plots and bivariate scatter plots. Skew and kurtosis were considered as summary statistics of distribution shape. While the plots, skew, and kurtosis (absolute value less than unity) indicated acceptable shape of distribution for all variables.

For the analyses, the outcomes were regressed within measurement waves in a two-group linear path model accounting for longitudinal correlation in the outcome variables. Using custom contrasts, we computed the differences in the regression coefficients from the measurement waves as the effects of time, and the difference in these time effects between groups was computed as the interaction effect.

Outcomes were tested for group-interaction over time using an interaction contrast in a linear model for the two longitudinal measurements. The model structure was set similar to the linear mixed model in order to account for within-person correlation, but it also permitted more general outcome variance structure specification and flexible handling of missing data with the maximum likelihood approach based on the missing-at-random (MAR) assumption. For continuous exposure variables (age and Cerad) the model included a within-subject part for the repeated measurements for each subject, and a between-subjects part contrasting the PTCT and PT groups based on regression coefficient differences. A similar model was used for binary exposure variables (sex and training compliance), but now the contrast was based on differences in expected marginal means. We report group means for each available measurement wave and group-by-time interactions as primary significance tests. As further subgroup contrasts, we also compared if the background factors and descriptive variables differed between PTCT and PT groups among men and women and high and low compliance groups. This analysis was carried out in SPSS for windows, version 26. The specific contrasts used for all comparisons are shown in the model and contrast specification section of the supplementary document. The path model analyses were conducted in Mplus, version 7.4 (Muthen and Muthén, 2017).

Results

Participants' mean age was in PT group was 74.4 and in PTCT group 74.5 years, approximately 60% of participants were women in both groups, 25% in PT group and 18% in PTCT group had the high level of education (**Table 1**).

Our previous study, suggest that PTCT group improved significantly more their performance in Stroop than PT group (Sipilä et al., 2021). This subgroup analysis shows that women, and the low-compliance groups in PTCT improved Stroop performance significantly more than in the corresponding PT subgroups (difference -8.758, p = 0.001 and difference -8.405, p = 0.010, respectively) (**Table 2**). In men and the high-compliance subgroups, no significant differences between

TABLE 1 Participant's characteristics.

	PTCT (n = 155)	PT (n = 159)
Age (years)	74.4 ± 3.9	74.5 ± 3.8
BMI	28.0 ± 4.9	27.9 ± 4.5
MMSE	27.9 ± 1.4	27.4 ± 1.5
CERAD	79.5 ± 8	79.0 ± 8.2
SEX, no (%)		
Feman	96 (62)	92 (58)
Man	59 (38)	67 (42)
Education, no (%)		
Low	23 (15)	25 (16)
Medium	94 (61)	106 (67)
High	38 (25)	28 (18)
Current physical activity, no (%)		
Low	56 (36)	70 (44)
Medium	80 (52)	68 (43)
High	19 (12)	21 (13)
Smoking status, no (%)		
Never	94 (61)	97 (61)
Former	52 (34)	57 (36)
Current	9 (6)	5 (3)
Self-rated health, no (%)		
Very good/good	73 (47)	68 (43)
Average/poor	82 (53)	91 (57)

Means and standard deviations. Frequencies and percentages. PTCT, Physical and cognitive training; PT, Physical training; BMI, Body Mass Index; MMSE, Mini-Mental State Examination; CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

TABLE 2 Means with 95% confidence intervals and unstandardized regression coefficients (B) with 95% confidence intervals for subgroup analysis of the Stroop outcomes.

Stroop[a]			PTCT			PT				PTCT-PT			
				95% CI				95% CI			95% CI		
Subgroup	*N*		Mean	Lower	Upper	*N*	Mean	Lower	Upper	Difference	Lower	Upper	*P*-value
Overall	155	BL	45.1	41.9	48.4	159	48.1	43.7	52.6	−6.766	−11.111	−2.421	0.002
		FU	34.0	31.2	36.8		43.8	40.5	47.1				
Men	59	BL	42.5	38.0	47.1	67	50.8	42.5	59.2	−3.575	−10.942	3.793	0.342
		FU	34.6	29.8	39.4		46.5	40.8	52.2				
Women	96	BL	46.7	42.3	51.2	95	46.2	41.6	50.8	−8.758	−13.873	−3.643	0.001
		FU	33.6	30.2	37.0		41.8	38.0	45.7				
Low compliance	95	BL	46.2	42.1	50.2	55	48.2	42.5	53.9	−8.405	−14.780	−2.031	0.010
		FU	35.1	31.5	38.7		45.5	39.9	51.1				
High compliance	60	BL	43.5	38.1	48.9	103	48.3	42.2	54.4	−5.966	−12.736	0.804	0.084
		FU	32.3	28.0	36.6		43.0	39.0	47.1				
			B	Lower	Upper		B	Lower	Upper	Difference	Lower	Upper	*P*-value
Age	155	BL	0.860	0.026	1.695	159	1.037	−0.126	2.200	0.654	−0.482	1.790	0.259
		FU	1.368	0.686	2.049		0.890	0.032	1.749				
CERAD[b]	141	BL	−0.538	−0.939	−0.136	147	−0.691	−1.141	−0.241	−0.090	−0.655	0.474	0.754
		FU	−0.514	−0.810	−0.218		−0.577	−0.902	−0.252				

[a]Lower time indicates better performance, [b]Comprises verbal fluency, modified Boston naming test, word lists constructional praxis, word list recall and word list recognition discriminability (total sum score range 0–100). B, unstandardized regression coefficient; CI, confidence interval; PTCT, physical and cognitive training; PT, physical training; CERAD, Consortium to Establish a Registry for Alzheimer's Disease. Men vs. Women, $p = 0.257$, Training less vs. more than 50% (PT only), $p = 0.596$, Training less vs. more than 50% (PT and CT), $p = 0.607$.

the PT and PTCT interventions were observed. Age or global cognition were not significantly associated with the interventions-induced changes in Stroop performance.

Post-intervention TMT B performance improved significantly in the low compliance PTCT subgroup and worsened, i.e., was below the baseline level, in the low compliance PT subgroup (difference -15.034, $p = 0.032$) (**Table 3**). No significant differences in the change in TMT B change were observed among men, women, or the high-compliance subgroups. Moreover, no significant associations of age or global cognition with change in TMT B by intervention type were observed.

No significant differences in change in Verbal Fluency were observed between the study subgroups (**Table 4**) and none of the participant characteristics were significantly associated with change in Verbal Fluency by intervention type.

Discussion

In this hypothesis-generating analysis, we investigated whether the training responses of different sub-domains of executive functioning were dependent on age, sex, training compliance or change in global cognition. Our earlier study suggested that the 1-year PTCT intervention provided additional benefit for inhibition compared to physical training alone (Sipilä et al., 2021). The present subgroup analyses suggests that the benefit found for inhibition may be driven by women sex and/or low compliance, defined as participation in less than half of the training. However, we found no statistically significant interactions between the sex subgroups and high- and low-compliance subgroups. The set shifting results showed that the participants in the low-compliance subgroup benefitted more from the PTCT than from physical training alone.

