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Interactions of cognitive and physical ageing

Marjon Stijntjes

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Mens sana in corpore sano
A sound mind in a healthy body

Juvenalis, Satire X (ca. 120 A.D.)

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Voorwoord

Alles veroudert. De onderzoeksgroep waar ik voor dit proefschrift deel van uitmaakte, verdiept zich in het verouderingsproces van de mens. Het fascinerende – en tegelijkertijd ook lastige – is dat elk verouderingsproces uniek is. Het voorschrijven van een recept voor een goede oude dag kan dan ook als een uitdaging worden beschouwd.

Het uitwisselen van wetenschappelijke kennis speelt een belangrijke rol in het steeds verder vergroten van het inzicht in dit verouderingsproces. Graag deel ik dan ook met u in de hierop volgende hoofdstukken de wetenschappelijke bevindingen die ik samen met mijn collega's heb gedaan betreffende twee kenmerkende aspecten van veroudering: de cognitieve en fysieke veroudering. Beide zijn bepalend voor de zelfredzaamheid van ouderen en daarmee voor de kwaliteit van leven.

Mijn dank gaat uit naar iedereen die heeft bijgedragen aan de totstandkoming van dit proefschrift: de deelnemers van de verschillende studies, mijn promotoren en co-promotor Eline Slagboom, Andrea Maier en Carel Meskers, collega's, vrienden en familie. Jullie enthousiasme, betrokkenheid en steun hebben mij als mens en wetenschapper verrijkt. Daarbij wil ik ook waarde collega's Robert Wagenaar en Ton de Craen noemen, opdat jullie bijdrage – in de stilte die is ontstaan – een blijvende herinnering zal zijn.

Leiden, juli 2016

Introduction

1

Introduction

Decline in cognitive and physical performance are striking characteristics of the ageing process. Declining performances are already observed from the third decade of life with a steeper decline from the sixth decade of life^{1,2}. Both cognitive and physical performance are important indicators of quality of life, strongly determining functional abilities and with that the ability to live independently^{3,4}. With increasing life expectancy, the number of elderly people with impaired cognitive and physical performance will grow rapidly, putting a high demand on health care resources⁵. Understanding the age-related changes in cognitive and physical performance and most importantly their interactions is required for the development of preventive and therapeutic paradigms.

However, the temporal order in which age-related changes in cognitive and physical performance occur is still largely unknown; it is unclear whether decline in cognitive performance precedes decline in physical performance, whether this temporal relationship is the other way around or whether they occur at the same time. Current literature is inconclusive showing uni- as well as bidirectional relationships between cognitive and physical performance⁶⁻⁹. Differences in findings between studies using different measures of cognitive and physical performance, i.e. global measures representing functioning on several cognitive or physical domains and domain specific measures, suggest dependence of the temporal relationship on these aspects⁹. Furthermore, it has become more and more evident in recent years that study findings might differ across different age ranges, especially for older populations aged 75 and over^{10,11}. Unfortunately, studies are lacking assessing the temporal relationship between cognitive and physical performance across different age ranges and including various global and domain specific measures. Therefore, important indicators for an effective clinical assessment, development and application of (already existing) interventions are missing as well.

Insights into the interactions between cognitive and physical performance might be suggestive for potential causal mechanisms. The temporal order of the interaction between cognitive and physical performance might indicate whether cognitive and physical performance are in each other's causal pathway or whether their decline has common underlying causes. Such common causes may be illustrated by previous studies showing a potential role for brain pathology or a role for biological aspects of ageing such as increases in the number of senescent cells, i.e. cells with a permanently arrested cell cycle, or the decline of metabolic control¹²⁻¹⁵. These aspects have been shown to be important indicators of biological age reflecting the ageing rate of an individual, which may deviate from its calendar age. However, the association of biological age with cognitive and physical performance is still unknown and with that the potential insight this might give in the ageing process.

For the assessment of physical performance, instrumented measures are increasingly introduced in research and clinical settings to obtain a more refined observation of the individual^{16,17}. These instrumented measures, obtained by e.g. camera-based systems, force plates or body fixed sensors, have been proven to be useful for the early identification and prediction of pathology such as Parkinson's Disease^{16,18}. The additional value of these measures for identification of age-related changes in physical performance and understanding of underlying determinants has not been established.

Aim of this thesis

The aim of this thesis was to enhance our understanding of age-related changes in cognitive and physical performance and their interactions. We focused on global and domain specific measures of cognitive and physical performance and assessed the interactions across different groups of calendar and biological age by including four study populations. Furthermore, instrumented measures of physical performance were introduced to assess their potential additional value.

Study populations

The Leiden Longevity Study

The Leiden Longevity Study (LLS) is a longitudinal cohort of families of at least two long-lived Caucasian siblings of Dutch descent fulfilling the age-criterion of 89 years or older for males and 91 years or older for females¹⁹. In this thesis, we used the middle-aged to older population of offspring of these nonagenarian siblings (n=500, mean age (standard deviation) 66 (6) years), who are enriched for familial factors of longevity, together with their partners as controls of similar age and sharing the same environmental conditions. Cross-sectional data was available on the cognitive domains of memory and executive function and the physical domains of standing balance, sit-to-stand transfers and walking across a 4-meter walk starting from standing position and across a steady-state 25-meter walk, i.e. without an acceleration or deceleration phase, both at usual pace. Thereby, a body fixed sensor positioned at the lower back was used during the performance of each of these physical tasks. This study population was especially used to get more insight into the sensitivity of different cognitive and physical domains to both calendar age and biological age, by comparing offspring of nonagenarian siblings with their partners, and assessing the associations with brain pathology.

The Longitudinal Aging Study Amsterdam

The Longitudinal Aging Study Amsterdam (LASA) consists of a random sample of middle-aged to older adults (n=3107, mean age (standard deviation) 71 (9) years) drawn from the population registers of eleven municipalities in three culturally distinct geographical areas in the Netherlands²⁰. Four repeated measurements on cognitive and physical performance assessed with a time interval of approximately three years were used. Besides domain

specific measures of memory and executive function, global cognitive function was assessed covering several domains like orientation, memory, attention and executive function. Physical domains included handgrip strength used as measure of overall muscle strength and walking speed across a 6-meter walk starting from standing position at maximal pace. This longitudinal study was used to assess the temporal relationship between global and domain specific measures of cognitive and physical performance across different age groups by stratification of the study population.

The Leiden 85-plus Study

The Leiden 85-plus Study includes inhabitants of the city of Leiden, the Netherlands, who all reached the age of 85 years (n=599) and were followed up yearly until the age of 90 years²¹. Global and domain specific measures of cognitive and physical performance that were used were similar to those included in LASA: global cognitive function and memory and executive function, handgrip strength and walking speed. This study population was added to the analyses on the temporal relationship between cognitive and physical performance in LASA, resulting together in an age range from 55 to 90 years.

Elderly outpatients

The cross-sectional study of elderly outpatients consists of community-dwelling elderly (n=299, mean age (standard deviation) 82 (7) years) referred to the geriatric outpatient clinic of a middle-sized teaching hospital (Bronovo Hospital, The Hague, The Netherlands) for a comprehensive geriatric assessment. This assessment included global and domain specific measures of cognitive and physical performance: global cognitive function, standing balance and walking speed across a 4-meter and 6-minute walk starting from standing position and a steady-state 10-meter walk, all at usual pace. Additional to the other three study populations, this particular population was used to assess the cross-sectional association between different cognitive and physical domains in a clinically relevant population giving insight into the possible influence of health status or biological age on this relationship.

Outline

Chapters two and three describe the sensitivity of domain specific measures of cognitive and physical performance to calendar and biological age assessed among the offspring of nonagenarian siblings and their partners of the LLS. In **chapter four**, the cross-sectional relationship between the cognitive and physical domains assessed in the LLS is presented and the influence of brain pathology on these domains as potential common underlying determinant. **Chapters five and six** focus on the cross-sectional relationship between different cognitive and physical domains in elderly outpatients. **Chapter seven** describes the temporal relationship between global and domain specific measures of cognitive and physical performance across different age groups of LASA and the Leiden 85-plus Study. Finally, in **chapter eight**, the main findings are summarized and discussed with a reflection on the clinical implications and future research.

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Familial longevity is marked by better
cognitive performance at middle age:
the Leiden Longevity Study

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Abstract

Background: Decline in cognitive performance is a highly prevalent health condition in elderly. We studied whether offspring of nonagenarian siblings with a familial history of longevity, perform better on cognitive tests compared to their partners as controls. This is relevant since it could provide insights into determinants underlying decline in cognitive performance.

Methods: Cross-sectional analysis within the longitudinal cohort of the Leiden Longevity Study consisting of middle-aged offspring of nonagenarian siblings together with their partners (n=500, mean age (SD) 66.3 (6.1) and 65.7 (7.2) years, respectively) as controls. Memory function, attention and processing speed were tested using the 15-Picture Learning Test, Stroop test and Digit Symbol Substitution Test. Data were analyzed with regression adjusted for age, gender, years of education and additionally for diabetes mellitus, cardiovascular diseases, alcohol use, smoking, inflammatory markers and *apolipoprotein E* genotype. Robust standard errors were used to account for familial relationships among the offspring.

Results: Cognitive performance was worse at higher calendar age ($p < 0.001$, all except Stroop test part 1). The offspring performed better compared to their partners on trial 3 ($p = 0.005$), the immediate ($p = 0.016$) and delayed ($p = 0.004$) recall of the 15-Picture Learning Test as well as on the interference and combined interference score of the Stroop test ($p = 0.014$ and $p = 0.036$, respectively) in the fully adjusted model. The difference between offspring and partners was estimated to be more than three years according to the observed difference in calendar age.

Conclusions: Offspring of nonagenarian siblings with a familial history of longevity have better cognitive performance compared to the group of their partners of comparable age. This effect is independent of age-related diseases and known possible confounders. Possible explanations might be differences in subclinical vascular pathology between both groups.

Introduction

Decline in cognitive performance is one of the most striking characteristics of the ageing process, already evident in middle age¹⁻³ and for some cognitive domains, like processing speed and spatial visualization, even at the age of 20 to 30 years⁴. With increasing life expectancy, the number of elderly people with severe cognitive impairment will grow rapidly, leading to a high demand on our health care. Understanding of decline in cognitive performance will therefore be one of the challenges of this century in order to be able to develop interventions focused on maintenance of cognitive performance with age.

Several causes and risk factors of decline in cognitive performance have been identified. Vascular pathology as well as cardiovascular risk factors, like alcohol use, smoking, hypertension and diabetes mellitus have been shown to play a prominent role in the development of cognitive decline⁵⁻¹⁰. Furthermore, decline in cognitive performance is associated with high systemic levels of inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6)^{8,11,12}. Low socioeconomic status (including education, occupation and financial conditions) has been reported as predictor of cognitive decline¹³⁻¹⁵. The most important genetic risk factor for decline in cognitive performance is the *apolipoprotein E (APOE)* gene. Carriers of the *APOE* $\epsilon 4$ allele are at an increased risk of dementia, whereas carriers of the *APOE* $\epsilon 2$ allele might be protected^{16,17}.

In the Leiden Longevity Study, we have previously demonstrated that middle-aged offspring of nonagenarian siblings with a familial history of longevity have a lower prevalence of age-related diseases, like myocardial infarction, hypertension and type II diabetes, compared to their partners sharing the same environmental conditions¹⁸. Major indicators of lifestyle however, i.e. body mass index, current smoking and level of education, are not different between both groups¹⁸. These results suggest that the biological age, which means a person's rate of ageing compared to their calendar age^{19,20}, of the offspring of nonagenarian siblings is lower compared to their partners. Based on this assumption, we studied whether the offspring of nonagenarian siblings perform better on cognitive tests than their partners.

Methods

Ethics statement

Ethics approval was provided through the Medical Ethical Committee of the Leiden University Medical Center. Written informed consent was obtained from all subjects.

The Leiden Longevity Study

The Leiden Longevity Study is a longitudinal cohort consisting of 421 families of long-lived Caucasian siblings of Dutch descent together with their offspring and the partners

thereof²¹. The partners of the offspring were included as controls being of comparable age and sharing the same socioeconomic and geographical background as the offspring. Families were recruited if at least two long-lived siblings were alive and fulfilled the age-criterion of 89 years for males and 91 years for females. Sex-specific age-criteria were used due to the higher life-expectancy of females compared to males^{18,21}. No selection criteria on health or demographic characteristics were applied. Recruitment took place between July 2002 and May 2006 and the families are followed up since that time. Cognitive performance was tested in a random subgroup of subjects (250 offspring and 250 partners thereof) during a visit at the research center between September 2009 and December 2010.

Cognitive performance

The primary outcome was cognitive performance, which was tested for different cognitive domains like memory function, attention and processing speed. Memory function was assessed by the 15-Picture Learning Test (15-PLT). Subjects were shown 15 pictures of well-known items and then asked to recall as many as possible. The test was repeated three consecutive times and after 20 minutes. Outcome parameters were the number of correct pictures after each trial and after 20 minutes (delayed recall). The total number of correct answers after three trials was defined as the immediate recall. Furthermore, the number of incorrect pictures was reported for each trial. Attention and processing speed were assessed by the Stroop test and the Digit Symbol Substitution Test (DSST). The Stroop test consisted of three parts in which the subject had to name 40 items shown on a card. In part 1, the subjects were instructed to read color words, which were printed in black on card 1. In part 2, the card contained colored blocks and the subjects were asked to name the printed colors. In part 3, the card again contained color words, however printed in a discongruous ink color. The subjects were asked to name the ink color of the words. During all parts, the subjects were encouraged to read the card as fast as possible. The time needed to process each of the different parts as well as the errors during each trial were used as outcome parameters. Furthermore, the interfering effect of words upon the naming of colors (interference score) was assessed by calculating the difference in time needed for part 3 and 2²². A combined interference score was calculated, in which both outcome parameters, time and number of errors, were combined. For each uncorrected error twice the average time per word for reading the card on which the error was made was added to the time needed to finish the card²². In the DSST, digits were presented and the subjects were asked to write the corresponding symbols in a blank space according to a given key. Outcome parameter was the number of correct digit-symbol combinations within 90 seconds. The DSST was added to the protocol later resulting in available data for 446 of the 500 subjects (223 offspring and 223 partners).

