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ORIGINAL STUDY

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

Anna Tirkkonen, MSc,[1] Tiia Kekäläinen, PhD,[1] Pauliina Aukee, MD, PhD,[2] Urho M. Kujala, MD, PhD,[3] Eija K. Laakkonen, PhD,[1] Katja Kokko, PhD,[1] and Sarianna Sipilä, PhD[1]

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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From the [1]Gerontology Research Center and Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland; [2]Department of Obstetrics and Gynecology, Central Finland Health Care District, Jyväskylä, Finland; and [3]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland.
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Address correspondence to: Anna Tirkkonen, MSc, Gerontology Research Center and Faculty of Sport and Health Sciences, University of Jyväskylä. Rautpohjankatu 8, PL 35 40014 Jyväskylän yliopisto, Finland. E-mail: anna.a-k.tirkkonen@jyu.fi

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

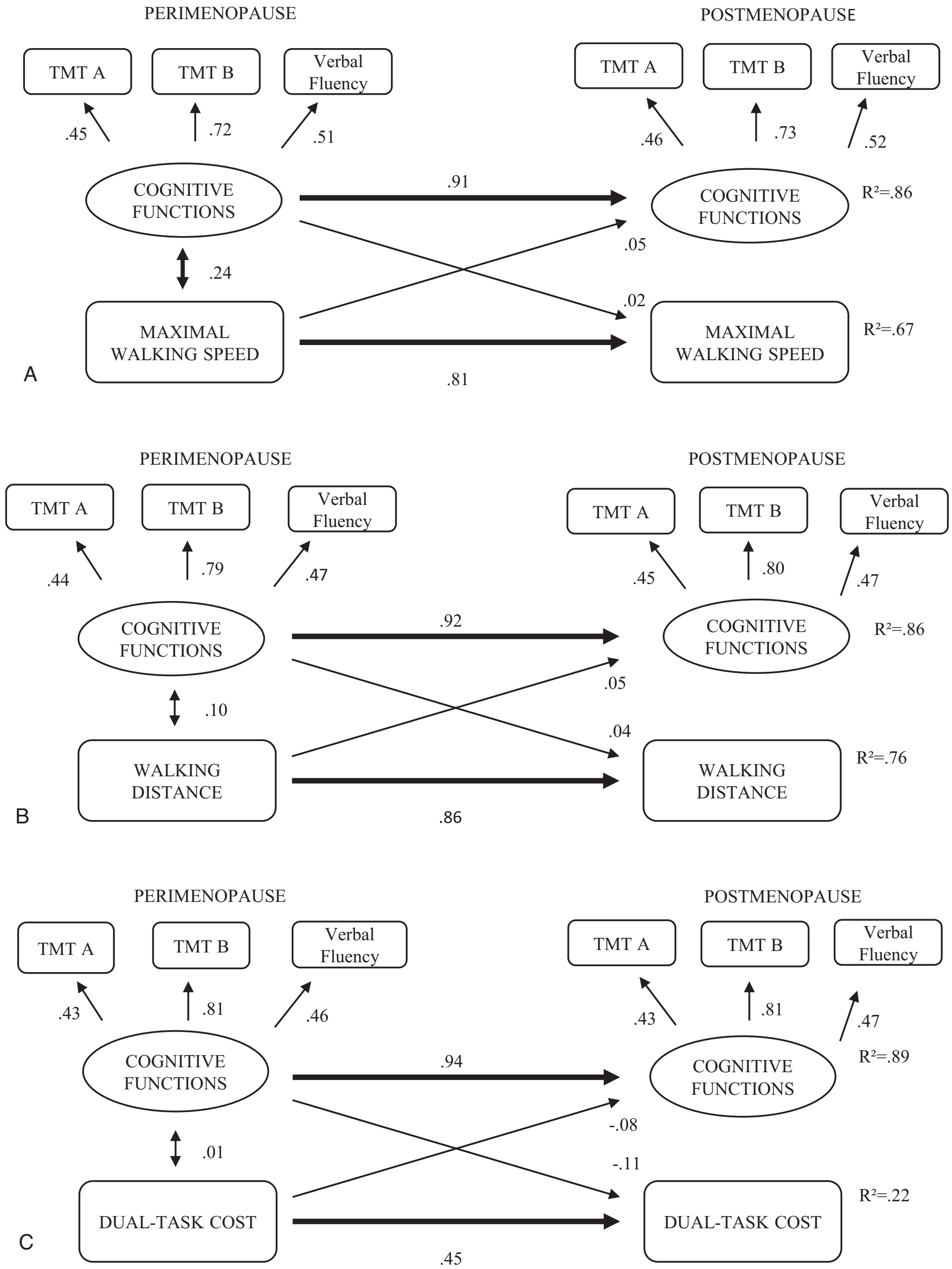

FIG. 1. Cross-sectional and longitudinal associations between cognitive functions and (**A**) 10-m maximal walking speed, (**B**) 6-minute walking distance, (**C**) dual-task cost in maximal walking speed. Adjusted for follow-up time. Structural equation model with standardized regression coefficients. 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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