We found that women who received the PTCT showed a significantly greater improvement in their post-intervention inhibition performance than those who received physical training alone. Women who received PTCT improved their performance in Stroop by 28% whereas women who received physical training alone improved their performance by 9%. The corresponding changes among men indicated a similar but lower, statistically non-significant effect. Men receiving PTCT improved their performance in Stroop by 19% and men receiving physical training by 9%. The mechanism underlying the lower mean response rate among men remains unclear. It may be that activation of the neural circuits and/or molecular mechanisms (Grissom and Reyes, 2019) utilized by the women to solve the challenges presented by our cognitive training contributed to their superior performance in inhibition. Additionally, women tend to experience less decline over time in executive functions compared to men (McCarrey et al., 2016) and it might be that therefore they were more responsive to

TABLE 3 Means with 95% confidence intervals and unstandardized regression coefficients (B) with 95% confidence intervals for subgroup analysis of the TMT-B outcomes.

TMT-B[a]		PTCT				PT				PTCT-PT			
				95% CI				95% CI			95% CI		
Subgroup		***N***	**Mean**	**Lower**	**Upper**	***N***	**Mean**	**Lower**	**Upper**	**Difference**	**Lower**	**Upper**	***P*-value**
Overall	BL	155	130.7	120.8	140.6	158	132.2	123.7	140.8	−5.349	−13.620	2.922	0.205
	FU		119.3	108.6	129.9		126.1	117.7	134.6				
Men	BL	59	134.4	120.3	148.4	67	143.1	127.4	158.7	−13.486	−27.924	0.952	0.067
	FU		117.2	104.7	129.7		139.4	123.0	155.8				
Women	BL	96	128.5	115.1	141.9	91	124.3	115.3	133.3	−0.494	−10.190	9.202	0.920
	FU		119.9	104.8	135.0		116.2	108.6	123.7				
Low compliance	BL	95	137.4	123.2	151.6	54	125.8	112.8	138.7	−15.034	−28.769	−1.299	0.032
	FU		127.9	112.0	143.8		131.3	115.2	147.4				
High compliance	BL	60	120.2	108.6	131.8	103	135.9	124.8	147.1	−1.775	−13.150	9.599	0.760
	FU		106.7	95.5	117.8		124.2	114.3	134.1				
			B	**Lower**	**Upper**		**B**	**Lower**	**Upper**	**Difference**	**Lower**	**Upper**	***P*-value**
Age	BL	155	5.358	2.941	7.774	158	3.741	1.537	5.945	−1.574	−3.747	0.599	0.156
	FU		4.470	1.802	7.138		4.427	2.276	6.578				
CERAD[b]	BL	141	−1.317	−2.148	−0.486	147	−2.939	−3.788	−2.089	0.268	−0.826	1.362	0.631
	FU		−1.136	−1.968	−0.303		−3.026	−3.830	−2.222				

[a]Lower time indicates better performance, [b]Comprises of verbal fluency, modified Boston naming test, word lists, constructional praxis, word list recall and word list recognition discriminability (total sum score range 0–100). B, unstandardized regression coefficient; CI, confidence interval; PTCT, physical and cognitive training; PT, physical training; CERAD, Consortium to Establish a Registry for Alzheimer's Disease. Men vs. Women, $p = 0.143$, Training less vs. more than 50% (PT only), $p = 0.001$, Training less vs. more than 50% (PT and CT), $p = 0.145$.

cognitive training compared to men. It is noteworthy that the women receiving the PTCT only gained additional benefit in inhibition. This might be due to our cognitive training program, which likely fosters goal maintenance, a key requirement for which is inhibition. Hence, the greatest improvement induced by cognitive training was found in the Stroop task (Sipilä et al., 2021).

We found that the additional benefit of the PTCT on inhibition and set- shifting compared to physical training alone was mostly observed in the low-compliance subgroups. In the low-compliance subgroup receiving PTCT, inhibition and set shifting improved by 24 and 7%, respectively, as compared to the 6% improvement in inhibition and the 4% reduction in set shifting in the low-compliance subgroup receiving physical training alone.

Our results showed that different sub-domains of executive functions responded differently to the two interventions, i.e., to the intervention combining PTCT and the intervention comprising physical training alone. It seems that combining PTCT is beneficial enhancing the inhibition of information overload. We found that low-level PTCT benefited inhibition significantly more than low-level physical training alone. A similar trend was observed among participants whose training was on a high level, although the difference between the subgroups was not statistically significant. Set shifting, in turn benefited from low level PTCT, whereas a low level of physical training alone was not sufficient to maintain or improve performance of this task. We therefore suggest that the process underlying the training response in set shifting differs from that underlying inhibition, and hence further investigation is needed to clarify these mechanisms. Our additional subgroup analyses showed (see **Supplementary material**) some selection bias for compliance and sex. For example, 70% of the men who received PTCT were in the low-compliance subgroup and 30% in the high-compliance subgroup, whereas only 27% of the men receiving physical training alone were in the low- and 73% in the high-compliance subgroup. A similar trend was observed among women. In addition, 70% of the participants who received PTCT and were in the high-compliance subgroup were women and only 30% were men. In the physical training group, the corresponding percentages were 52 and 48%.

Our analyses showed that the training responses in executive functioning were not dependent on age or change in global cognition. To our knowledge, this is the first study to investigate whether these background factors are associated with the greater beneficial effect of the PTCT on executive functions compared to physical training alone. Therefore, more research is needed to investigate the associations of different background factors with

TABLE 4 Means with 95% confidence intervals and unstandardized regression coefficients (B) with 95% confidence intervals for subgroup analysis of the verbal fluency outcomes.

Verbal fluency[a]		PTCT				PT				PTCT-PT			
				95% CI				95% CI			95% CI		
Subgroup		***N***	**Mean**	**Lower**	**Upper**	***N***	**Mean**	**Lower**	**Upper**	**Difference**	**Lower**	**Upper**	***P*-value**
Overall	BL	155	42.3	40.3	44.4	159	40.9	38.9	42.9	0.291	−1.753	2.335	0.780
	FU		46.0	43.7	48.3		44.3	42.2	46.4				
Men	BL	59	39.5	36.0	43.0	67	35.7	32.7	38.7	−0.937	−4.116	2.241	0.563
	FU		41.4	37.6	45.1		38.6	35.4	41.7				
Women	BL	96	44.1	41.6	46.6	92	44.7	42.3	47.1	0.894	−1.725	3.514	0.503
	FU		48.8	46.1	51.5		48.5	46.0	50.9				
Low compliance	BL	95	41.2	38.8	43.9	55	40.9	37.8	44.0	−0.436	−3.551	2.676	0.784
	FU		44.2	41.4	47.0		44.3	40.9	47.7				
High compliance	BL	60	44.1	40.9	47.3	103	40.9	38.2	43.5	1.424	−1.284	4.133	0.303
	FU		48.9	45.1	52.7		44.2	41.6	46.9				
			B	**Lower**	**Upper**		**B**	**Lower**	**Upper**	**Difference**	**Lower**	**Upper**	***P*-value**
Age	BL	155	0.141	−0.392	0.675	159	−0.449	−0.975	0.078	−0.173	−0.705	0.360	0.525
	FU		−0.099	−0.689	0.492		−0.516	−1.066	0.035				
CERAD[b]	BL	141	0.539	0.328	0.749	147	0.409	0.207	0.611	−0.075	−0.350	0.200	0.593
	FU		0.510	0.296	0.724		0.455	0.252	0.659				