Potential confounders

Total number of years of education was calculated for each subject, based on self-reported information about the highest completed level of education. Conversion from highest educational level to total number of years of education was based on the Dutch educational system. Information on medical history was requested from the subjects' treating physician including diabetes mellitus and cardiovascular diseases, defined as myocardial infarction, stroke and hypertension¹⁸. Information was obtained from 440 of the 500 subjects from the treating physicians. Questionnaires were used to obtain information about alcohol use and smoking. Inflammatory markers, i.e. high-sensitivity (hs) CRP and IL-6, were available in non-fasting serum samples for 480 of the 500 subjects at baseline. In 20 subjects non-fasting serum samples were not available due to technical problems or refusal of the subject. For hsCRP, the Hitachi Modular P 800 from Roche, Almere, the Netherlands was used²³. IL-6 levels were determined with the Pelikine Compact human IL-6 ELISA kit from Sanquin reagents, Amsterdam, the Netherlands. *APOE* genotypes were determined within a genome-wide association study²⁴. Three groups were defined for the statistical analysis including homozygotes of the *APOE* $\epsilon 3$ allele ($\epsilon 3\epsilon 3$), carriers of the *APOE* $\epsilon 2$ allele ($\epsilon 2\epsilon 2$ and $\epsilon 2\epsilon 3$) and carriers of the *APOE* $\epsilon 4$ allele ($\epsilon 4\epsilon 4$, $\epsilon 3\epsilon 4$, $\epsilon 2\epsilon 4$).

Statistical analysis

A cross-sectional analysis was performed to assess the association of cognitive performance with calendar age as well as with familial longevity in 250 offspring and 250 partners of the Leiden Longevity Study.

First, the association between calendar age and cognitive performance was assessed using linear regression analysis. Two different models were applied. In model 1, the analysis was adjusted for gender and years of education. Model 2 was as model 1 with further adjustments for comorbidities, alcohol use, smoking, inflammatory markers and *APOE* genotype. Subjects with hsCRP levels higher than 30 mg/L (n=4) or IL-6 levels higher than 10 pg/mL (n=2) were excluded from the analysis in model 2 in order to exclude possible influences of acute inflammatory conditions. Logistic regression was applied to assess the association between calendar age and the dichotomized number of mistakes reported for the 15-PLT and the Stroop test, i.e. one group with subjects having no mistakes and one group with subjects having one or more mistakes. The same two models described above were used for the logistic regression analysis.

Second, linear regression analysis was used to investigate the association between familial longevity (offspring versus partner status) and cognitive performance. Logistic regression analysis was used for the association between familial longevity and the two groups of subjects with and without mistakes for the 15-PLT and Stroop test. Again, two different models were applied. Model 1 included age, gender and years of education. Model 2 was as model 1 with further adjustments for comorbidities, alcohol use, smoking, inflammatory

markers and *APOE* genotype. All p-values for differences between offspring and partners were adjusted for familial relationships among the offspring using robust standard errors.

Finally, a sensitivity analysis was performed excluding the subjects with the *APOE* $\epsilon 2\epsilon 4$ genotype for both the analysis with calendar age and familial longevity. This subgroup was excluded because they have both the allele for an increased and decreased risk of dementia and could therefore attenuate the influence of *APOE* genotype on the results. Furthermore, the difference in cognitive performance between offspring and partners was expressed in years according to calendar age. For this calculation, the difference in cognitive performance between offspring and partners was divided by the difference in cognitive performance with calendar age per year of the fully adjusted model.

All statistical analyses were performed with Stata (version 12.0 for Windows, USA) and SPSS (version 20.0 for Windows, USA). P-values <0.05 were considered statistically significant.

Results

Table 1 shows the characteristics of the study population. Offspring and partners had similar age and years of education. The prevalence of age-related diseases, like diabetes mellitus and hypertension, was lower among the offspring compared to their partners.

Table 2 and 3 present the association between calendar age and cognitive performance. Overall, higher calendar age was associated with worse cognitive performance. The association between calendar age and cognitive performance remained statistically significant after adjustment for known possible confounders, except for the Stroop test part 1 (Table 2). The number of subjects with mistakes was higher at higher calendar age for the Stroop test part 3. No association with calendar age was found for the Stroop test part 2 and the 15-PLT (Table 3). Sensitivity analysis excluding the subjects with the *APOE* $\epsilon 2\epsilon 4$ genotype did not change the results.

Table 4 and 5 show the association of familial longevity and cognitive performance, comparing offspring of nonagenarian siblings with a familial history of longevity with their partners. In the fully adjusted model, the offspring performed better compared to their partners on part 3, the immediate and delayed recall of the 15-PLT as well as on the (combined) interference score of the Stroop test (Table 4). The number of subjects with mistakes reported for the 15-PLT was not different between offspring and partners. Among the offspring, the number of subjects with mistakes was lower for the Stroop test part 2 and 3 compared to their partners. After adjustment for possible confounders, the association remained statistically significant for the Stroop test part 3 (Table 5). Sensitivity analysis excluding the subjects with the *APOE* $\epsilon 2\epsilon 4$ genotype did not change the results.

Table 1. Characteristics

	Offspring (N=250)	Partners (N=250)
Demographics		
Females, n (%)	114 (45.6)	139 (55.6)
Age, years	66.3 (6.1)	65.7 (7.2)
Years of education, median (IQR)	12 (10 - 15)	12 (10 - 15)
Anthropometrics		
Height, cm	172.5 (8.9)	171.6 (8.8)
Weight, kg	78.7 (13.4)	79.2 (13.7)
Comorbidities[*], n (%)		
Diabetes mellitus	7 (3.2)	20 (9.1)
Myocardial infarction	4 (1.8)	8 (3.6)
Stroke	5 (2.2)	5 (2.3)
Hypertension	56 (25.7)	66 (30.6)
COPD	13 (5.9)	9 (4.1)
Malignancy	13 (5.9)	21 (9.6)
Rheumatoid arthritis	2 (0.9)	3 (1.4)
Intoxications, n (%)		
Users of alcohol [†]	192 (78.0)	194 (78.5)
Former and/or current smokers	158 (64.2)	185 (74.9)
Inflammatory markers[‡], median (IQR)		
hsCRP, mg/L	1.2 (0.65 - 2.49)	1.4 (0.71 - 2.87)
IL-6, pg/mL	0.30 (0.11 - 0.65)	0.36 (0.13 - 0.62)
APOE genotype, n (%)		
$\epsilon 2\epsilon 2$	2 (0.8)	1 (0.4)
$\epsilon 2\epsilon 3$	27 (11.1)	21 (8.4)
$\epsilon 2\epsilon 4$	11 (4.5)	10 (4.0)
$\epsilon 3\epsilon 3$	151 (60.4)	166 (66.7)
$\epsilon 3\epsilon 4$	51 (20.4)	47 (18.9)
$\epsilon 4\epsilon 4$	2 (0.8)	4 (1.6)

Values are expressed as mean (standard deviation), unless otherwise indicated. Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; *APOE*, *apolipoprotein E*. ^{*}n=220 for offspring and n=220 for partners. [†]Using ≥ 1 units per week. [‡]n=240 for offspring and n=240 for partners.

Figure 1 and 2 show the estimated mean values of the 15-PLT and Stroop test, respectively, stratified for tertiles of calendar age (upper panel) and stratified for offspring and partners (lower panel). Preservation of cognitive performance of offspring compared to partners was estimated to be more than three years based on the difference in cognitive performance with calendar age per year in trial 3, the immediate and delayed recall of the 15-PLT as well as in the (combined) interference score of the Stroop test. The delayed recall of the 15-PLT showed the largest difference, with an estimated preservation of cognitive performance of the offspring of more than seven years.

Table 2 Cognitive performance dependent on calendar age in years.

Cognitive performance tests	All subjects [*]	Model 1			Model 2		
	N=500	β	95% CI	p	β	95% CI	p
15-PLT, # pictures							
trial 1	7.4 (0.08)	-0.06	-0.08, -0.04	<0.001	-0.07	-0.10, -0.04	<0.001
trial 2	10.4 (0.09)	-0.09	-0.12, -0.06	<0.001	-0.11	-0.14, -0.08	<0.001
trial 3	12.0 (0.09)	-0.08	-0.10, -0.06	<0.001	-0.08	-0.11, -0.06	<0.001
immediate recall	29.7 (0.23)	-0.23	-0.29, -0.17	<0.001	-0.26	-0.33, -0.19	<0.001
delayed recall	11.2 (0.10)	-0.07	-0.10, -0.05	<0.001	-0.08	-0.11, -0.05	<0.001
Stroop test, s							
part 1	20.3 (0.26)	0.08	0.01, 0.16	0.036	0.08	-0.01, 0.16	0.081
part 2	24.8 (0.23)	0.18	0.11, 0.24	<0.001	0.18	0.10, 0.25	<0.001
part 3	49.4 (0.65)	0.83	0.65, 1.00	<0.001	0.89	0.69, 1.08	<0.001
Interference score	24.6 (0.56)	0.65	0.50, 0.81	<0.001	0.71	0.54, 0.89	<0.001
Comb. int. score	26.3 (0.69)	0.79	0.60, 0.98	<0.001	0.85	0.64, 1.07	<0.001
DSST[†], # answers	46.2 (0.51)	-0.71	-0.84, -0.58	<0.001	-0.67	-0.82, -0.52	<0.001

*Values are expressed as mean (standard error). †N=446. Abbreviations: β , estimate; CI, confidence interval; 15-PLT, 15-Picture Learning Test; #, number; comb. int., combined interference; DSST, Digit Symbol Substitution Test. Model 1: adjusted for gender and years of education. Model 2: as model 1 + diabetes mellitus, cardiovascular diseases (myocardial infarction, stroke and hypertension), alcohol use, smoking, high-sensitivity C-reactive protein, interleukin-6 and *apolipoprotein E* genotype.

Table 3 Cognitive performance expressed as number of subjects with mistakes dependent on calendar age in years.

Cognitive performance tests	All subjects [*]	Model 1			Model 2		
	N=500	OR	95% CI	p	OR	95% CI	p
15-PLT[†]							
trial 1	28 (5.6)	1.00	0.95, 1.07	0.90	1.01	0.94, 1.09	0.74
trial 2	28 (5.6)	1.00	0.94, 1.06	0.88	1.01	0.94, 1.08	0.76
trial 3	20 (4.0)	0.99	0.92, 1.06	0.78	1.00	0.92, 1.09	0.97
immediate recall	47 (9.4)	1.00	0.96, 1.05	0.89	1.01	0.96, 1.07	0.71
delayed recall	35 (7.1)	0.98	0.93, 1.04	0.50	1.00	0.94, 1.06	0.96
Stroop test[†]							
part 2	36 (7.2)	1.05	0.99, 1.11	0.081	1.04	0.98, 1.11	0.22
part 3	134 (27.0)	1.09	1.05, 1.13	<0.001	1.10	1.06, 1.15	<0.001

*Values are expressed as number (%). †Subjects with no mistakes = 0, subjects with one or more mistakes = 1. Abbreviations: OR, odds ratio; CI, confidence interval; 15-PLT, 15-Picture Learning Test. Model 1: adjusted for gender and years of education. Model 2: as model 1 + diabetes mellitus, cardiovascular diseases (myocardial infarction, stroke and hypertension), alcohol use, smoking, high-sensitivity C-reactive protein, interleukin-6 and *apolipoprotein E* genotype.

Table 4 Cognitive performance dependent on familial longevity (offspring versus partner status^{*}).

Cognitive performance tests	Offspring [†]	Partners [†]	Model 1			Model 2		
	N=250	N=250	β	95% CI	p	β	95% CI	p
15-PLT, # pictures								
trial 1	7.4 (0.11)	7.4 (0.12)	-0.13	-0.44, 0.18	0.40	-0.28	-0.63, 0.07	0.11
trial 2	10.4 (0.13)	10.3 (0.14)	-0.23	-0.56, 0.10	0.17	-0.30	-0.67, 0.07	0.11
trial 3	12.1 (0.12)	11.9 (0.12)	-0.32	-0.63, -0.01	0.042	-0.47	-0.80, -0.15	0.005
immediate recall	29.9 (0.31)	29.6 (0.33)	-0.69	-1.48, 0.10	0.088	-1.06	-1.92, -0.19	0.016
delayed recall	11.3 (0.14)	11.1 (0.14)	-0.42	-0.77, -0.07	0.020	-0.58	-0.98, -0.18	0.004
Stroop test, s								
part 1	20.9 (0.38)	19.7 (0.34)	-1.27	-2.31, -0.23	0.017	-0.91	-2.13, 0.32	0.15
part 2	25.3 (0.33)	24.4 (0.30)	-0.86	-1.74, 0.02	0.057	-0.75	-1.77, 0.27	0.15
part 3	48.8 (0.86)	50.0 (0.97)	1.62	-0.67, 3.91	0.17	2.02	-0.56, 4.61	0.13
Interference score	23.5 (0.74)	25.7 (0.84)	2.52	0.50, 4.54	0.015	2.84	0.57, 5.10	0.014
Comb. int. score	25.1 (0.92)	27.5 (1.02)	2.80	0.30, 5.30	0.028	3.12	0.21, 6.03	0.036
DSST[‡], # answers	46.3 (0.71)	46.2 (0.74)	-0.32	-2.16, 1.52	0.73	-0.82	-2.86, 1.21	0.43

^{*}Offspring = 0, partner = 1. [†]Values are expressed as mean (standard error). [‡]n=223 for offspring and n=223 for partners. Abbreviations: β , estimate; CI, confidence interval; 15-PLT, 15-Picture Learning Test; #, number; comb. int., combined interference; DSST, Digit Symbol Substitution Test. Model 1: adjusted for age, gender and years of education. Model 2: as model 1 + diabetes mellitus, cardiovascular diseases (myocardial infarction, stroke and hypertension), alcohol use, smoking, high-sensitivity C-reactive protein, interleukin-6 and *apolipoprotein E* genotype. Robust standard errors were used to account for familial relationships among the offspring.

Table 5 Cognitive performance expressed as number of subjects with mistakes dependent on familial longevity (offspring versus partner status^{*}).

Cognitive performance tests	Offspring [†]	Partners [†]	Model 1			Model 2		
	N=250	N=250	OR	95% CI	p	OR	95% CI	p
15-PLT[‡]								
trial 1	13 (5.2)	15 (6.0)	1.13	0.53, 2.44	0.75	1.33	0.48, 3.68	0.58
trial 2	15 (6.0)	13 (5.2)	0.89	0.41, 1.94	0.77	0.95	0.37, 2.45	0.92
trial 3	10 (4.0)	10 (4.0)	1.09	0.44, 2.71	0.85	0.81	0.29, 2.28	0.69
immediate recall	24 (9.6)	23 (9.2)	0.94	0.51, 1.73	0.85	0.88	0.43, 1.82	0.74
delayed recall	16 (6.4)	19 (7.7)	1.32	0.63, 2.76	0.47	1.28	0.55, 2.99	0.57
Stroop test[‡]								
part 2	12 (4.8)	24 (9.6)	2.10	1.02, 4.32	0.043	2.03	0.86, 4.82	0.11
part 3	56 (22.6)	78 (31.3)	1.64	1.08, 2.50	0.021	1.69	1.05, 2.70	0.029

^{*}Offspring = 0, partner = 1. [†]Values are expressed as number (%). [‡]Subjects with no mistakes = 0, subjects with one or more mistakes = 1. Abbreviations: OR, odds ratio; CI, confidence interval; 15-PLT, 15-Picture Learning Test. Model 1: adjusted for age, gender and years of education. Model 2: as model 1 + diabetes mellitus, cardiovascular diseases (myocardial infarction, stroke and hypertension), alcohol use, smoking, high-sensitivity C-reactive protein, interleukin-6 and *apolipoprotein E* genotype. Robust standard errors were used to account for familial relationships among the offspring.

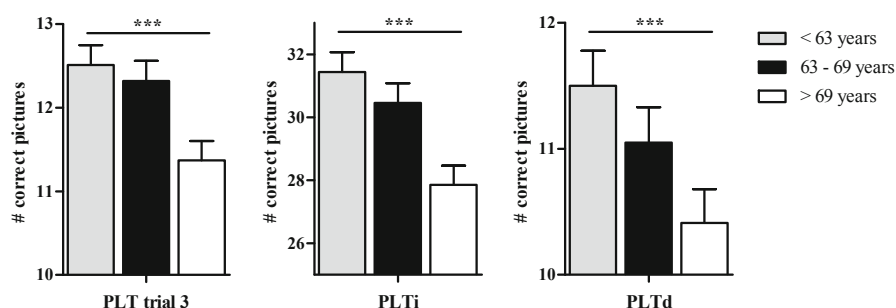
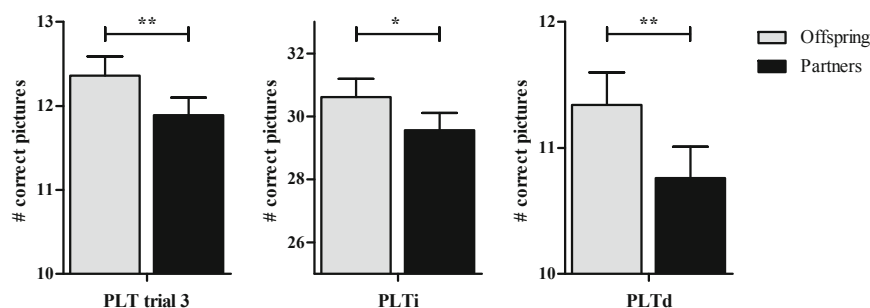
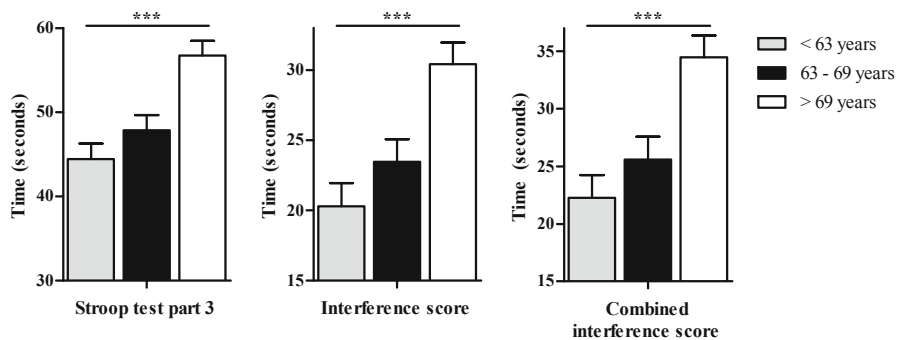
Calendar age**Offspring versus partner status**

Figure 1 Association of the 15-Picture Learning Test with calendar age and familial longevity. In the upper and lower panel, estimated mean values for trial 3, the immediate (PLTi) and delayed (PLTd) recall of the 15-Picture Learning Test are shown in tertiles of calendar age and for offspring versus partner status, respectively. Error bars indicate standard error. Analyses on calendar age are adjusted for gender, years of education, diabetes mellitus, cardiovascular diseases, alcohol use, smoking, high-sensitivity C-reactive protein, interleukin-6 and *apolipoprotein E* genotype. P-values indicate p for trend. Analyses on offspring versus partner status are adjusted additionally for age and for familial relationships among the offspring using robust standard errors. P-values indicate the difference between offspring and partners.

***: $p < 0.001$, **: $p < 0.01$, *: $p < 0.05$

Calendar age



Offspring versus partner status

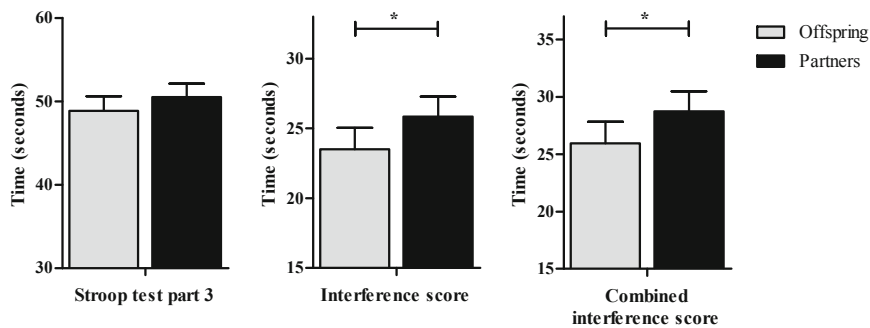


Figure 2 Association of the Stroop test with calendar age and familial longevity. In the upper and lower panel, estimated mean values for part 3, the interference score and combined interference score of the Stroop test are shown in tertiles of calendar age and for offspring versus partner status, respectively. Error bars indicate standard error. Analyses on calendar age are adjusted for gender, years of education, diabetes mellitus, cardiovascular diseases, alcohol use, smoking, high-sensitivity C-reactive protein, interleukin-6 and *apolipoprotein E* genotype. P-values indicate p for trend. Analyses on offspring versus partner status are adjusted additionally for age and for familial relationships among the offspring using robust standard errors. P-values indicate the difference between offspring and partners. Take note that lower Stroop scores indicate better cognitive performance.

***: $p < 0.001$, *: $p < 0.05$

Discussion

The aim of this study was to compare cognitive performance between middle-aged offspring of nonagenarian siblings with a familial history of longevity and the group of their partners of comparable age and sharing the same environmental conditions. Cognitive performance was better among the offspring compared to their partners, even after adjustment for known possible confounders. Furthermore, higher calendar age was associated with worse cognitive performance. According to calendar age, the preservation of cognitive performance of the offspring compared to their partners was estimated to be more than three years.

Despite the relative small age range and relatively good health status of the subjects of the Leiden Longevity Study, a significant association between calendar age and cognitive performance was found. Adjustment for possible risk factors for cognitive decline, such as diabetes mellitus, cardiovascular diseases, alcohol use, smoking, systemic inflammation and *APOE* genotype did not change the results. The association between calendar age and cognitive performance was found in all cognitive domains that were tested, i.e. memory function, attention and processing speed. This makes it likely that processes during the ageing course play a prominent role in the development of decline in cognitive performance even from middle age¹⁻³.

Cognitive performance was better among the offspring of nonagenarian siblings compared to their partners, with whom they share their life. The difference in cognitive performance between offspring and partners remained statistically significant after adjustment for possible confounders⁸⁻¹⁰. This indicates that the difference in cognitive performance between offspring and partners cannot be accounted for by diabetes mellitus, cardiovascular diseases, alcohol use and smoking. Neither changed the results after adjustment for inflammatory markers, of which high systemic levels have been reported to be associated with decline in cognitive performance as well^{8,11,12}. Furthermore, the association of cognitive performance with familial longevity remained statistically significant after adjustment for *APOE* genotype. The *APOE* genotype is besides one of the most important genetic risk factors for cognitive decline^{16,17}, consistently shown to be associated with survival and longevity^{25,26}. A genome wide association study performed in the nonagenarian participants of the Leiden Longevity Study identified the *APOE* $\epsilon 4$ isoform as deleterious to longevity, which was confirmed in a meta-analysis of three different replication cohorts²⁴. Adjustment for familial relationships among the offspring did not change the results either, which excludes the influence of familial resemblance on the difference between offspring and partners in cognitive performance.

Altogether, the independence of the difference in cognitive performance between offspring and partners of above mentioned risk factors, suggests that the results have to be explained

by other factors. One possible explanation is that the offspring are biologically younger compared to their partners, which means that the person's rate of ageing of the offspring is slower compared to their partners. Based on the effect sizes of the association of cognitive performance with calendar age and familial longevity, the preservation of cognitive performance of the offspring was estimated to be more than three years according to calendar age. This finding of the offspring being biologically younger compared to their partners is in line with several other observations. The younger biological age of the offspring is reflected by their lower mortality rate, beneficial glucose and lipid metabolism, preservation of insulin sensitivity, preservation of naïve T-cell pool and resistance to cellular stress^{18,21,27-29}.

Another possible explanation is that the offspring have a better health status compared to their partners due to a more favorable development in utero or during early childhood. This explanation might be supported by the fact that the differences between offspring and partners in cognitive performance are already visible at middle age, when decline in cognitive performance is relatively small. However, data to test this possible explanation are currently not available and would require a familial multigenerational design.

Very recently we found differences in subclinical vascular pathology between offspring and partners. Assessment of magnetic resonance imaging scans in a subgroup of offspring and partners showed that the offspring had a lower periventricular as well as subcortical white matter load and a lower prevalence of lacunar infarcts compared to their partners³⁰. Further research on the relation between the differences in subclinical vascular pathology and cognitive performance among the offspring and their partners is needed to get more insight into this possible causal pathway.

One of the strengths of our study is the unique study design of comparing middle-aged individuals, who are enriched for familial factors of longevity, to their partners. This gives the possibility to get more insight into determinants of healthy longevity. By including couples, the influence of socioeconomic status was relatively low making the groups highly comparable. The relative young age of the subjects is both a strength and limitation of the study. Differences in cognitive performance with calendar age in this relatively young study population were already observable; however, differences between offspring and partners may therefore be underestimated. Another limitation is the cross-sectional design of the present analysis, as cognitive performance data became available just recently.

In conclusion, offspring of nonagenarian siblings with a familial history of longevity showed a better cognitive performance compared to their partners being independent of known possible confounders. This makes it likely that cognitive performance is preserved with familial longevity. Further research on the possible causes of the relation between

cognitive performance and familial longevity is needed in order to be able to get a better understanding of preservation of cognitive performance with age.

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Effect of calendar age on physical performance:
a comparison of standard clinical measures with
instrumented measures in middle-aged to older adults

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Abstract

Background: Decline in physical performance is highly prevalent during ageing. Identification of sensitive markers of age-related changes in physical performance is important for early detection, development of therapeutic strategies and insight into underlying mechanisms. We studied the association of calendar age and familial longevity with standard clinical and instrumented measures of physical performance in a cohort of healthy middle-aged to older adults.

Methods: Cross-sectional analysis within the Leiden Longevity Study consisting of offspring of nonagenarian siblings and their partners (n=300, mean age (SD) 65.3 (6.7) years). Standard clinical measures were 25-meter walking speed and total duration of the chair stand test (CST). Instrumented measures were determined using a body fixed sensor. Dependence of physical performance on calendar age and familial longevity (offspring versus partner status) was analyzed using linear and logistic regression, respectively, adjusted for gender and height.

Results: Higher calendar age was associated with slower walking speed and longer duration of the CST (standardized β (95% CI) -0.024 (-0.042;-0.006) and 0.035 (0.014;0.056), respectively). Instrumented measures showed similar effect sizes with strongest associations for gait stability and symmetry in mediolateral direction and for the extension and flexion phase of sit-to-stand and stand-to-sit transfers, respectively. No differences were observed between offspring of nonagenarian siblings and their partners.

Conclusions: Standard clinical and instrumented measures of physical performance are associated with similar effect size to age-related changes in physical performance observable from middle age. The potential added value of instrumented measures for understanding underlying mechanisms requires further attention.

Introduction

Decline in physical performance is highly prevalent during ageing leading to loss of independence and a poorer quality of life¹. Furthermore, older adults with impaired physical performance have a high risk of falls, further reducing the quality of life and placing a heavy economic burden on society². Identification of sensitive markers of age-related changes in physical performance is of utmost importance for the early detection, development of therapeutic strategies and insight into underlying mechanisms.

Assessment of physical performance is part of the comprehensive geriatric assessment (CGA) in clinical practice. Important clinical measures of physical performance commonly include walking speed and the duration of repeated sit-to-stand movements, assessed by the chair stand test (CST)^{3,4}. Walking speed is an important indicator of health status and function by reflecting the interaction of several underlying systems, such as the central and peripheral nervous, sensory, muscular, skeletal, and cardiopulmonary system^{5,6}. Sit-to-stand movements are one of the most mechanically demanding functional tasks during daily activities⁷. Furthermore, the CST is an important indicator for the performance of other daily activities, like climbing stairs, by measuring lower body strength⁸.

Standard clinical measures of physical performance, using simply total time as the outcome, provide a common output representing a combination of possible underlying mechanisms. Based on previous studies showing the association of calendar age with various instrumented measures of physical performance and their use in the early identification and prediction of pathology⁹⁻¹¹, instrumented measures might be sensitive markers of age-related changes in physical performance providing possible insights into underlying determinants. Therefore, we assessed the association of calendar age with standard clinical and instrumented measures of the 25-meter walk and CST in a study population of offspring of nonagenarian siblings together with their partners. We used this study population of middle-aged to older adults to be able to assess changes in physical performance that are already observable from middle age in the absence of overt diseases. Additionally, we compared both measures between the offspring of nonagenarian siblings, who are enriched for familial factors of longevity, and their partners to assess the sensitivity for familial longevity representing the biological age of the participants, i.e. the person's rate of ageing compared to their calendar age.

Methods

The Leiden Longevity Study

The Leiden Longevity Study is a longitudinal cohort consisting of 421 families of long-lived Caucasian siblings of Dutch descent¹². Families were recruited if at least two long-lived siblings were alive and met the age criteria of ≥ 89 years for males and ≥ 91 years for

females. Additionally, the offspring of these long-lived families were included together with their partners as controls being of comparable age and sharing the same socioeconomic and geographical background. Enrolment took place between July 2002 and May 2006. Physical performance was assessed among a random subgroup of participants ($n=300$) between September 2009 and December 2010. All physical performance tests were performed in the Leiden University Medical Center by two research nurses. The Medical Ethical Committee of the Leiden University Medical Center approved the study and written informed consent was obtained from all participants.