[a]Higher number of named words indicates better performance. [b]Comprises of verbal fluency, modified Boston naming test, word lists, constructional praxis, word list recall and word list recognition discriminability (total sum score range 0–100). B, unstandardized regression coefficient; CI, confidence interval; PTCT, physical and cognitive training; PT, physical training. Men vs. Women, $p = 0.383$, $p = 0.863$, Training less vs. more than 50% (PT and CT), $p = 0.377$.

intervention-induced improvements in executive functions and determine whether specific subgroups gain additional benefit from the PTCT compared to physical training alone.

The strengths of this study include the representative sample of community-dwelling older adults who did not meet the physical activity guidelines. We used measures appropriate for assessing older adult's executive functions and global cognition. In addition, the fact that the cognitive measurements were conducted by same research assistant at both time points is likely to enhance the reliability of our results. This study also has its limitations. The main limitation of this study is its hypothesis-generating, exploratory design, which makes it impossible to apply the power calculations of the PASSWORD-study to the subgroup analysis. Moreover, our results cannot be generalized to other age groups or persons with an active lifestyle, adverse medical conditions, or impaired cognitive functions.

In conclusion, PTCT improved older adults' executive functions, especially among the women and the participants who only occasionally complied with the training regimen. However, the additional benefit from PTCT was uniquely expressed in each of the executive functions investigated in this study. Information provided by this study is of value when developing effective interventions to promote executive functions in older adults.

Data availability statement

The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of Central Finland Health Care District. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AT, TT, and SS: acquisition, analysis, interpretation of data, and drafting of the manuscript. TT: statistical analyses. All authors: critical revision of the manuscript, concept, and design.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.1038673/full#supplementary-material

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IV

BIDIRECTIONAL ASSOCIATIONS BETWEEN COGNITIVE FUNCTIONS AND WALKING PERFORMANCE AMONG MIDDLE-AGED WOMEN

by

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OPEN

ORIGINAL STUDY

Bidirectional associations between cognitive functions and walking performance among middle-aged women

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Abstract

Objective: This study investigated whether (1) cognitive functions change after the transition from the perimenopausal to the postmenopausal stage, (2) cognitive functions and walking are associated in middle-aged women, and (3) cognitive functions assessed in perimenopause are associated with walking after reaching the postmenopause or vice versa.

Methods: In total, 342 women, categorized as early ($n = 158$) or late perimenopausal ($n = 184$), were included in the study and followed up until postmenopausal. Psychomotor speed, executive functions related to set-shifting and updating, working memory, and visual memory were assessed. Walking was assessed with walking speed, walking distance, and dual-task cost in walking speed. Data was analyzed using the paired-samples *t* test, Wilcoxon signed rank test, multiple linear regression analysis, and structural equation modeling.

Results: We found small but significant improvements in psychomotor speed ($P = 0.01$) and working memory ($P < 0.001$) among early perimenopausal and in psychomotor speed ($P = 0.001$), set-shifting ($P = 0.02$), visual memory ($P = 0.002$), and working memory ($P < 0.001$) among late perimenopausal women after the transition from peri- to postmenopause. Walking speed ($\beta = 0.264$, $P = 0.001$) and dual-task cost ($\beta = 0.160$, $P = 0.03$) were associated with updating, and walking distance was associated with updating and set-shifting ($\beta = 0.198$, $P = 0.02$, $\beta = -0.178$ $P = 0.04$ respectively) among the late perimenopausal women. We found no longitudinal associations between cognitive functions and walking.

Conclusion: Cognitive performance remained unchanged or improved after reaching postmenopause. Cognitive functions and walking were associated during the late perimenopause, but the association depended on the cognitive process and nature of the physical task. Cognitive performance was not associated with walking after reaching postmenopause or vice versa.

Key Words: Executive functions – Menopause – Physical functions.

In Western societies, menopause, ie, the final menstrual period, usually occurs between ages 46 and 56. During the menopausal transition, the level of the pituitary gonadotropins, ie, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), increases significantly in concert with the decline in the production of estrogens, ie, estrone (E_1) and 17β-estradiol (E_2).[1] These dramatic changes in hormonal levels are suggested to have negative effects on women's cognitive[2,3] and physical functions.[4]

Estrogens have been shown to maintain neuromuscular functions.[5] Thus, estrogen deficiency may affect muscle function leading to physical limitations as early as in mid-life.

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Previous studies have shown that postmenopausal women are more prone to physical limitations than premenopausal women.[4,6] In the same sample as is used in the present study, Bondarev et al[4] found that postmenopausal women had significantly lower muscle function and maximal walking speed than premenopausal women.

In addition to a decline in physical functions, decreased estrogen levels may be associated with reduced cognitive functions. Previous studies investigating the role of estrogen on cognition have shown partially conflicting results. Some cross-sectional studies have found an association between menopausal stage and at least a domain-dependent decline in cognitive functions,[3,7] while others have found no evidence of an association between serum estradiol concentration or menopausal stage and cognition in middle-aged women.[8] In addition, some of the limited number of longitudinal studies published on the topic found a subtle but significant decline in processing speed,[2] verbal memory,[2,9] and verbal fluency[10] during the menopausal transition, whereas others found no decline in working memory or perceptual speed during this phase.[11] Moreover, Gorenstein et al[12] found no evidence that hormone therapy (HT) significantly improves cognition whereas another study[13] found that HT improved performance in task related executive functions, working memory, and short-term memory. It has been hypothesized that the loss of estrogen may cause challenges related to cognitive functions during the menopausal transition,[14] as estrogen has been shown to induce the formation and plasticity of synapses[14-16] and affect the amount of neurotransmitters in experimental animal studies.[14]

Dual-task (DT) performance, ie, performing a secondary cognitive task while walking, has been shown to reduce walking speed in both older (mean age 72 y) and younger (mean age 27 y) adults.[17] DT performance requires simultaneous cognitive and physical functioning and challenges the ability to divide attention between the two tasks.[18] In older adults, this ability is reduced owing to the age-related decline in mental flexibility,[19] and therefore walking in the DT condition is challenging. In younger adults, the reduction in walking speed is more dependent on task prioritization.[17]

Previous studies have shown a link between cognitive functions—especially executive functions—and physical functions among older adults. In addition, it has been suggested that the association between physical and cognitive functions is bidirectional.[20] For example, it has been found that slow walking speed predicts decline in cognitive functions[21] and that reduced cognitive functions predict slower walking speed among older adults.[22]

Research on the potential associations between cognition, especially executive functions, and walking performance among middle-aged women is sparse. In addition, it remains partially unclear how the menopausal transition is linked to different subdomains of cognition such as psychomotor speed, executive functions, working memory and visual memory. Therefore, the aim of this study was to investigate whether performance in cognitive functions changes over the menopausal transition. The changes observed in walking performance over the menopausal transition have been published previously.[23] In addition, we investigated whether cognitive functions and walking performance are associated in the perimenopausal stage and whether better performance in cognitive functions in the perimenopausal stage is associated with better walking performance after the transition from the perimenopausal to postmenopausal stage and/or vice versa.