Instrumentation

During the 25-meter walk and CST, a body fixed sensor (DynaPort® Hybrid, McRoberts BV, The Hague, The Netherlands) was inserted in an elastic belt and positioned on the lower back at the height of the second lumbar vertebra¹³. The sensor consisted of one triaxial accelerometer and three uniaxial gyroscopes with a sampling rate of 100 Hz. The start and end of each physical performance test was marked by the research nurse using a remote control. Participants wore non-slip socks during all physical performance tests.

25-meter walk

The 25-meter walk was performed twice in steady state over a length of 30 m, i.e. time started at 2.5 m and stopped at 27.5 m. Participants were asked to walk at their preferred speed. Gait characteristics were determined over the time interval of begin till end marker of the test. Walking speed was used as standard clinical measure and determined by dividing the distance of 25 m by the total duration of the test. Instrumented measures of gait performance were determined using a previously developed algorithm, of which the precision, reliability and validity has been shown in earlier studies^{14,15}. Because of the relatively short distance of the 25-meter walk for determination of some gait characteristics, like stride-to-stride variability or local dynamic stability¹⁶, we used only those variables with an ICC ≥ 0.80 over two repeated measurements. This resulted in four different gait characteristics, i.e. gait kinematics, stability, symmetry and variability, which were included in the statistical analyses for each participant. Data were aligned to a common, body centered reference frame with axes in the vertical (VT), mediolateral (ML) and anterior-posterior (AP) direction. Thereby the VT direction was defined as the direction of the mean acceleration signal. Stride time was estimated as measure of gait kinematics. The standard deviation of the acceleration signal, defined as the movement intensity which is equivalent to the acceleration root mean square, was used as measure of gait stability. Gait symmetry was estimated by the harmonic ratio. The amplitude of the dominant frequency of the signal's power spectral density within the frequency range of locomotion (0.5 – 3 Hz) was used as measure for consistency and variability of gait. Gait stability, symmetry and variability were determined in VT, ML and AP direction. For each parameter, the mean

of the two measurements was used for analyses. Due to missing data, data was available for 292 subjects (97%) (Figure 1).

Chair stand test

The ability to rise from a chair was tested by the CST. Participants were asked to stand up and sit down five times as quickly as possible from a straight-backed chair with default seat height. Total duration of the CST was used as standard clinical measure and determined by the time between begin and end marker of the test. Repeated sit-to-stand and stand-to-sit transfers were detected automatically by a commercially available algorithm of which the precision, validity and reliability has been shown previously in older adults^{11,13,17}. Thereby, four main phases were distinguished; sit-to-stand, standing, sitting and stand-to-sit. The sit-to-stand and stand-to-sit phases were distinguished further into a flexion and extension phase, according to flexion and extension of the lower back. For each repetition, the duration of the different phases was determined as well as the maximum angular velocity (in deg/s) of the flexion and extension phases. For each parameter of the four main phases, mean values of at least four repeated transfers were calculated and used for statistical analyses. Due to technical problems in the automated signal analysis, data on the CST was available for 221 (74%) participants (Figure 1), which was a random loss of participants.

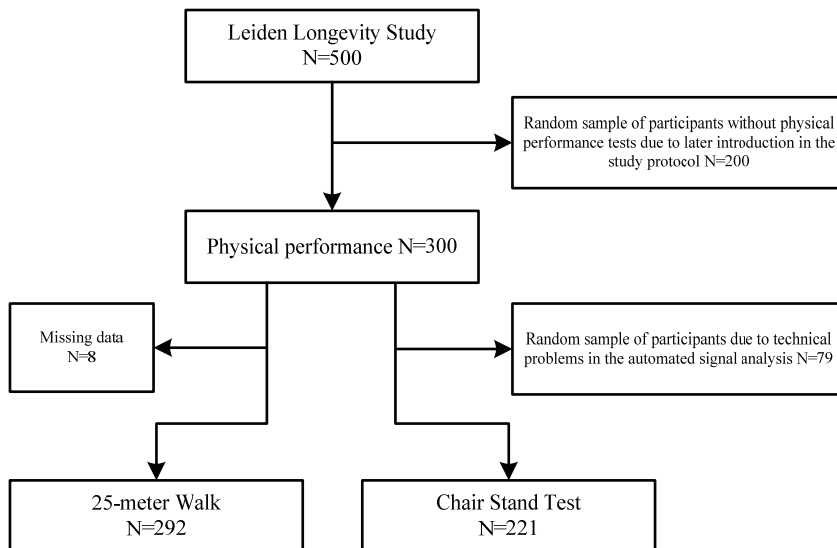


Figure 1 Flow chart of the study population with available data on the different physical performance tests.

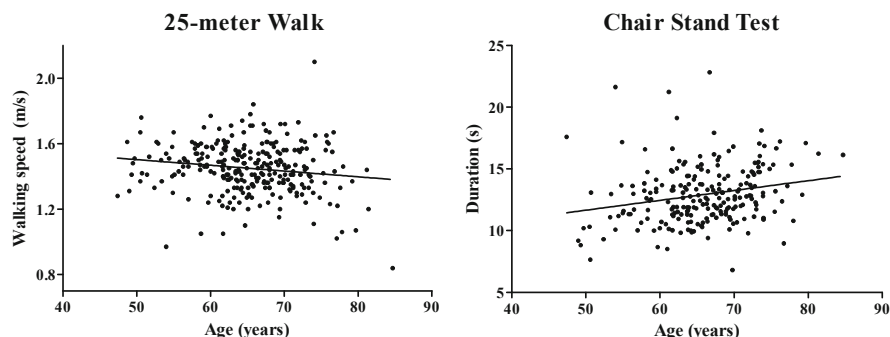


Figure 2 Scatter plots with trend lines of standard clinical measures of the 25-meter walk and chair stand test, i.e. walking speed in meter per seconds (m/s) and duration in seconds (s), respectively, plotted against calendar age in years.

Statistical analysis

Continuous variables with Gaussian distribution are presented as mean and standard deviation, non-Gaussian distributed variables as median and interquartile range, and categorical variables as number and percentage. Linear and logistic regression analysis was used to assess the cross-sectional association between calendar age and physical performance and between familial longevity (offspring versus partner status) and physical performance, respectively. Results were adjusted for gender and height. In the analysis testing differences depending on familial longevity, results were adjusted additionally for calendar age and for familial relationships among the offspring using robust standard errors.

All statistical analyses were performed with the normal values of physical performance (defined as unstandardized) and with the parameters of physical performance expressed as z-scores to enable the comparison of effect sizes. The relation between calendar age and standard clinical measures of physical performance were visualized by using scatter plots. The comparison of effect sizes was visualized by plotting the estimated mean (standard error) of the z-scores of the standard clinical and instrumented measures of the 25-meter walk and CST in tertiles of calendar age. For the instrumented measures of the 25-meter walk and CST, the parameters with the highest effect sizes for each of the gait characteristics, i.e. kinematics, stability, symmetry and variability, and for each phase of the CST were plotted.

P values less than 0.05 were considered statistically significant. All statistical analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, USA) and Stata version 12.0 (Stata, College Station, USA). Figures were made with GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, USA).

Results

The characteristics of the participants are shown in Table 1 together with the characteristics stratified for offspring and partners. Mean age (SD) of all participants was 65.3 (6.7) years. Offspring and partners had similar calendar age, years of education and measures of anthropometrics. The prevalence of age-related diseases, like diabetes mellitus and hypertension, was lower among offspring compared to their partners. In Figure 2, the 25-meter walking speed and duration of the CST for all participants is plotted against calendar age.

Table 2 presents the association between calendar age and physical performance. Participants with a higher calendar age had a slower walking speed and longer duration of the CST (standardized β (95% CI) -0.024 (-0.042;-0.006) and 0.035 (0.014;0.056), respectively). According to the instrumented measures of gait characteristics, i.e. gait kinematics, stability, symmetry and variability, a higher calendar age was associated with a longer stride time, lower movement intensity and harmonic ratio in ML and AP direction and a higher amplitude of the dominant frequency in VT direction. During the sit-to-stand phase of the CST, a higher calendar age was associated with a longer duration and slower

Table 1 Characteristics of all participants and stratified by offspring of nonagenarian siblings and their partners.

	All (N=300)	Offspring (N=151)	Partners (N=149)
Demographics			
Females, n (%)	152 (50.7)	71 (47.0)	81 (54.4)
Age, years	65.3 (6.7)	65.7 (6.1)	65.0 (7.3)
Education, years*	12 (10 - 15)	12 (10 - 15)	12 (10 - 15)
Anthropometrics			
Height, cm	172.4 (8.5)	172.4 (8.8)	172.4 (8.2)
Weight, kg	79.3 (14.1)	78.5 (13.9)	80.1 (14.2)
Comorbidities			
Diabetes Mellitus	18 (6.8)	4 (3.0)	14 (10.6)
Myocardial infarction	8 (3.0)	3 (2.2)	5 (3.7)
Stroke	8 (2.9)	3 (2.2)	5 (3.7)
Hypertension	73 (27.1)	32 (23.4)	41 (31.1)
COPD	9 (3.3)	5 (3.6)	4 (3.0)
Malignancy	17 (6.3)	7 (5.1)	10 (7.6)
Rheumatoid arthritis	4 (1.5)	2 (1.5)	2 (1.5)
Intoxications			
Users of alcohol†	237 (79.3)	116 (77.3)	121 (81.2)
Former and/or current smokers	203 (67.9)	94 (62.7)	109 (73.2)

Values are expressed as mean (standard deviation), unless otherwise indicated. Abbreviations: n, number; COPD, Chronic Obstructive Pulmonary Disease. *Values are expressed as median (interquartile range). †Using ≥ 1 units per week.

Table 2 Physical performance dependent on calendar age in years presented unstandardized and expressed as z-score.

	All subjects	Unstandardized		Expressed as z-score		p
		β	95% CI	β	95% CI	
25-meter Walk[‡]						
<i>Standard measure</i>						
Walking speed, m/s	1.45 (.009)	-.004	-.007;-.001	-.024	-.042;-.006	.008
<i>Gait kinematics</i>						
Stride time, s	.98 (.004)	.001	.000;.002	.017	.001;.033	.041
<i>Gait stability</i>						
Movement intensity VT, m/s ²	3.13 (.040)	-.012	-.024;.000	-.017	-.035;.000	.057
Movement intensity ML, m/s ²	2.15 (.034)	-.016	-.025;-.006	-.027	-.044;-.011	.001
Movement intensity AP, m/s ²	2.08 (.027)	-.010	-.018;-.002	-.022	-.040;-.005	.013
<i>Gait symmetry</i>						
Harmonic ratio VT	3.58 (.052)	-.009	-.024;.007	-.010	-.027;.008	.28
Harmonic ratio ML	2.83 (.043)	-.020	-.032;-.008	-.027	-.043;-.010	.002
Harmonic ratio AP	3.12 (.044)	-.014	-.028;-.001	-.019	-.037;-.002	.034
<i>Gait variability</i>						
Ampl. dominant freq. VT, psd	1.37 (.020)	.009	.003;.015	.026	.008;.044	.004
Ampl. dominant freq. ML, psd	.77 (.018)	.001	-.004;.006	.003	-.012;.019	.66
Ampl. dominant freq. AP, psd	.87 (.015)	.002	-.002;.007	.009	-.009;.026	.33
Chair Stand Test[†]						
<i>Standard measure</i>						
Duration chair stand test, s	12.9 (.16)	.083	.034;.13	.035	.014;.056	.001
<i>Sit-to-stand</i>						
Flexion duration, s	.61 (.01)	.002	.000;.004	.019	-.002;.040	.071
Extension duration, s	.55 (.01)	.005	.003;.007	.045	.024;.065	<.001
Flexion max. angular vel., °/s	172.3 (2.4)	-.70	-1.47;.06	-.020	-.041;.002	.071
Extension max. angular vel., °/s	59.9 (1.5)	-.57	-1.04;-.11	-.025	-.046;-.005	.016
<i>Standing</i>						
Duration, s	.10 (.007)	.003	.000;.005	.024	.003;.045	.022
<i>Sitting</i>						
Duration, s	.39 (.02)	-.001	-.006;.005	-.003	-.025;.018	.75
<i>Stand-to-sit</i>						
Flexion duration, s	.58 (.01)	.006	.003;.009	.043	.022;.063	<.001
Extension duration, s	.72 (.009)	.002	.000;.005	.019	-.002;.039	.075
Flexion max. angular vel., °/s	84.4 (1.6)	-.95	-1.42;-.48	-.041	-.061;-.021	<.001
Extension max. angular vel., °/s	141.4 (2.8)	-1.19	-2.03;-.34	-.029	-.050;-.008	.006

Abbreviations: n=number; β , estimate; CI, confidence interval; p, p-value; VT, vertical; ML, mediolateral; AP, anterior-posterior; ampl., amplitude; freq., frequency; max., maximum; vel., velocity; psd, power spectral density. Associations were assessed by linear regression and adjusted for gender and height. Unstandardized effect sizes and effect sizes with the physical performance parameters expressed as z-scores are given.*Values are expressed as mean (standard error). [‡]Data available in n=292 and [†]n=221 participants.