METHODS

Participants

This study utilized baseline and longitudinal data from the Estrogenic Regulation of Muscle Apoptosis (ERMA) study. A detailed description of the design and recruitment of the ERMA study has been published elsewhere.[24] Briefly, recruitment started with an information letter and a prequestionnaire sent to a total of 6,878 women aged 47 to 55 years living in the city of Jyväskylä and neighboring municipalities in Central Finland. Potential participants were eligible for the study if they were willing to participate, had relatively good health, and did not meet exclusion criteria (estrogen-containing medications, bilateral oophorectomy, pregnancy, lactation, polycystic ovary syndrome, severe obesity, or musculoskeletal disorders). Finally, after the stepwise exclusion procedure 1,393 women were assigned to premenopausal, early perimenopausal, late perimenopausal, and postmenopausal groups based on their FSH levels and the regularity of their menstrual cycle self-reported on a menstrual calendar.[25] Out of the 1,158 women who participated in laboratory measurements for physiological and psychological abilities (including walking tests and measurements of cognitive functions). ERMA longitudinal study included 381 early or late perimenopausal women who were willing to participate in the follow-up study.

This paper reports the results for early and late perimenopausal women, who were followed up throughout the menopausal transition and from whom cognition was measured. Participants were assigned to the early perimenopausal group if their FSH levels were between 17 and 25 IU/L and their menstrual cycle was irregular and to the late perimenopausal group if their FSH levels were between 25 and 30 IU/L and they had experienced occasional menstrual bleeding during the past 3 months. After the baseline measurements (early perimenopausal group $n = 158$, late perimenopausal group $n = 184$), participants were screened for hormonal status in 3- to 6-month cycles until they had reached the postmenopausal stage (FSH >30 IU/L and no menstrual bleeding during the past 6 mo, or FSH>39 IU/L and no menstrual bleeding during the past 3 mo, or FSH>130 IU/L and possible occasional bleeding). After reaching the postmenopausal stage ($n = 236$), the baseline physiological and psychological measurements were repeated. Participants who started HT during the follow-up ($n = 35$) or whose menopausal status remained unclear ($n = 6$) were excluded from the longitudinal analyses. However, one participant informed that she had started HT 2 days prior to the follow-up measurements. She was considered to be postmenopausal. As we did not consider such a short period to affect cognitive functions, her data was included in the analysis. In addition, participants ($n = 2$) who did not participate in the follow-up measurements of cognitive functions were excluded from the paired sample *t* test and Wilcoxon signed rank test.

Ethical approval

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Central Finland Health Care District (K-S shp Dnro 8U/2014). All participants signed an informed consent before participation in any of the study phases.

Measurements

Walking performance

Walking performance was assessed with the10-m maximal walking speed, dual-task cost in walking speed, and 6-minute walking distance tests. In the *10-meter maximal walking speed* (maximal walking speed) test, participants were instructed to walk for 10 m at their maximal walking speed;[4] 2 to 3 m were allowed for acceleration. The time to complete the walk was measured by photocells. The best of two maximal trials was recorded as the result and walking speed (m/s) calculated. In the *dual-task walking speed* test (DT walking speed), participants were asked to name as many Finnish first names beginning with randomly selected letter K, S, or T simultaneously with the 10-m maximal walking speed test. The DT walk was performed once only, after the 10-m maximal walking speed test. Finally, the difference in time taken to perform the 10-m maximal walking speed and DT walk tests (DT cost) was calculated. In the *six-minute walking distance* (6-min walking distance) test, which assesses walking endurance,[4] participants were asked to walk back and forth on a 20-m course with the aim of walking the longest possible distance.

Cognition

Executive functions were assessed with the Trail Making Test (TMT) A and B and a verbal fluency test (VF). In TMT A, which assesses psychomotor speed, participants were instructed to combine numbers 1 and 2 and so on until number 25 as quickly as possible.[26] Part B assesses the ability to shift attention between two tasks. In this part, participants were instructed to combine number 1 and letter A and letter A and number 2 and so on with a line as quickly as possible. The time (s) to complete part A and B was measured with a stopwatch. In VF, which assesses the ability to update and monitor working memory representations (updating), participants were asked to name as many animals as possible in 1 minute.[27] The total number of named animals was taken as the result. *Working memory* was assessed with the digit span test and word list test. In the digit span test, participants were asked to repeat the extended number sequences after the examiner, first forwards and then backwards, for as long as they were able to remember the sequence. The scores (one point per correctly remembered sequence) of the two tasks were summed.[28] In the word list test, participants were asked to repeat as many words as they could remember from a list of 12 words read aloud by the examiner.[29] The test was repeated four times. After at least 15 minutes, participants were asked to first recall and then recognize all the words that they could remember from the list of words. Finally, the number of words remembered and recalled of all lists was calculated as total scores. *Visual memory* was assessed with Family Pictures.[29] In this test, participants were asked to remember details of four pictures of family members in different situations. All four pictures were shown to the participants at 10-second intervals. After seeing all the pictures, they were asked to recall which family members were in a specific picture, what were they doing and where they were located in the pictures. After at least 15 minutes, participants were asked to recall the same details without seeing the pictures again. The test was scored according to the number of recalled details.

Background variables

Participants' birth date was extracted from the Finnish Digital and Population Data Services Agency and age at the baseline measurement date calculated. Body height and weight were measured by a study nurse after overnight fasting, and body mass index (BMI) was calculated. Level of FSH hormone and E_2 were assessed from serum by immunoassay (IMMULITE 2000 XPi, Siemens Healthcare Diagnostics, Camberley, UK).

Information about menopausal symptoms, physical activity, and education was collected by a questionnaire at baseline. Participants reported their menopausal symptoms by selecting from the following options: sweating, hot flashes, sleep disturbance and insomnia, headache, joint ache, fatigue, changes in mood or melancholia, vaginal symptoms, urinary symptoms, sexual reluctance, and other possible symptoms.[30,31] For the analysis, symptoms were re-coded as vasomotor (sweating, hot flashes), somatic and pain (headache, joint ache), psychological (sleep disturbance and insomnia, fatigue, depression), and urogenital (vaginal symptoms, urinary symptoms, sexual reluctance) symptoms.