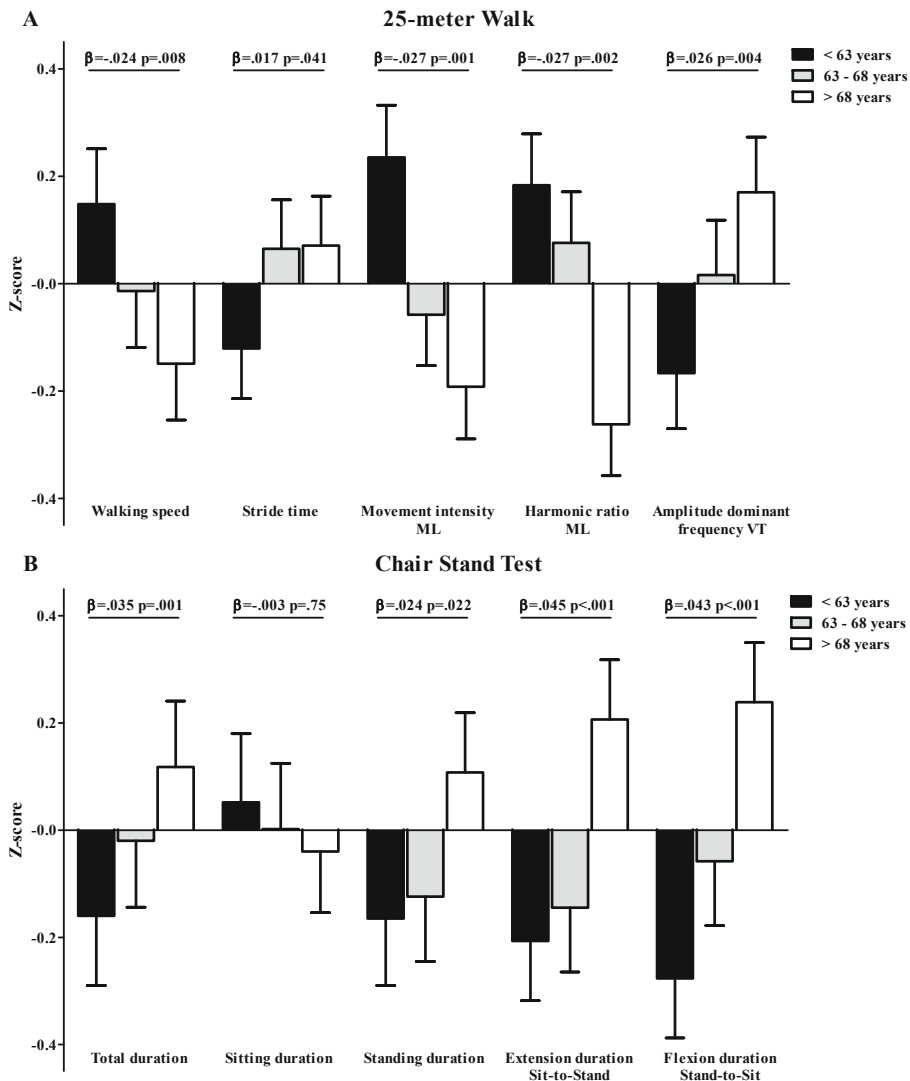


Figure 3 Association of calendar age with standard clinical measures and instrumented measures of the 25-meter walk (A) and chair stand test (B). Estimated mean values expressed as z-scores are given in tertiles of calendar age. Error bars indicate standard error. Standard clinical measures are represented by walking speed and the total duration of the CST. Results are adjusted for gender and height. P-values indicate p for trend. Abbreviations: β , estimate; ML, mediolateral; VT, vertical.

maximum angular velocity of the extension phase. During the stand-to-sit phase, a higher calendar age was associated with a longer duration of the flexion phase and a slower maximum angular velocity of the flexion and extension phase. According to the sitting and standing phase, a higher calendar age was associated with a longer standing duration.

Supplementary Table 1 shows the association of familial longevity with physical performance comparing offspring of nonagenarian siblings with their partners. No statistically significant difference was found between offspring and partners, except for the amplitude in the dominant frequency in AP direction.

In Figure 3, the estimated mean values of the standard clinical and instrumented measures of the 25-meter walk (Figure 3A) and CST (Figure 3B) expressed as z-scores are presented in tertiles of calendar age. Similar effect sizes are shown for walking speed, used as standard clinical measure, movement intensity and the harmonic ratio in ML direction and the amplitude of the dominant frequency in VT direction. According to the CST, the effect sizes of the total duration of the CST as standard clinical measure and the extension and flexion duration of the sit-to-stand and stand-to-sit transfer, respectively, were similar.

Discussion

In this study population of middle-aged to older adults, physical performance assessed with the 25-meter walk and CST was lower at higher calendar age. The effect size for the standard clinical measures dependent on calendar age was similar to those of instrumented measures assessed with a body fixed sensor at the lower back. No statistically significant association was found between familial longevity and both standard clinical and instrumented measures of physical performance, comparing offspring of nonagenarian siblings with their partners.

The association of calendar age with instrumented measures of the 25-meter walk was found in the four different gait domains that were measured, i.e. gait kinematics, stability, symmetry and variability. At higher calendar age, participants had a longer stride time and a lower movement intensity, i.e. a lower magnitude of the trunk acceleration, and less symmetrical gait pattern in ML and AP direction. This is in concordance with earlier findings in healthy older adults¹⁸⁻²⁰ as well as in older adults with Parkinson's Disease²⁰ or dementia¹⁹. Because movement intensity is positively associated with walking speed²¹, the lower movement intensity might indicate that participants at higher age adapt their walking speed to remain a stable gait pattern. However, it is only possible to speculate about the order of changes in gait characteristics because the measurements were performed at the participant's preferred speed and not at a fixed walking speed. The associations of gait stability and symmetry with calendar age were strongest in the ML direction, which is the direction that is in general strongly related to the ability to control balance and falls^{22,23}.

Furthermore, participants with a higher calendar age had a more consistent and less variable gait pattern in VT direction, as was quantified by a higher amplitude of the dominant frequency of the signal's power spectral density. So, additionally to walking speed the assessment of instrumented measures enhanced our understanding of changes in gait characteristics with calendar age.

According to the instrumented measures of the CST, participants with a higher calendar age had in general longer durations and slower angular velocities in the different phases. This is in concordance with a previous study in a small sample of healthy young subjects and older adults recruited from a residential care home²⁴. The strongest association with calendar age was found for the extension duration during the sit-to-stand phase and the flexion duration during the stand-to-sit phase. These phases represent the dynamic transitions during the CST⁷. The extension phase during the sit-to-stand phase represents the dynamic transition from a three-point stable support to a two-point stable support. The flexion phase during the stand-to-sit phase represents the dynamic transition in the other direction, from a two-point stable support to a three-point stable support. The necessity of a good balance control and the power to shift the center of mass of the trunk within the base of support in these dynamic transitions might explain the stronger association with calendar age compared to the other phases of the CST.

The instrumented measures of the 25-meter walk and CST assessed in this study show similar effect sizes to changes in calendar age as the standard clinical measures, i.e. walking speed and total duration of the CST. These results indicate that both standard clinical and instrumented measures can be used for the detection of age-related changes in physical performance from middle age. The association of calendar age with specific instrumented measures of the 25-meter walk and CST in this study, i.e. gait stability and symmetry especially in the ML direction and the dynamic transition phase of the CST, enhanced our understanding of possible underlying mechanisms. Additionally to the standard clinical measures, addressing physical performance as a common output representing a combination of underlying systems, the instrumented measures indicated that especially a good balance control is an important determinant for the performance on both tasks. Future studies are needed to further investigate the potential added value of instrumented measures of balance control in the identification of sensitive markers for age-related changes in physical performance and understanding of underlying mechanisms. Finally, this might lead to the possibility to characterize different groups of individuals based on deterioration of specific underlying systems, like deterioration of the sensory system (including vision and the vestibular and proprioceptive system), low muscle mass or strength or cognitive impairment⁶, and development of interventions tailored to individual needs.

No differences in performance on the 25-meter walk and CST were found between offspring of nonagenarian siblings and their partners as controls. Unless a significant

decline in physical performance during ageing, familial longevity as strong indicator of healthy ageing is not marked by a better physical performance at middle age. Besides the relatively young age of the participants, the shared environmental conditions of the offspring and partners might be an explanation leading to similar levels of daily physical activity in both groups by performing the activities together. This is supported by previous findings, showing no difference between offspring and partners among other major indicators of lifestyle like body mass index, current smoking and level of education²⁵. Furthermore, these results indicate that the younger biological age of the offspring compared to their partners, based on the lower prevalence of age-related diseases^{12,25}, better cognitive performance²⁶, preserved insulin sensitivity²⁷ and fewer senescent cells²⁸ cannot be detected by physical performance at middle age.

One of the strengths of this study is the study population consisting of middle-aged to older adults with a relatively good health status. This enhanced our insight into sensitive markers for age-related changes in physical performance already observable from middle age and without the presence of overt diseases. Furthermore, the inclusion of offspring of nonagenarian siblings and their partners made it possible to study whether standard clinical and instrumented measures of physical performance are sensitive to familial longevity. The assessment of different physical performance tests and the use of a body fixed sensor made it possible to assess the potential added value of instrumented measures in assessing age-related changes in physical performance from middle age and to enhance our insight into possible underlying mechanisms. Future studies including a wider age range and specific patient populations with repeated measures taken over time are needed to further investigate this. A limitation is the availability of the CST in only 74% of the participants due to technical problems. However, missing data were randomly distributed. The distance of the walk trajectory is both a strength and a limitation. The distance of 25 m enabled the reliable assessment of instrumented measures of gait characteristics additional to walking speed. However, a longer distance or a higher number of strides is needed for the determination of gait characteristics like local dynamic stability and stride-to-stride variability measures¹⁶. These parameters have been shown to be associated with calendar age and to be important predictors of falls^{15,29,30} suggesting that they might be important parameters in the detection of age-related changes in physical performance as well.

In conclusion, standard clinical and instrumented measures of physical performance are associated with similar effect sizes to age-related changes in physical performance in middle-aged to older adults. The assessment of instrumented measures needs further investigation to be able to distinguish different groups of individuals to ultimately tailor interventions to individual needs.

Acknowledgements

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Supplementary material

Supplementary Table 1 Physical performance dependent on familial longevity (offspring versus partner status*) presented unstandardized and expressed as z-score.

	Offspring [§]	Partners [§]	Unstandardized		Expressed as z-score		p
			β	95% CI	β	95% CI	
25-meter Walk[‡]							
<i>Standard measure</i>							
Walking speed, m/s	1.45 (.01)	1.45 (.01)	-.002	-.038;.035	-.011	-.24;.22	.93
<i>Gait kinematics</i>							
Stride time, s	.98 (.01)	.98 (.01)	-.005	-.019;.008	-.081	-.29;.13	.45
<i>Gait stability</i>							
Movement intensity VT, m/s ²	3.12 (.06)	3.14 (.05)	.015	-.13;.16	.022	-.20;.24	.84
Movement intensity ML, m/s ²	2.15 (.04)	2.16 (.05)	-.015	-.14;.11	-.025	-.24;.19	.82
Movement intensity AP, m/s ²	2.08 (.04)	2.07 (.04)	-.007	-.11;.093	-.016	-.24;.20	.89
<i>Gait symmetry</i>							
Harmonic ratio VT	3.50 (.07)	3.67 (.07)	.15	-.053;.36	.17	-.059;.41	.14
Harmonic ratio ML	2.84 (.06)	2.82 (.06)	-.056	-.22;.11	-.075	-.30;.15	.51
Harmonic ratio AP	3.13 (.06)	3.11 (.07)	-.030	-.21;.15	-.040	-.28;.20	.75
<i>Gait variability</i>							
Ampl. dominant freq. VT, psd	1.34 (.03)	1.40 (.03)	.070	-.010;.15	.21	-.031;.45	.088
Ampl. dominant freq. ML, psd	.77 (.03)	.77 (.02)	-.029	-.091;.034	-.095	-.30;.11	.37
Ampl. dominant freq. AP, psd	.91 (.02)	.84 (.02)	-.072	-.13;-.015	-.28	-.50;-.059	.013
Chair Stand Test[†]							
<i>Standard measure</i>							
Duration chair stand test, s	12.8 (.22)	13.0 (.23)	.30	-.30;.91	.12	-.13;.38	.33
<i>Sit-to-stand</i>							
Flexion duration, s	.61 (.01)	.62 (.01)	.002	-.024;.028	.018	-.26;.29	.90
Extension duration, s	.55 (.01)	.55 (.01)	.002	-.025;.030	.023	-.24;.29	.86
Flexion max. ang. vel., °/s	169.9 (3.5)	174.9 (3.3)	4.16	-5.50;13.8	.12	-.15;.38	.40
Extension max. ang. vel., °/s	58.6 (2.0)	61.3 (2.4)	.93	-4.95;6.81	.041	-.22;.30	.76
<i>Standing</i>							
Duration, s	.10 (.01)	.10 (.01)	.003	-.025;.031	.024	-.23;.28	.85
<i>Sitting</i>							
Duration, s	.37 (.02)	.40 (.03)	.038	-.032;.11	.15	-.12;.42	.29
<i>Stand-to-sit</i>							
Flexion duration, s	.57 (.01)	.58 (.01)	.016	-.019;.052	.11	-.14;.36	.37
Extension duration, s	.72 (.01)	.71 (.01)	-.002	-.036;.032	-.016	-.28;.25	.90
Flexion max. ang. vel., °/s	85.6 (2.2)	83.1 (2.2)	-4.65	-10.7;1.39	-.20	-.46;.06	.13
Extension max. ang. vel., °/s	142.1 (3.8)	140.7 (4.0)	-3.70	-14.7;7.28	-.091	-.36;.18	.51

Abbreviations: n=number; β , estimate; CI, confidence interval; p, p-value; VT, vertical; ML, mediolateral; AP, anterior-posterior; ampl., amplitude; freq., frequency; max., maximum; ang., angular; vel., velocity; psd, power spectral density. Associations were assessed by logistic regression and adjusted for calendar age, gender and height. Robust standard errors were used to account for familial relationships among the offspring. Unstandardized effect sizes and effect sizes with the physical performance parameters expressed as z-scores are given. *Offspring = 0, partner = 1. [§]Values are expressed as mean (standard error). [‡]Data available in n=148 offspring and n=144 partners and in [†]n=114 offspring and n=107 partners.

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Cerebral microbleeds and lacunar infarcts are
associated with walking speed independent of
cognitive performance in middle-aged to older adults

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Abstract

Background: The positive relationship between cognitive and physical performance has been widely established. The influence of brain structure on both domains has been shown as well. We studied whether the relationship between brain structure and physical performance is independent of cognitive performance.

Methods: Cross-sectional analysis within 297 middle-aged to older adults (mean age (SD) 65.4 (6.8) years). Memory function, executive function and physical performance measured by the tandem stance test, chair stand test (CST), 4-meter walk and 25-meter walk were assessed. Magnetic resonance imaging was available in 237 participants and used to determine the (sub)cortical gray matter, white matter, hippocampal and basal ganglia volumes and the presence of cerebral small vessel disease (CSVD), i.e. white matter hyperintensities, cerebral microbleeds (CMBs) and lacunar infarcts (LIs). Regression analysis was used adjusting for age, gender, education and whole brain volume. A Bonferroni correction was applied considering p-values <0.017 as statistically significant.

Results: Poor memory function was associated with a slower 4-meter walking speed ($p<0.01$). No association was found between brain structure and cognitive performance. The presence of CMBs and LIs was associated with a slower 25-meter walking speed ($p<0.001$). This result did not change after additional adjustment for cognitive performance.

Conclusions: In middle-aged to older adults, CMBs and LIs are associated with walking speed independent of cognitive performance. This emphasizes the clinical relevance of identifying each of the possible underlying mechanisms of physical performance, which is required for the development of timely and targeted therapies.

Introduction

The positive relationship between cognitive and physical performance has been widely established. The role of higher-order cognitive performance, especially of executive functioning, in the performance of physical tasks has been shown as well as the influence of the level of physical activity and performance on risk of dementia and cognitive decline¹⁻⁴. Because of the co-occurrence of cognitive and physical impairment frequently seen with advancing age, a common underlying cause such as brain pathology has been suggested^{5,6}.