Self-reported physical activity was assessed on a seven-point scale. Response options were 1 = I do not move more than is necessary in my daily routines/chores, 2 = I go for casual walks and engage in light outdoor recreation 1-2 times a week, 3 = I go for casual walks and engage in light outdoor recreation several times a week, 4 = I engage 1-2 times a week in brisk physical activity (eg, yard work, walking, and cycling) to the point of perspiring and some degree of breathlessness, 5 = I engage 3 to 5 times a week in brisk physical activity (eg, yard work, walking, and cycling) to the point of perspiring and some degree of breathlessness, 6 = I do keep-fit exercises several times a week in a way that causes rather strong shortness of breath and sweating during the activity, and 7 = I participate in competitive sports and maintain my fitness through regular training.[32] For the analysis, three categories were formed: 1 = low level of physical activity (categories 1, 2), 2 = moderate level of physical activity (categories 3, 4), and 3 = high level of physical activity (categories 5, 6, 7).[33]

Education was categorized as 1 = basic (primary and secondary school), 2 = college (applied science degree, bachelor's degree, or nurse training), and 3 = university (master's degree or PhD). Number of days between the baseline and follow-up measurements was calculated and recorded as follow-up time.

Statistical analyses

Data analyses were conducted with IBM SPSS statistics 26.0 and Mplus statistical package version 7.3.[34] Participants' characteristics and their walking and cognitive functions at baseline were expressed as means and standard deviations (SD). Differences in baseline characteristics between the perimenopausal groups (total $n = 342$) were tested with the independent samples *t* test for normally distributed data, Mann-Whitney *U* test for non-normally distributed data, and chi-square test for categorical variables. The same tests were applied when comparing participants who were followed up throughout the menopausal transition with no HT (longitudinal analyses, $n = 195$) and participants who started HT during the follow-up ($n = 35$). Changes in cognitive functions and walking performance from the peri- to postmenopausal stage were tested with the paired samples *t* test for normally distributed data and Wilcoxon signed rank test for non-normally distributed data.

Cross-sectional associations between cognitive functions and walking performance were analyzed with multiple linear regression analysis. Analyses were carried out separately for the early and the late perimenopausal groups and for each psychomotor speed and executive function subdomain (TMT A, TMT B, and VF). All the walking tests (maximal walking speed, DT walking speed, 6-min walking distance) were entered in the regression models separately as the main explanatory variables. Control variables in all the regression models were age, physical activity, education, and vasomotor, psychological, and somatic or pain symptoms. For the regression models, two dummy variables were created, one for education and the other for physical activity.

Longitudinal bidirectional associations between cognitive functions and walking performance were analyzed with structural equation modeling (SEM) using a cross-lagged path model. For the SEM, subdomains of executive functions and psychomotor speed (TMT A, TMT B, and VF) were combined into a latent variable of cognitive functions and the TMT variables reversed to make the direction of the latent variable reasonable (higher values indicating better cognitive functions). These variables were chosen for the SEM models, as executive functions, in particular, have been shown to be associated with walking performance.[20] In all the SEM models, maximum likelihood estimation with robust standard errors and scale-corrected chi-square values (MLR estimator) was used. The longitudinal analyses started with latent variable measurement invariance testing. Invariance was tested through several models.[35] First, the least restricted latent factor model was estimated. The error terms of the corresponding indicators of the latent variables were allowed to correlate (eg, error terms of baseline and follow-up TMT A). Next, a series of models with increasing restrictions were estimated: a weak factorial invariance model (ie, equal factor loadings between time points), a strong factorial invariance model (ie, equal factor loadings and intercepts between time points), and a strict factorial invariance model (ie, equal factor loadings, intercepts, and error variances between time points). Finally, the suitability of the model structure for both groups (early and late perimenopausal) was tested with multigroup modeling. The final models included the correlations between cognitive functions and walking performance in perimenopause, and longitudinal paths from baseline executive functions to follow-up walking performance and from baseline walking performance to follow-up cognitive functions. In addition, models investigated stability over time in cognitive functions and walking performance. No residual covariances between cognitive functions and walking performance in postmenopause needed to be released. Models were evaluated with a chi-square test (acceptable fit $P > 0.05$), comparative fit index (CFI) (acceptable fit >0.95) and standardized root meet residuals (SRMR) (acceptable fit ≤ 0.08).[36-38] Longitudinal models were adjusted for follow-up time.

RESULTS

Participant characteristics at baseline and follow-up time are shown in Table 1. The women in the late perimenopausal group were on average 1 year older than those in the early perimenopausal group. They also had a shorter follow-up time (mean 13.8 mo SD 8.6 mo) than those in the early perimenopausal group (mean 17.7 mo SD 9.0 mo $P = 0.002$). The early perimenopausal women performed significantly better in the Family Pictures and 6-min walking distance tests than the late perimenopausal women (Table 1). No other differences between the groups were observed. Participants who attended only the baseline measurements were younger (50.4 y SD1.8 y vs 51.8 y SD 1.9 y $P < 0.001$) and performed better in TMT A (23.2 s SD 6.5 vs 25.0 s SD 7.2 $P = 0.02$) than those who were followed up to postmenopause. No other differences were observed. Participants who started HT during the follow-up were younger (50.6 y SD 1.9 y vs 51.7 y SD 1.9 y $P = 0.001$) compared to women who did not start HT during the follow-up. No other background differences were observed. Duration of HT varied from 17 days to 337 days and was on average 211 (SD 58.6) days.

The early perimenopausal group showed a significant improvement in the TMT A and word list tests after reaching the postmenopausal compared to perimenopausal stage (Table 2). In addition to the TMT A and word list tests, the women in the late perimenopausal group performed significantly better in the TMT B and Family Pictures test after reaching the postmenopausal stage than during the perimenopausal stage (Table 2). Among both groups maximal walking speed remained unchanged, and distance travelled during 6-minutes improved during the follow-up (as also