Deterioration of several brain structures has been shown to be associated with cognitive and physical performance. Poor cognitive performance is commonly indicated by brain atrophy and accumulation of white matter hyperintensities (WMHs)^{7,8}. Thereby, the association of hippocampal volume with global cognitive performance and memory function and of frontal gray matter volumes with executive function have been most consistently shown⁹. According to physical performance, especially the association of white matter atrophy and accumulation of WMHs with poor physical performance has been reported⁶. The relation with specific regional and subcortical gray matter volumes is less clear. The few studies incorporating different gray matter volumes showed that especially atrophy of the hippocampus and basal ganglia are associated with poor physical performance^{6,10,11}.

It is unclear whether the influences of cognitive performance and brain structure on physical performance are independent of each other. In this study, we assessed the relationship between cognitive and physical performance and the relationship of brain structure with both domains within a study population of relatively healthy middle-aged to older adults in the absence of overt diseases.

Methods

The Leiden Longevity Study

The Leiden Longevity Study is a longitudinal cohort comprising of 421 long-lived Caucasian families of Dutch descent recruited between 2002 and 2006¹². Families were enrolled if at least two long-lived siblings were alive and fulfilled the age-criterion of 89 years or older for males and 91 years or older for females. Additionally, the offspring of these long-lived siblings were included together with their partners as controls representing the general population¹³. For the current study, participants were recruited from this population of middle-aged to older adults visiting the research center during the follow-up measurement between September 2009 and December 2010. Participants were included if they had complete data on both cognitive and physical performance leading to 297 participants (149 offspring and 148 partners). The Medical Ethical Committee of the Leiden University Medical Center approved the study and written informed consent was obtained from all participants.

Cognitive performance

Cognitive performance was tested for two different cognitive domains; memory and executive function. Memory function was assessed by the immediate and delayed recall of the 15-Picture Learning Test (15-PLTi and 15-PLTd, respectively). For the immediate recall, fifteen pictures of well-known items were shown to the participant at three consecutive times. After each time, the participant was asked to recall as many pictures as possible. The sum of the number of correct pictures during the three trials was defined as the immediate recall. The delayed recall was defined as the number of correct pictures the participant was able to recall after 20 min.

Executive function was assessed by attention and processing speed using the abbreviated Stroop test trial 3 and the Digit Symbol Substitution Test (DSST), respectively. The abbreviated Stroop test trial 3 consisted of a card containing 40 color words printed in a discongruous ink color. The participant was asked to name the ink color of the words as fast as possible. In the DSST, digits were given on a card as well as a key for the formation of specific digit-symbol combinations. The outcome parameter was the number of correct digit-symbol combinations the participant was able to make in 90 s.

Physical performance

Four different aspects of physical performance were assessed; the ability to maintain standing balance, the ability to rise from a chair and walking speed over a short and long distance^{14,15}. The ability to maintain standing balance was assessed by the tandem stance test. Participants were asked to place their feet in tandem position, i.e. placing both feet in line with one foot touching the toe of the other foot, and maintain balance for 10 s. The chair stand test (CST) was used to assess the ability to rise from a chair. Participants were asked to stand up and sit down 5 times as quickly as possible from a straight-backed chair. The test was started in sitting position and ended when the participant was standing with straight back for the fifth time. Walking speed was assessed over 4 and 25 m of walking. During the 4-meter walking test, participants started from standing position and were instructed to walk at their preferred speed over a length of 5 m without slowing down before the 4-meter line. Time was started at the moment the first foot passed the starting line until the moment the first foot passed the 4-meter line completely. The fastest time out of two measurements was used for the calculation of walking speed. Walking speed during 25 m of walking was assessed in steady state over a length of 30 m, i.e. time started at 2.5 m and stopped at 27.5 m. Again, participants were asked to walk at their preferred speed. Mean walking speed over two measurements was used for analyses.

During all physical performance tests, participants wore non-slip socks and a body fixed sensor (Dynaport® Hybrid, McRoberts BV, The Hague, the Netherlands) on the lower back positioned with an elastic belt at the height of the second lumbar vertebra. The sensor consisted of a triaxial accelerometer and three uniaxial gyroscopes of which the signals

were recorded with a sample frequency of 100 Hz. A remote control was used for marking the start and end of each measurement.

Brain structure

Magnetic resonance imaging (MRI) was used to determine whole brain volume, the cortical gray and white matter volumes, the subcortical gray matter volumes of the hippocampus and basal ganglia, including the nucleus accumbens, caudate nucleus, pallidum and putamen and the presence of cerebral small vessel disease (CSVD) including WMH volume and the presence of cerebral microbleeds (CMBs) and lacunar infarcts (LIs)^{16,17}. Three-dimensional (3-D) T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR) and T2*-weighted images were acquired using a whole-body MR system operating at a field strength of 3T (Philips Medical Systems, Best, the Netherlands) with the following imaging parameters: repetition time 9.7 ms, time to echo 4.6 ms, flip angle 8° and field of view 224x177x168 mm resulting in a normal voxel size of 1.17x1.17x1.4 mm.

Different tools of the FMRIB Software Library (FSL, Release 5.0 (c) 2012)^{18,19} were used for the determination of brain volumes. Whole brain, gray matter and white matter volumes were calculated using the FSL-tool Structural Image Evaluation, using Normalization of Atrophy (SIENAX)^{20,21}. For the determination of the subcortical hippocampus and basal ganglia volumes, the FMRIB's Registration and Segmentation Tool (FIRST) was used.

MRI scans were visualized using the freely available software Medical Imaging Processing, Analysis and Visualization (MIPAV). WMHs, CMBs and LIs were analyzed blinded to subject identity, sex, age and being offspring or partner by two independent reviewers. Discrepancies were re-analyzed in a consensus meeting with a third reviewer. WMHs were defined as areas within the cerebral white matter with increased signal intensity on both FLAIR and T2*-weighted images without mass effect. CMBs were defined as focal areas of signal void on T2-weighted images increasing in size on T2*-weighted imaged. Presence of LIs, defined as having a diameter >2 mm, was assessed on 3-D T1 weighted, FLAIR and T2-weighted images. The presence of CMBs and LIs was combined into one variable consisting of participants with either CMBs or LIs or both. Due to contraindications for MRI, data was available for 237 out of 297 (80%) participants. Most frequent reported contraindications were metal splinters, pacemaker and claustrophobia as was determined by application of the standard MRI patient questionnaire of the Leiden University Medical Center.

Statistical analysis

Continuous variables are presented as mean and standard deviation, non-Gaussian distributed variables as median and interquartile range, and categorical variables as number and percentage.

First, the association between cognitive and physical performance was assessed using linear regression analysis. Logistic regression analysis was used for the dichotomous outcome of the tandem stance test, i.e. participants being either unable or able to maintain 10 s of balance in tandem position. Results were adjusted for age, gender and education.

Second, linear regression analysis was used to assess the relationship between brain structure and cognitive performance and subsequently between brain structure and physical performance. Again, logistic regression analysis was used for the tandem stance test. All measures of brain structure were expressed as z-scores. For the basal ganglia volume, a composite z-score was calculated by averaging the z-scores of the nucleus accumbens, caudate nucleus, pallidum and putamen. Results were adjusted for age, gender and whole brain volume. An additional adjustment model was used in the analysis of the relationship between brain structure and physical performance including besides age, gender and whole brain volume also cognitive performance. For this analysis, a composite z-score of cognitive performance was calculated by averaging the z-scores of the 15-PLTi, 15-PLTd, abbreviated Stroop test trial 3 (multiplied by minus one because of the reverse direction of scoring compared to the other cognitive performance tests) and DSST.

The independent t-test and χ^2 test were used to assess whether the characteristics of participants with and without MRI data were significantly different. Because of the number of dependent variables within each of the comparisons that were investigated, i.e. the relationship between cognitive and physical performance, brain structure and cognitive performance and brain structure and physical performance, a Bonferroni correction was applied to avoid type I errors. P-values lower than 0.017 were considered statistically significant. All statistical analyses were performed with SPSS version 22.0 (IBM Corp., Amonk, NY, USA).

Results

Characteristics of the participants are shown in Table 1. Mean age (SD) of all participants was 65.4 (6.8) years.

Table 2 shows the association between cognitive and physical performance. According to memory function, participants with a worse performance on the immediate and delayed recall had a slower 4-meter walking speed. No associations were found for executive function or other physical domains.

Table 3 and 4 present the association between brain structure and cognitive and physical performance, respectively. No association was found between brain structure and cognitive performance. According to the different domains of physical performance, the presence of CMBs and LIs was associated with a slower 25-meter walking speed.

Table 5 shows that additional adjustment for cognitive performance in the association between brain structure and physical performance did not change the results. There were no differences between the participants with and without MRI data, except for weight and the prevalence of cardiovascular disease, which were both higher in the group without MRI data ($p=0.026$ and $p=0.021$, respectively).

Table 1 Characteristics of the participants.

	All (N=297)
Demographics	
Females, n (%)	150 (50.5)
Age, years	65.4 (6.8)
Education, years*	12 (10 - 15)
Anthropometrics	
Height, cm	172.4 (8.5)
Weight, kg	79.2 (14.1)
Comorbidities^a	
Diabetes mellitus, n (%)	18 (6.8)
Cardiovascular disease, n (%) [†]	79 (29.8)
Intoxications	
Users of alcohol, n (%) [†]	234 (79.1)
Former and/or current smokers, n (%)	201 (67.9)
Cognitive performance	
15-PLTi, correct pictures	30.1 (5.0)
15-PLTd, correct pictures*	11 (10 - 13)
Stroop time part 3, s*	46 (39 - 54)
DSST, correct answers	47.1 (10.6)
Physical performance	
Able to perform tandem stance, n (%)	286 (96.6)
Duration of the chair stand test, s	12.6 (2.4)
4-meter walking speed, m/s	1.13 (.20)
25-meter walking speed, m/s ^b	1.45 (.16)
Brain structure	
Whole brain volume, cm ^{3c}	1090 (92)
Gray matter volume, cm ^{3c}	542 (39)
White matter volume, cm ^{3c}	548 (61)
Hippocampal volume, cm ^{3c}	8.0 (.8)
Basal ganglia volume, cm ^{3c}	21.8 (2.2)
WMH volume, cm ^{3*d}	.50 (.083 - 2.2)
Presence of CMBs/LIs, n (%) ^c	37 (15.7)

Values are expressed as mean (standard deviation), unless otherwise indicated. *Values are expressed as median (interquartile range). ^aDefined as myocardial infarction, stroke and hypertension. [†]Using ≥ 1 units per week. Abbreviations: n, number; 15-PLTi and 15-PLTd, 15 Picture Learning Test immediate and delayed recall, respectively; DSST, Digit Symbol Substitution Test; WMH, white matter hyperintensity; CMBs, cerebral microbleeds; LIs, lacunar infarcts. Data available for ^an=265, ^bn=277, ^cn=237, and ^dn=211 participants.

Table 2 Association between cognitive and physical performance (N=297).

Cognitive performance	Tandem Stance ^a			Duration CST, s			4-meter walking speed ¹ , m/s			25-meter walking speed ^{1a} , m/s		
	OR	95% CI	p	β	95% CI	p	β	95% CI	p	β	95% CI	p
Memory function												
15-PLTi, # pictures	1.05	.92;1.20	.50	-.063	-.12;-.003	.040	.078	.025;.13	.004	-.0008	-.043;.041	.97
15-PLTd, # pictures	1.02	.73;1.43	.91	-.047	-.19;.092	.51	.17	.047;.29	.007	-.044	-.14;.053	.37
Executive function												
Stroop trial 3, s	1.01	.96;1.07	.65	.014	-.009;.036	.24	-.001	-.003;.001	.39	-.001	-.002;.001	.37
DSSST, # answers	1.0	.93;1.07	.91	-.020	-.050;.010	.18	.001	-.001;.004	.27	.001	-.001;.003	.21

Abbreviations: OR, odds ratio; CI, confidence interval; p, p-value; β , estimate; CST, chair stand test; 15-PLTi and 15-PLTd, 15 Picture Learning Test immediate and delayed recall, respectively; #, number; DSSST, Digit Symbol Substitution Test. Associations were assessed using linear regression and adjusted for calendar age, gender and education. ¹Logistic regression was used with 0 unable and 1 able to perform the tandem stance. ^{1a} β and 95% CI are expressed per 10 units of cognitive performance test. ^an=277 participants. Bold indicates statistically significant p-values after Bonferroni correction (p<0.017).

Table 3 Association between brain structure and cognitive performance (N=237).

Brain structure [†]	15-PLTi, # pictures			15-PLTd, # pictures			Stroop trial 3, s			DSSST, # answers		
	β	95% CI	p	β	95% CI	p	β	95% CI	p	β	95% CI	p
Cortical												
Gray matter volume	.75	-.39;1.89	.20	-.13	-.63;.38	.63	.70	-2.42;3.83	.66	-.41	-2.88;2.05	.74
White matter volume	-.71	-1.69;.27	.15	.11	-.32;.54	.62	-.85	-3.54;1.84	.53	.36	-1.76;2.48	.74
Subcortical												
Hippocampal volume	-.064	-.76;.63	.86	-.13	-.43;.17	.40	-1.31	-3.19;.58	.17	-.42	-1.90;1.07	.58
Basal ganglia volume	-.26	-.94;.43	.47	-.22	-.52;.075	.14	.31	-1.58;2.20	.75	-.84	-2.34;.66	.27
CSVD												
WMH volume ^a	-.037	-.71;.64	.91	-.021	-.32;.28	.89	.72	-1.10;2.36	.44	-.37	-1.77;1.04	.61
Presence of CMBs/LIs [‡]	-.16	-1.73;1.42	.84	.31	-.38;1.0	.38	-1.72	-6.04;2.59	.43	2.78	-62.6;18	.11

Abbreviations: β , estimate; CI, confidence interval; p, p-value; 15-PLTi and 15-PLTd, 15 Picture Learning Test immediate and delayed recall, respectively; #, number; DSSST, Digit Symbol Substitution Test; CSVD, cerebral small vessel disease; WMH, white matter hyperintensity; CMBs, cerebral microbleeds; LIs, lacunar infarcts. Associations were assessed using linear regression adjusted for age, gender and whole brain volume (standardized for skull size). [†]Brain volumes are standardized for skull size and expressed as z-scores. WMH volume is transformed to the natural logarithm and expressed as z-score. [‡]0 is defined as reference group having no CMBs or no LIs. ^an=211 participants. P-values <0.017 considered as statistically significant after Bonferroni correction.

Table 4 Association between brain structure and physical performance (N=237).

Brain structure [†]	Tandem Stance [*]			Duration CST, s			4-meter walking speed, m/s			25-meter walking speed ^b , m/s		
	OR	95% CI	p	β	95% CI	p	β	95% CI	p	β	95% CI	p
Cortical												
Gray matter volume	2.21	.48;10.2	.31	-.10	-.70;.49	.73	.022	-.029;.073	.40	.030	-.010;.069	.15
White matter volume	.34	.10;1.10	.072	.13	-.38;.64	.62	-.019	-.062;.025	.40	-.028	-.062;.007	.11
Subcortical												
Hippocampal volume	2.36	.96;5.84	.062	-.30	-.66;.066	.11	.033	.002;.063	.035	.010	-.015;.034	.43
Basal ganglia volume	1.40	.60;3.27	.44	.11	-.25;.47	.54	-.017	-.047;.014	.29	-.015	-.039;.009	.21
CSVD												
WMH volume ^a	1.85	0.89;3.82	.098	.013	-.32;.35	.94	.005	-.024;.034	.73	-.023	-.045;-.0002	.048
Presence of CMBs/LIs [‡]	2.98	.29;30.3	.36	-.039	-.85;.78	.93	-.080	-.15;-.011	.024	-.11	-.17;-.060	<.001

Abbreviations: OR, odds ratio; CI, confidence interval; p, p-value; β , estimate; CST, chair stand test; CSVD, cerebral small vessel disease; WMH, white matter hyperintensity; CMBs, cerebral microbleeds; LIs, lacunar infarcts. Associations were assessed using linear regression adjusted for age, gender and whole brain volume (standardized for skull size). ^{*} Logistic regression was used with 0 unable and 1 able to perform the tandem stance. [†] Brain volumes are standardized for skull size and expressed as z-scores. WMH volume is transformed to the natural logarithm and expressed as z-score. [‡]0 is defined as reference group having no CMBs or no LIs. ^an=211 and ^bn=220 participants. Bold indicates statistically significant p-values after Bonferroni correction (p<0.017).

Table 5 Association between brain structure and physical performance, adjusted additionally for cognitive performance (N=237).

Brain structure [†]	Tandem Stance [*]			Duration CST, s			4m walking speed, m/s			25m walking speed ^b , m/s		
	OR	95% CI	p	β	95% CI	p	β	95% CI	p	β	95% CI	p
Cortical												
Gray matter volume	2.25	.49;.10.2	.30	-.10	-.69;.49	.74	.023	-.028;.074	.37	.030	-.010;.069	.15
White matter volume	.33	.10;.1.08	.67	.13	-.38;.64	.63	-.020	-.063;.024	.38	-.028	-.062;.007	.11
Subcortical												
Hippocampal volume	2.39	.96;.5.95	.062	-.30	-.66;.064	.11	.033	.003;.063	.034	.010	-.015;.034	.43
Basal ganglia volume	1.42	.61;.3.34	.42	.086	-.27;.44	.64	-.015	-.045;.016	.35	-.015	-.039;.009	.21
CSVD												
WMH volume ^a	1.88	.90;.3.94	.094	.006	-.33;.34	.97	.006	-.023;.034	.69	-.023	-.046;-.0002	.048
Presence of CMBs/LIs [‡]	2.93	.29;.30.1	.37	.004	-.81;.82	.99	-.084	-.15;-.015	.017	-.11	-.17;-.061	<.001

Abbreviations: OR, odds ratio; CI, confidence interval; p, p-value; β , estimate; CST, chair stand test; CSVD, cerebral small vessel disease; WMH, white matter hyperintensity; CMBs, cerebral microbleeds; LIs, lacunar infarcts. Associations were assessed using linear regression adjusted for age, gender, whole brain volume (standardized for skull size) and cognitive performance expressed as composite z-score. [†]Logistic regression was used with 0 unable and 1 able to perform the tandem stance. ^aBrain volumes are standardized for skull size and expressed as z-scores. WMH volume is transformed to the natural logarithm and expressed as z-score. [‡]0 is defined as reference group having no CMBs or no LIs. ^an=211 and ^bn=220 participants. Bold indicates statistically significant p-values after Bonferroni correction (p<0.017).

Discussion

In this study population of middle-aged to older adults, poor memory function was associated with a slower 4-meter walking speed. The presence of CMBs and LIs was associated with a slower 25-meter walking speed. No association was found between brain structure and cognitive performance, and the relationship between brain structure and physical performance did not change after adjustment for cognitive performance.

The association between cognitive and physical performance has been confirmed by several studies^{1,2,22,23}. However, these studies especially show the role of executive function in gait performance commonly illustrated by the performance of dual-tasks^{1,24-27}. The association between memory function and physical performance has been shown less frequently; although the incorporation of memory processes in physical performance has been emphasized previously as well^{11,28,29}. The association of memory function with the 4-meter walking speed and not with the 25-meter walking speed, suggests that specifically the initiation of movements relates to memory processes. In the 4-meter walk, walking speed was measured from starting position including the initiation phase instead of the steady state assessment of walking speed in the 25-meter walk. These findings are supported by a previous study in elderly outpatients, showing largest effect sizes of the association between cognitive performance and walking speed for the 4-meter walk compared to a steady state 10-meter walk and a 6-minute walk³⁰.

Among the different physical domains that were assessed, i.e. the ability to maintain standing balance, the ability to rise from a chair and walking speed over a short and long distance, brain structure was specifically associated with walking speed. This emphasizes the role of walking speed as important indicator of overall health status^{31,32}. Of the two different walking tests that were performed, the 25-meter walking speed and not the 4-meter walking speed was associated with brain structure, i.e. the presence of CMBs and LIs. This specific association might be explained by the dependence of longer distance walks on the cardiovascular determined endurance factor, considering that the presence of CMBs and LIs is accelerated by cardiovascular disease and vascular risk factors^{30,33}. Unless the consistent associations of cortical and subcortical brain volumes with walking speed found in literature⁶, no association was found for each of the brain volumes in this study. These results might be explained by differences in calendar age between the study populations. Most studies showing a positive association between brain structure and walking speed are in slightly older populations (mean age of seventy years and older)⁶, while the null results of this study are in accordance with a previous study in a comparable population of healthy middle-aged to older adults walking at preferred speed over a long distance³⁴.

The relationship between brain structure and physical performance did not change after adjustment for cognitive performance, which is consistent with the fact that we did not find an association between brain structure and cognitive performance. Previously, neither an association of measures of brain microstructure, i.e. mean magnetization transfer ratio (MTR), MTR histogram peak height, fractional anisotropy and mean diffusivity, with cognitive performance was found in this study population³⁵. The relatively young age might explain these results if we compare them with the positive associations found in studies in older community-dwelling individuals without cognitive impairment^{9,36,37}. Thereby, the measures used for the assessment of the relation between brain structure and cognitive performance might be not sensitive enough for this population⁹. Future studies focusing on which measures are most sensitive for these non-clinical populations might provide more insight into this. The association of the presence of CMBs and LIs with a slower 25-meter walking speed independent of cognitive performance suggests that the influences of brain structure and cognitive performance on physical performance are two independent processes. This is supported by the positive association found between memory function and 4-meter walking speed, while no association was found of the hippocampal volume, known to play an important role in memory function^{9,38}, with 4-meter walking speed. These results therefore emphasize the importance of identifying possible underlying mechanisms of physical performance in order to be able to develop targeted therapies. Longitudinal studies covering a broader age range are needed to further explore this and to finally get insight into the optimal timing with respect to prevention and disease progression.

One of the strengths of this study is the availability of data on cognitive and physical performance and for 80% of the participants on brain structure with all measurements of one participant performed on the same day. This enabled to get insight into the role of cognitive performance and brain structure on physical performance. The different cognitive and physical domains that were assessed enabled to specify this even further. The study population consisting of middle-aged to older adults enhanced our understanding of changes that are already observable from middle-age in the absence of overt diseases. As a result of this age range and good health status of the participants, the variation among participants able and unable to performance the tandem stance test was very low. This could have led to an underestimation of the associations of cognitive performance and brain structure with standing balance. Future studies are needed including a more demanding standing condition, for example with eyes closed, to further investigate the association of cognitive performance and brain structure with standing balance. Another limitation is the availability of MRI data in 80% of the participants due to contraindications for MRI. The higher prevalence of cardiovascular disease in the group of participants without MRI data is in concordance with our expectations because of the contraindications for MRI. Exclusion of these participants could have led to an underestimation of the results, in specific for the association of the presence of CSVD with 25-meter walking speed.

In conclusion, the presence of CMBs and LIs is associated with walking speed in middle-aged to older adults, independent of cognitive performance. This supports that in this age range the influences of brain structure and cognitive performance on physical performance are two independent processes. Identifying the possible influence of these underlying mechanisms of physical performance is of clinical relevance in order to be able to develop targeted therapies with optimal timing to maintain physical performance with advancing age.

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Low cognitive status is associated with a lower ability to maintain standing balance in elderly outpatients

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Abstract

Background: Evidence is emerging that cognitive performance is involved in maintaining balance and thereby involved in falls in the elderly. The aim of this study was to investigate the association of cognitive status with measures of standing balance in elderly outpatients.

Methods: In a cross-sectional study, 197 community-dwelling elderly (mean age (SD) 81.9 (7.1) years) referred to a geriatric outpatient clinic were included and subsequently dichotomized into a group with low and normal cognitive status based on cut-off values of the Mini-Mental State Examination, Montreal Cognitive Assessment and Visual Association Test. The ability to maintain standing balance as well as the Center of Pressure (CoP) movement were assessed during 10 s of side-by-side, semi-tandem and tandem stance with eyes open and eyes closed. Logistic and linear regression were used to examine the association between cognitive status and measures of standing balance adjusted for age, gender and highest completed education.

Results: Low cognitive status in elderly outpatients was associated with a lower ability to maintain 10 s of balance in side-by-side stance with eyes closed (Odds Ratio (OR) (95% CI): 3.57 (1.60;7.97)) and in semi-tandem stance with eyes open and eyes closed (OR (95% CI): 3.93 (1.71;9.00) and OR (95% CI): 2.32 (1.11;4.82), respectively). Cognitive status was not associated with CoP movement.

Conclusion: Low cognitive status associates with a lower ability to maintain standing balance in more demanding standing conditions in elderly outpatients. This may have implications for routine geriatric screening strategies and interpretation of results of either standing balance or cognitive tests.

Introduction

Impaired standing balance is one of the major complaints reported by elderly to physicians and is strongly related with falls^{1,2}. Standing balance is required for most daily living activities. Impaired standing balance may easily result in serious medical, physical, emotional, and social consequences, including loss of independence and social isolation^{1,3}. Understanding underlying determinants of impaired standing balance enables early detection and the development of tailored intervention.

Standing balance depends on the functioning of multiple organ systems, like the sensory (vestibular, proprioceptive and visual), musculoskeletal, nervous and cardiovascular system⁴⁻⁶. Moreover, it becomes more and more evident that standing balance relies on high-order cognitive performance controlled by the cerebral cortex instead of being a fully automatic process⁷⁻⁹. The involvement of the cerebral cortex on standing balance may be mediated by corticospinal loops and communication with the cerebellum and basal ganglia¹⁰. Involvement may grow with advanced age as neuroimaging studies showed that elderly exhibit more elaborate brain activation compared to young controls during the performance of fine motor tasks¹¹⁻¹⁴. Deterioration of the multiple organ systems with advanced age and diseases for which must be compensated may result in increased involvement of the cerebral cortex¹⁵. Changes in the white matter of the cortex, like leukoaraiosis and periventricular white matter change, are frequently found in dementia. Those changes may result in less ability to compensate and therefore could result in impaired balance and mobility decline¹⁶⁻¹⁸.

Previous cross-sectional studies investigated the association between cognitive status with standing balance in relatively homogeneous and pre-specified study populations of middle-aged to older adults. These studies showed that a lower cognitive status is associated with a lower ability to maintain standing balance¹⁹⁻²² and with increased Center of Pressure (CoP) movement^{15,23,24}. CoP movement is a measure for the steadiness of the body while maintaining balance and is assessed using a force plate, which measures the ground reaction forces. In general, an increased CoP movement is assumed to reflect impaired standing balance. However, the association of cognitive status with standing balance remains to be established in a clinically relevant population.

In this study, we assessed the association of cognitive status with the ability to maintain standing balance and Center of Pressure movement in a population of community-dwelling elderly referred to a geriatric outpatient clinic, with its typical variety of comorbidities, use of medication and mobility impairments. Elderly outpatients with low cognitive status were expected to exhibit worse standing balance, as reflected by less ability to maintain standing balance and increased CoP movement, compared with patients with normal cognitive status.

Methods

Study setting

The study population consisted of community-dwelling elderly (n=207) referred to a geriatric outpatient clinic in a middle-sized teaching hospital (Bronovo Hospital, The Hague, The Netherlands) between March 2011 and January 2012 for a comprehensive geriatric assessment (CGA)²⁵. CGA was performed by trained nurses and medical staff during a 2-hour visit. All measurements were performed in the same conditions, in a quiet room and in a fixed order; first cognitive status tests, second standing balance tests. Therefore, the trained nurses and medical staff were aware of the cognitive status of the patient. Measurements took place between 9 am and 4 pm during the day. The study was reviewed and approved by the institutional review board of the Leiden University Medical Center (Leiden, the Netherlands). Because this research is based on regular patient care, the need for individual informed consent was waived. Ten patients (4.8%) were excluded from the analyses due to missing data, leaving 197 patients.

Elderly outpatient characteristics

Extensive characterization of the population for validity purposes was performed as described below. Patients were asked to complete questionnaires on marital status, living arrangements, highest completed education, current smoking and alcohol use. Body mass index (BMI) was assessed by measuring weight and height. Information on diseases and use of medication was extracted from medical records. Multimorbidity was defined as the presence of two or more diseases, including chronic obstructive pulmonary disease, heart failure, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson's disease, (osteo)arthritis, transient ischemic attack and stroke. Depressive symptoms were assessed by the Hospital Anxiety and Depression Scale (HADS)²⁶; a depression subscore higher than 8 out of 21 points indicated depressive symptoms. Physical functioning was assessed by handgrip strength, preferred gait speed during a steady state 10-meter walk and the Short Physical Performance Battery (SPPB)²⁷. Furthermore, patients were asked to complete questionnaires on maximal daily physical activity, experienced falls during the previous 12 months and use of walking aids.