TABLE 1. *Participants' characteristics at baseline*

	All ($n = 342$)	Early perimenopausal ($n = 158$)	Late perimenopausal ($n = 184$)	P	Follow-up ($n = 195$)
Age	51.2 ± 1.9	50.6 ± 1.9	51.7 ± 1.9	<0.001[a]	51.8 ± 1.9
Height (cm)	165.1 ± 0.1	165.4 ± 0.1	164.9 ± 0.1	0.45[b]	164.8 ± 0.1
Weight (kg)	70.0 ± 11.2	69.9 ± 11.5	70.2 ± 11.0	0.78[a]	69.6 ± 11.3
BMI	25.7 ± 3.9	25.6 ± 3.9	25.8 ± 3.9	0.59[a]	25.6 ± 4.0
Education, *n* (%)				0.11[c]	
Basic	6 (2)	1 (1)	5 (3)		5 (3)
College	180 (53)	91 (58)	89 (49)		103 (53)
University	154 (45)[d]	65 (41)[e]	89 (49)[f]		86 (44)[g]
Level of physical activity (%)				0.27[c]	
Low	35 (10)	20 (13)	15 (8)		16 (8)
Moderate	99 (29)	41 (26)	58 (32)		56 (29)
High	206 (61)[d]	96 (61)[e]	110 (60)[f]		122 (63)[g]
Vasomotor symptoms (%)				0.13[c]	
Yes	201 (59)	86 (55)	115 (63)		123 (63)
No	139 (41)[d]	71 (45)[e]	68 (37)[f]		71 (37)[g]
Psychological symptoms (%)				0.18[c]	
Yes	167 (49)	71 (45)	96 (52)		100 (52)
No	173 (51)[d]	86 (55)[e]	87 (48)[f]		94 (48)[g]
Somatic or pain symptoms (%)				0.65[c]	
Yes	95 (28)	42 (27)	53 (29)		53 (27)
No	245 (72)[d]	115 (73)[e]	130 (71)[f]		141 (73)[g]
TMT A (s)	24.2 ± 7.0	23.7 ± 6.7	24.7 ± 7.2	0.24[a]	25.0 ± 7.2
TMT B (s)	62.1 ± 19.7 [h]	63.0 ± 20.2	61.4 ± 19.3 [f]	0.60[a]	61.9 ± 18.8
Verbal Fluency (no of words)	28.5 ± 6.2	28.1 ± 6.7	28.8 ± 5.7	0.30[b]	28.8 ± 6.2
Digit Span test (score)	15.7 ± 3.3	15.8 ± 3.3	15.7 ± 3.4	0.52[a]	15.7 ± 3.3
Word List test (score)	63.9 ± 7.0	64.4 ± 7.0	63.6 ± 7.0	0.27[b]	64.1 ± 7.1
Family Pictures (score)	79.0 ± 18.9	81.4 ± 19.5	77.0 ± 18.1	0.02[a]	79.2 ± 18.8
10-m walking speed (m/s)	2.6 ± 0.48[i]	2.6 ± 0.48[j]	2.6 ± 0.49[k]	0.59[a]	2.6 ± 0.46[l]
Dual-task cost (m/s)	0.34 ± 0.26[m]	0.35 ± 0.28[j]	0.33 ± 0.25[n]	0.64[a]	0.32 ± 0.26[o]
6-min walking distance (m)	663.7 ± 66.6[p]	672.0 ± 64.9[q]	656.7 ± 67.4[r]	0.04[b]	658.48 ± 61.0[s]

Means and standard deviations and frequencies and percentages.
BMI, body mass index; TMT, Trail Making Test, smaller time indicates better performance. In Verbal Fluency, higher number of words indicates better performance. In Digit Span Test, Word List test, and in Family Pictures higher scores indicates better performance.
[a]Mann–Whitney *U* test.
[b]Independent samples *t* test.
[c]Chi-square test.
[d]$n = 340$.
[e]$n = 157$.
[f]$n = 183$.
[g]$n = 194$.
[h]$n = 341$.
[i]$n = 337$.
[j]$n = 156$.
[k]$n = 181$.
[l]$n = 192$.
[m]$n = 336$.
[n]$n = 180$.
[o]$n = 191$.
[p]$n = 311$.
[q]$n = 143$.
[r]$n = 168$.
[s]$n = 181$.

TABLE 2. *Performance in tests for memory and executive functions in middle-aged women assessed in perimenopause*

	Early perimenopausal			Late perimenopausal		
	Baseline ($n = 64$)	Follow-up ($n = 64$)	P	Baseline ($n = 129$)	Follow-up ($n = 129$)	P
TMT A (s)	25.9 ± 7.3	23.5 ± 5.4	0.01[b]	24.5 ± 7.2	22.5 ± 5.9	0.001[b]
TMT B (s)	64.0 ± 19.6	62.3 ± 18.1	0.66[b]	60.7 ± 18.6	57.6 ± 17.3	0.02[b]
Verbal fluency (No of words)	28.3 ± 7.1	28.0 ± 6.2	0.67[a]	29.0 ± 5.7	29.0 ± 5.9	0.94[a]
Family Pictures (scores)	83.8 ± 18.8	81.9 ± 21.6	0.33[a]	76.9 ± 18.4	82.2 ± 18.5	0.002[b]
Word List test (scores)	64.9 ± 6.6	68.0 ± 7.0	<0.001[a]	63.6 ± 7.3	66.9 ± 7.2	<0.001[a]
Digit Span Test (scores)	15.7 ± 3.1	16.0 ± 2.8	0.30[a]	15.7 ± 3.3	16.0 ± 3.4	0.07[b]

Means and standard deviations.
TMT, Trail Making Test, in TMT smaller time indicates better performance. In Verbal Fluency, higher number of words indicates better performance, in Digit Span Test, Word List test, and in Family Pictures higher scores indicates better performance.
[a]Paired samples *t* test.
[b]Wilcoxon signed rank test.

TABLE 3. *Multiple linear regression analysis of association between walking performance and executive functions in middle-aged women at baseline*

	TMT A			TMT B			Verbal fluency		
	β	R^2	*P*	β	R^2	*P*	β	R^2	*P*
Early perimenopausal									
10 m max (m/s)	−0.100	0.006	0.24	−0.036	0.049	0.66	0.082	0.086	0.31
Dual-task cost (m/s)	−0.115	0.009	0.17	0.057	0.051	0.48	0.082	0.086	0.31
Walking distance (m)	−0.138	0.029	0.12	0.106	0.087	0.21	0.035	0.107	0.68
Late perimenopausal									
10 m max (m/s)	−0.025	0.037	0.76	−0.110	0.053	0.18	0.264	0.100	0.001
Dual-task cost (m/s)	−0.106	0.050	0.16	−0.001	0.042	0.99	0.160	0.064	0.03
Walking distance (m)	−0.055	0.022	0.52	−0.178	0.058	0.04	0.198	0.064	0.02

Adjusted for age, physical activity, education, vasomotor symptoms, psychological symptoms, and somatic or pain symptoms.
TMT, Trail making test.

earlier reported by Bondarev et al[23]). In addition, performance in dual-task walking test improved significantly among late perimenopausal women (supplementary Table 1, http://links.lww.com/MENO/A855).

After adjusting for age, education, physical activity, and menopausal symptoms, no statistically significant cross-sectional associations between walking performance and cognitive functions were observed in the early perimenopausal group (Table 3). However, better performance in the 6-min walking distance test was associated with better performance in TMT B and VF in the late perimenopausal group. In addition, faster 10-m walking speed was associated with better performance in VF. Surprisingly, we found that greater DT cost in walking speed. ie, worse performance in the DT condition, was associated with better performance in VF among the late perimenopausal women (Table 3).

The latent structure for cognitive functions showed strict factorial invariance: the factor loadings (X^2-difference test compared to the least restricted model $X^2 = 0.483$(df 2) $P = 0.79$), intercepts ($X^2 = 0.521$(df 4) $P = 0.97$), and error variances ($X^2 = 1.42$(df 7) $P = 0.98$) did not differ between time points. Multigroup modelling indicated no statistically significant differences in the factor structure of the latent variable ($X^2 = 10.867$ (df 7), $P = 0.14$) or longitudinal paths (maximal walking speed, $X^2 = 2.700$ (df 6) $P = 0.85$, walking distance, $X^2 = 1.363$ (df 6) $P = 0.97$, dual-task cost $X^2 = 3.514$ (df 6) $P = 0.74$) between the early and late perimenopausal groups, and thus the main models were conducted using the combined sample.

The cross-lagged path models are shown in Figure 1. Model fit evaluations showed adequate fit for all models (maximal walking speed: $X^2 = 28.889$ (df27), $P = 0.37$, CFI = 0.996, RMSEA = 0.019; walking distance: $x^2 = 16.627$ (df27), $P = 0.94$, CFI = 1.000, RMSEA = 0.000; DT cost: $x^2 = 30.081$ (df 27), $P = 0.31$ CFI = 0.992, RMSEA = 0.024).

The cross-sectional paths in the SEM models showed statistically significant associations between better cognitive functions and faster maximal walking speed in the perimenopausal phase (Fig. 1A). No other cross-sectional associations were observed.

In longitudinal models, cognitive functions (β=0.91-0.94, $P < 0.005$), maximal walking speed (β=0.81 $P < 0.005$), and 6- min walking distance (β=0.86, $P < 0.005$) showed high stability over time. DT cost showed moderate stability over time (β=0.45, $P < 0.005$). Performance in cognitive functions in the perimenopausal stage was not associated with walking performance after reaching the postmenopausal stage nor was walking performance in the perimenopausal stage associated with cognitive functions after reaching the postmenopausal stage.

DISCUSSION

In this study, we found a small but significant improvement in psychomotor speed and working memory during the transition from the early perimenopausal to the postmenopausal stage, and in psychomotor speed, working memory, set shifting and visual memory during the transition from the late perimenopausal to the postmenopausal stage. In addition, we found that greater walking speed and longer 6-minute walking distance were associated with better performance in the executive functions related to set-shifting and updating in late perimenopausal women. However, performance in cognitive functions at perimenopause was not related to walking performance after the menopausal transition or vice versa. It has been suggested that at least some sub-domains of cognitive functions decline during the menopausal transition.[2,9] Contrary to this suggestion, we found no decline in cognitive functions after the transition from the perimenopausal stage to the postmenopausal stage. Instead, cognitive functions remained unchanged or even improved after reaching the postmenopausal stage compared to the perimenopausal stage. Our results are thus in line with previous reports[8,11] indicating no link between menopausal stage or decline in estrogen levels and reduced cognitive function. However, according to Greendale et al,[2] cognitive functions may decline during the perimenopausal stage and normalize after reaching the postmenopausal stage. Based on this hypothesis our participants were first assessed at a time when their cognitive functions were potentially at their lowest, ie, in the early or late perimenopausal instead of premenopausal stage. The same hypothesis might also explain the small but significant improvement that we found in psychomotor speed, set shifting, working memory and visual memory after reaching the postmenopausal stage. Another factor that might influence

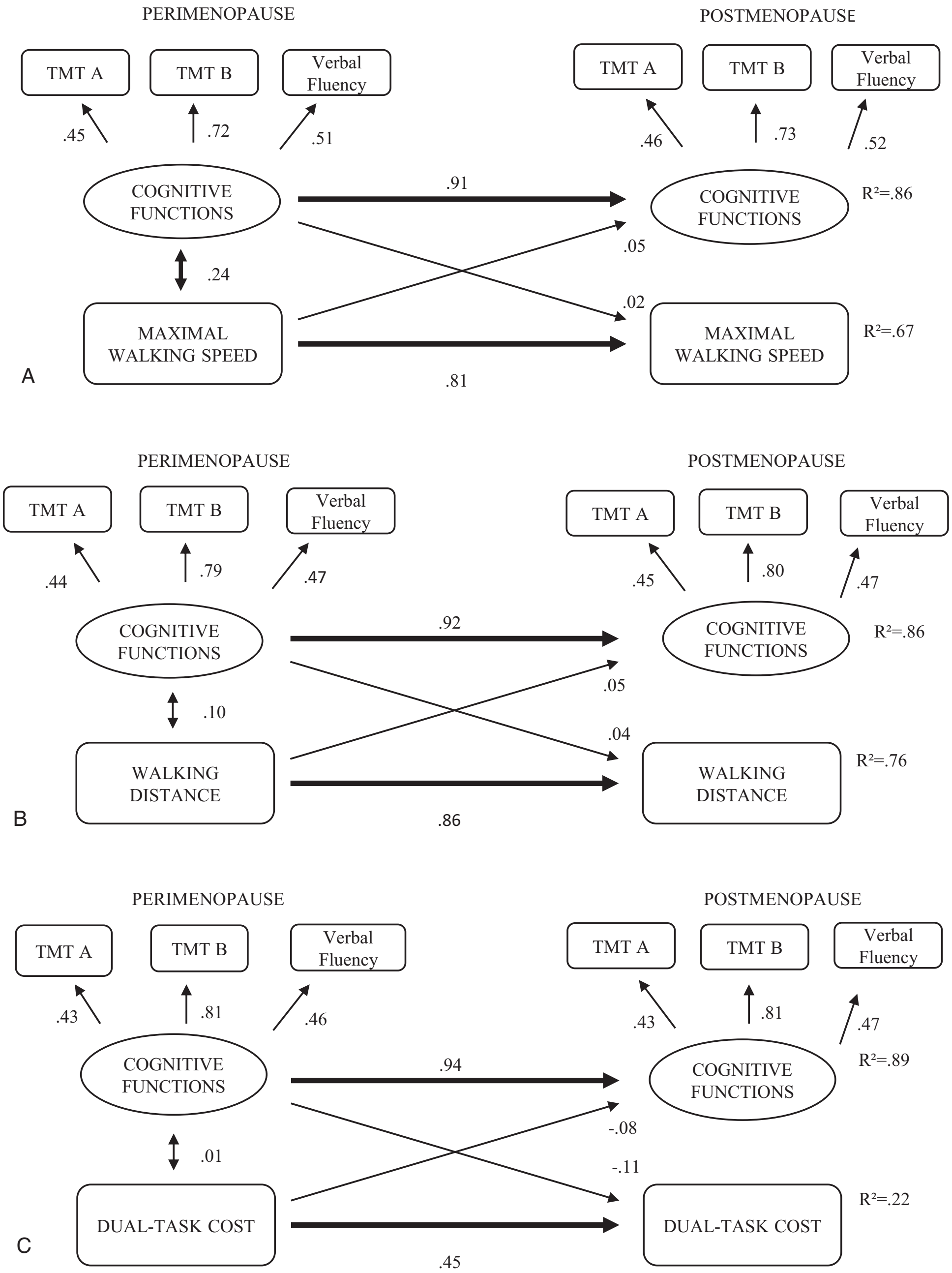

FIG. 1. Cross-sectional and longitudinal associations between cognitive functions and (**A**) 10-m maximal walking speed, (**B**) 6-minute walking distance, (**C**) dual-task cost in maximal walking speed. Adjusted for follow-up time. Structural equation model with standardized regression coefficients. Statistically significant ($P < 0.05$) coefficients are bolded. TMT, Trail Making Test.

our results is learning. It has been suggested that middle-aged women are better able to learn from repeated experiences of the same cognitive test than same-aged men and older adults.[39] Owing to the relatively young age of our sample and the short follow-up time (mean 1.5 years in the early perimenopausal and 1.2 years in the late perimenopausal group), it may be that at follow-up our participants were able to utilize their prior experience of the same cognitive tests.

Previous studies among older adults have reported associations between cognitive functions – especially executive functions – and walking performance.[20] Our results suggest that this link might be present already in mid-life, although relatively modest in size. We found an association between better performance in updating-related executive functions and greater walking speed and longer 6-min walking distance and between better performance in set shifting-related executive functions and longer 6-min walking distance among the late perimenopausal women. Surprisingly, we found that better performance in updating among the late perimenopausal women was also associated with greater DT cost in walking speed. However, we found no associations between cognitive functions and walking performance among the early perimenopausal women.

Few studies have investigated the potential links between cognitive functions and walking performance among middle-aged or younger populations. Killane et al[40] found an association between better performance in psychomotor speed and sustained attention and habitual walking speed, but not between executive functions and habitual walking speed among community-dwelling adults over age 50 in single-task conditions. Their results suggest that executive functions are only associated with walking performance in DT conditions. Gonzales et al[41] found a link between psychomotor speed and fast-pace walking speed and DT walking, but not between set-shifting-related executive functions or working memory and fast-pace walking speed or DT walking performance among 32- to 41-year-old women.

Interestingly, we found that cognitive functions and walking performance were associated only among the late perimenopausal women, who were slightly older than the early perimenopausal women. It has been suggested that the association between cognitive functions and walking performance becomes stronger with increasing age.[42] In addition, the late perimenopausal group had progressed further in the menopausal transition and thus showed greater changes in estrogen levels than the early menopausal group, a factor that might have a role in the association observed between cognition and walking performance. In addition, vasomotor symptoms, such as hot flashes, are most prevalent during the late perimenopausal stage,[43] and thus the late perimenopausal women are likely to have suffered longer from these symptoms than the early perimenopausal group. It has been suggested that vasomotor symptoms could have a role in middle-aged women's cognition[44]; if so, this may also have a role in the association between cognition and walking performance.

To our knowledge, no previous studies have investigated the role of menopausal stage in the links between cognitive functions and walking performance. Our results suggest that changes in the hormonal milieu caused by the ongoing transition from peri- to postmenopause may contribute to the associations between cognitive functions and walking performance. It has previously been shown that middle-aged women are prone to cognitive decline specifically during the late perimenopausal stage[2] and thus it is possible that changes in cognitive functions experienced in late perimenopause explain the associations found in this study between cognitive function and walking performance.

Contrary to previous research findings that poor cognitive functions are associated with worse performance in DT conditions, ie, greater dual-task cost,[45] we found that better performance in updating was associated with greater DT cost. Yogev-Seligmann et al[17] suggest that, in dual-task conditions, individuals with good postural and cognitive reserve might prioritize the cognitive task over the physical task, at least in instances when the physical task is simple. In our study, DT cost was assessed during maximal walking speed in a safe laboratory environment. It might therefore be that the participants with better cognitive functions prioritized the cognitive over the walking task, leading them to reduce their walking speed below the level achieved without the simultaneous cognitive challenge. We observed no longitudinal associations between cognitive functions and walking performance during the transition from the perimenopausal to the postmenopausal stage. However, we observed relatively high stability in both cognitive functions and walking performance over the follow-up. Previous studies using regression models to clarify the association between walking performance and cognition have found that slow walking speed predicts cognitive decline[21] and that cognitive functions predict walking speed in later life.[22] Studies that have investigated the bidirectional relations between cognition and walking performance using cross-lagged models have mainly been conducted among older adults. These studies have indicated that the association between walking speed and cognitive functions is bidirectional,[46] ie, decline in walking speed is associated with decline in cognitive functions[47] and worse performance in cognitive functions is associated with decline in gait speed.[48] Stintjes et al[48] also found that poor performance in cognitive functions in earlier life was associated with a steeper decline in walking speed in later life among middle-aged men and women but not, however, vice versa. The follow-up time in these previous studies was significantly longer than in our study. We observed relatively high rank-order stability in both cognitive functions and walking performance over the transition from perimenopausal stage to postmenopausal stage. This high stability and short follow-up time probably explain why we did not find any cross-lagged longitudinal associations between cognitive functions and walking performance. In addition, the cross-lagged path model assessed the association of perimenopausal cognitive functioning with walking performance over the transition to postmenopausal stage and vice versa, but not the association between changes in these variables. Further studies with more focus on the association between changes are therefore suggested.

Motoric Cognitive Risk (MCR) syndrome, ie, the presence of both cognitive complaint and slow walking speed without dementia or mobility disability, has been shown to be predictive of future dementia, at least in older adults.[49] According to Maggio and Lauretani,[50] almost 10% of adults aged 60 or older worldwide are affected by this syndrome and are at high risk for future disability. However, according to our results, the menopausal transition does not seem to accelerate this predictive syndrome.

This study has its limitations. The main limitation is the lack of cognitive and walking performance assessments in the premenopausal stage. When their cognitive functions were first assessed, our participants had already experienced changes in their hormonal milieu that might have affected our results. Since the first assessment was in the perimenopausal stage, our participants reached postmenopausal stage in a rather short time. Therefore, our mean follow-up time was also rather short, an average 1.2 to 1.5 years. However, Bondarev et al[23] showed with this same sample significant decline in muscle strength and power during the transition from perimenopausal to postmenopausal stage. Therefore, it was reasonable to expect that changes in cognitive performance would appear during the same time. In addition, due to fluctuation of FSH levels during the transition to perimenopausal stage to postmenopausal stage and our requirement for no menstrual bleeding during the past 6 months instead of 12 months, it is possible that some women were categorized as postmenopausal when they were still on their late perimenopausal stage.

The strengths of this study include a representative sample of 47- to 55-year-old women carefully classified for menopausal stage and closely monitored up to the postmenopausal stage. Therefore, although the follow-up time was rather short, it was individualized, and each participant was measured soon after reaching the postmenopausal stage instead of at a fixed-length follow-up. Our study design allowed cross-sectional and longitudinal investigation of the potential associations between cognitive functions and physical functions. Furthermore, we assessed cognitive functions and walking performance with a comprehensive battery including tests that challenge different sub-domains of cognitive functions such as executive functions, working memory and visual memory. Walking performance was assessed with tests that challenge cognitive as well as physical functions.

CONCLUSIONS

In conclusion, we found that performance in cognitive functions remains stable or even improve during the transition from the perimenopause to the early postmenopause. We also found that executive functions and walking performance were associated cross-sectionally among the late perimenopausal but not early perimenopausal women. However, better walking performance in the perimenopausal stage was not associated with better performance in cognitive functions after reaching the postmenopausal stage or vice versa. Thus, it may be that the transition from perimenopausal to postmenopausal stage is not a critical period for cognition and walking in middle-aged women. Further longitudinal studies starting from premenopausal stage, with longer follow-up, careful characterization of menopausal stage and comprehensive assessments for cognition and walking are needed to confirm these findings.

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