Cognitive status

Global cognitive status was assessed by Mini-Mental State Examination (MMSE)²⁸ and Montreal Cognitive Assessment (MoCA)²⁹, assessing executive function, arithmetic, memory and orientation in time and space. MMSE and MoCA scores both range from 0 to 30 points. One point was added to the total MoCA score if the highest completed education was at low or middle level (comparable with <12 years of education). Version A of the Visual Association Test³⁰, in which a maximum number of six objects can be recalled, was used to assess recollecting memory. VAT scores range from 0 to 6 points. For all cognitive

tests, lower scores indicate lower cognitive status. The tests scores of the three cognitive tests were combined to form two groups of patients, i.e. a group with low and a group with normal cognitive status. Low cognitive status was defined as scoring below clinically used cut-off values (MMSE <24 points, MoCA <23 points and VAT <3 points³⁰⁻³²) in minimal two out of three cognitive tests. If only two cognitive tests were available (n=40), low cognitive status was defined as scoring below clinically used cut-off values in minimal one cognitive test. The group including all other cases, i.e. scoring equal to or above the clinically used cut-off points, was defined as the normal cognitive status group. Patients with only one (n=1) or no cognitive tests (n=1) were excluded.

Standing balance

Ability to maintain standing balance

The ability to maintain balance was measured in six standing conditions, i.e. three different standing positions characterized by a progressive narrowing of the base support both with the eyes open and eyes closed. Patients wore non-slip socks and were asked to maintain standing balance for 10 s without moving their feet, first with their feet as closely together as possible (side-by-side stance), second with the medial side of the heel of one foot touching the big toe of the other foot (semi-tandem stance) and third with both feet in line while the heel of one foot touched the toes of the other foot (tandem stance). A maximum of three trials for each condition was allowed in case standing balance was lost prematurely. When the patients were not able to maintain standing balance in a specific position within the three trials allowed, the consecutive more demanding condition was not performed. All standing conditions were performed in a fixed order, starting with the measurements with eyes open, as part of the SPPB, and subsequently with eyes closed. Six of the 197 patients (3.0%) did not attempt the standing positions with eyes closed due to lack of time or lack of motivation, leaving 191 patients for analyses of standing balance positions with eyes closed.

Center of Pressure movement

All standing conditions were performed on a triangular 6 degrees of freedom force plate (Forcelink BV, Culemborg, The Netherlands) to measure CoP movement during 10 s. Only successful trials (i.e. completion of 10 s of maintaining standing balance) were considered for further analysis. Due to technical problems (n=18) and unknown reasons (n=29), CoP movement was available for n=136 patients.

As age-related differences have been shown to be most pronounced in medio-lateral (ML) direction³³ and impaired ability to control balance in this direction is well associated with falls³⁴, only CoP movement in ML direction was included in the analysis. Time series of CoP movement in ML direction were used to calculate five CoP parameters, i.e. the mean amplitude, the amplitude variability, the range, the mean velocity and the velocity variability. CoP parameters were transformed into z-scores, resulting in standardized CoP

parameters with a mean of 0 and standard deviation of 1. Averaging those z-scores resulted in a composite score of the CoP movement in ML direction³³.

Statistical analysis

Continuous variables with Gaussian distribution are presented as mean and standard deviation (SD), otherwise as median and interquartile range (IQR) or number and percentage. Independent T-tests, Chi Square tests and Mann-Whitney tests were used to assess whether characteristics of both groups were significantly different. Logistic regression analysis was used to assess the association of cognitive status with the ability to maintain standing balance with adjustments for age, gender and highest completed education. The association of cognitive status with CoP movement was assessed using linear regression analysis with the same adjustments. Furthermore, a subgroup analysis was performed in all patients with available data of the HADS depression score (n=121), in which we additionally adjusted for depressive symptoms. The statistical package SPSS for Windows version 20.0 (SPSS Inc, Chicago, USA) was used for analyzing the data. P-values below 0.05 were considered statistically significant. Graphs were made with GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, USA).

Results

The characteristics of the elderly outpatients are presented in Table 1 together with the characteristics stratified for low and normal cognitive status. Mean age (SD) of the patients was 81.9 (7.1) years. Measures of physical functioning, i.e. handgrip strength, gait speed and SPPB score, were lower in the low compared to the normal cognitive status group. The number of self-reported fall incidents in the previous 12 months was higher in the low cognitive status group.

Figure 1 shows the percentage of elderly outpatients able to maintain balance in different standing conditions stratified for low and normal cognitive status. Ability to maintain balance decreased in both groups with increasing difficulty of standing condition. Less than 2% of the patients were able to maintain tandem stance with eyes closed.

The CoP movement in ML direction is shown in Supplementary Table 1. The CoP parameters, used to calculate the CoP composite scores, were higher in more difficult standing conditions.

Cognitive status and standing balance

Ability to maintain standing balance

The association between cognitive status and the ability to maintain standing balance is given in Figure 2. Patients in the low cognitive status group were less likely to be able to maintain standing balance in the semi-tandem stance with eyes open (Odds Ratio (OR)

(95% CI): 3.93 (1.71;9.00)) and in the side-by-side and semi-tandem stance with eyes closed (OR (95% CI): 3.57 (1.60;7.97) and OR (95% CI): 2.32 (1.11;4.82)) compared with patients in the normal cognitive status group. The odds ratio was higher for side-by-side stance with eyes closed compared with semi-tandem stance with eyes closed. Additional adjustment for depressive symptoms did not change the results (data not shown).

Table 1 Elderly outpatient characteristics.

	All (N=197)	Cognitive status		p
		Low (N=56)	Normal (N=139)	
Socio-demographics				
Age, years	81.9 (7.1)	83.0 (7.5)	81.5 (6.9)	0.19
Men, n (%)	78 (39.6)	19 (33.9)	58 (41.7)	0.31
Widowed, n (%)	80 (41.5)	23 (41.8)	56 (41.2)	0.94
Independent living, n (%)	154 (79.4)	40 (72.7)	113 (82.5)	0.13
Highest completed education, n (%)				0.44
Low	48 (24.7)	17 (31.5)	31 (22.5)	
Middle	62 (32.0)	18 (33.3)	42 (30.4)	
High	55 (28.4)	12 (22.2)	43 (31.2)	
University	29 (14.9)	7 (13.0)	22 (15.9)	
Current smoking, n (%) ^a	22 (16.2)	4 (10.5)	18 (18.8)	0.25
Excessive alcohol use, n (%) [*]	8 (4.1)	1 (1.9)	7 (5.1)	0.32
Health characteristics				
BMI, kg/m ^{2b}	25.8 (4.5)	25.8 (4.0)	25.7 (4.7)	0.90
Multimorbidity, n (%) ^{†b}	95 (50.3)	22 (40.0)	72 (54.5)	0.07
Median number of medication (IQR) ^b	5 (3-7)	5 (3 - 7)	5 (3 - 7)	0.45
HADSd > 8 points, n (%) ^{‡c}	28 (23.1)	9 (25.7)	19 (22.6)	0.72
Physical functioning				
Handgrip strength, kg	26.1 (8.2)	24.1 (8.4)	27.0 (8.0)	0.028
Gait speed, m/s ^{§b}	0.87 (0.29)	0.73 (0.32)	0.93 (0.26)	<0.001
Median SPPB, points (IQR)	7 (5-10)	6 (4 - 8)	8 (6 - 10)	<0.001
Indoor daily physical activity, n (%)	31 (16.0)	6 (10.7)	25 (18.1)	0.20
Fall incident previous 12 months	127 (64.5)	45 (80.4)	80 (57.6)	0.003
Use of walking aid	108 (55.1)	36 (64.3)	71 (51.4)	0.10
Cognitive status				
Median MMSE, points (IQR)	27 (24 - 29)	22 (19 - 24)	28 (27 - 29)	<0.001
Median MoCA, points (IQR) ^d	24 (20 - 26)	18 (15 - 20)	25 (23 - 27)	<0.001
Median VAT, points (IQR)	5 (3 - 6)	2 (1 - 4)	6 (5 - 6)	<0.001

All parameters are presented as mean with standard deviation unless indicated otherwise. Abbreviations: BMI, body mass index; HADSd, depression subscore of the Hospital Anxiety and Depression Scale; IQR, interquartile range; SPPB, Short Physical Performance Battery; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; VAT, Visual Association Test. ^{*}Defined as >14 units per week for females or >21 units per week for males. [†]Present in case of two or more diseases, including chronic obstructive pulmonary disease, heart failure, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson's disease, (osteo)arthritis, transient ischemic attack and stroke. [‡]Present with a depression subscore >8 on the Hospital Anxiety and Depression Scale. [§]Preferred gait speed during a steady state 10-meter walk. Data available in ^an=136, ^bn=190, ^cn=121 and ^dn=158.

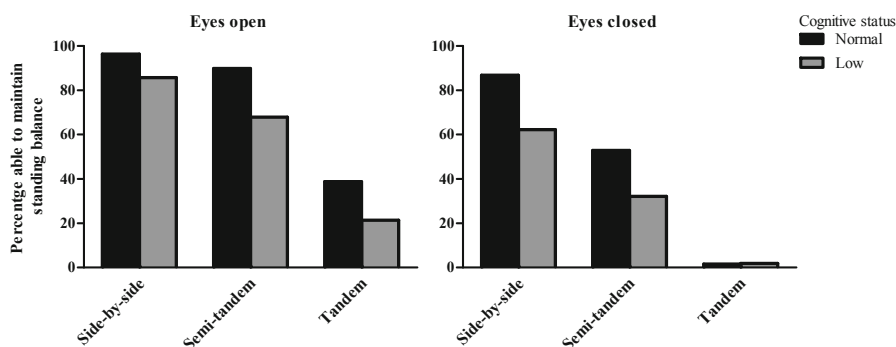


Figure 1 Percentage of elderly outpatients able to maintain balance in different standing conditions, i.e. side-by-side, semi-tandem and tandem stance with eyes open and eyes closed. Results are stratified for low and normal cognitive status.

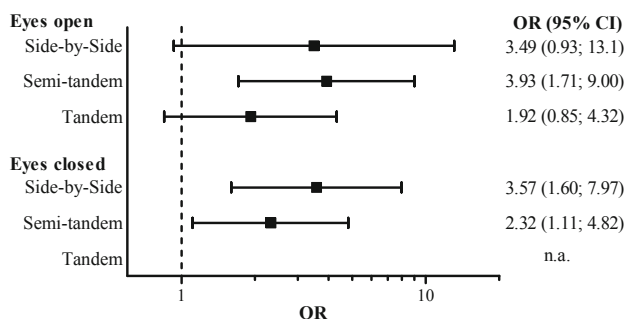


Figure 2 Forest plot of the association between cognitive status and the ability to maintain balance in different standing conditions, i.e. side-by-side, semi-tandem and tandem stance with eyes open and eyes closed. The low and normal cognitive status groups are represented by 0 and 1, respectively. The ability to maintain standing balance is defined as 0 not being able to maintain standing balance and 1 being able to maintain standing balance. Results are presented in odds ratios and 95% confidence intervals adjusted for age, gender and highest completed education. Abbreviations: OR, odds ratio; CI, confidence interval; n.a., not applicable, number of elderly outpatients able to maintain balance in the standing condition is <5.

Table 2 Association between cognitive status and Center of Pressure movement in medio-lateral direction in different standing conditions.

	Side-by-side [†]			Semi-tandem [‡]			Tandem [§]		
	β	SE	p	β	SE	p	β	SE	p
Cognitive status*									
Eyes open	-0.02	0.18	0.91	0.17	0.21	0.43	0.29	0.35	0.41
Eyes closed	0.35	0.19	0.07	0.29	0.29	0.32	n.a.		

*Cognitive status with 0 representing the group of elderly outpatients with low cognitive status and 1 the group with normal cognitive status based on clinically used cut-off values. Dependent variable: Center of Pressure composite score in medio-lateral direction. Results are adjusted for age, gender and highest completed education. Abbreviations: β , estimate; SE, standard error; p, p-value; n.a., not applicable, number of elderly outpatients able to maintain balance in the standing condition is <5. Data available in [†]n=135 and n=116, [‡]n=119 and n=72, [§]n=56 and n=2 for eyes open and closed, respectively.

Center of Pressure movement

Table 2 shows the results of the association of cognitive status with CoP movement in ML direction. The association was not statistically significant for each standing position, both with eyes open and eyes closed. The association between cognitive status and CoP movement in ML direction during tandem stance with eyes closed was not applicable due to a low number of patients who could perform this standing condition.

Discussion

The aim of this study was to establish the association of cognitive status with standing balance in a clinically relevant population of elderly outpatients. We found that low cognitive status was associated with a lower ability to maintain standing balance. Cognitive status was not associated with CoP movement in ML direction.

Our findings are in concordance with previous studies showing a cross-sectional association between low cognitive status and a lower ability to maintain standing balance in middle-aged to older adults in which the study population is further specified on e.g. cognitive or mobility impairments and the presence of comorbidities¹⁹⁻²². In this study, we showed that this relation is also present in community-dwelling elderly visiting the geriatric outpatient clinic with common comorbidities and mobility impairments. In this population, deterioration of the different organ systems involved in standing balance, i.e. the sensory, musculoskeletal, nervous and cardiovascular system, is very likely. The presence of the association between cognitive status and the ability to maintain standing balance supports the important role of the brain in controlling standing balance instead of being a fully automatic process⁷⁻⁹. Furthermore, it emphasizes the clinical relevance of measuring standing balance in patients with low cognitive status. Especially because of the large impact of impaired standing balance on most of daily living activities and the strong relation of impaired standing balance with falls^{1,2}. The latter is also supported by this study showing a higher reported fall incidence over the previous 12 months in the low compared to the normal cognitive status group. No differences in maximal daily physical activity were found between groups. Although, in this case it is difficult to distinguish cause and effect, as less daily activity could be caused by impaired standing balance, but less daily activity could also cause impaired standing balance.

The association between cognitive status and the ability to maintain standing balance was found in 3 of the 6 standing conditions, namely side-by-side stance with eyes closed and semi-tandem stance with eyes open and eyes closed. This could be explained by the increasing difficulty of the standing conditions, i.e. reducing the base of support and eliminating visual information. More difficult standing conditions put higher demands on balance control. Aforementioned standing conditions will therefore be more difficult for patients with a low cognitive status compared with patients with a normal cognitive status.

No association between cognitive status and the ability to maintain balance in tandem stance with eyes closed could be found, as only four patients were able to maintain balance during this condition.

No association was found between cognitive status and CoP movement. The inconsistency in the association of cognitive status with the ability to maintain standing balance and CoP movement emphasizes that both outcome parameters of standing balance assess different properties. The ability to maintain standing balance is a measure of standing balance referring to whether someone is able to stay upright or not, whereas CoP movement is a more indirect measure of standing balance referring to the steadiness of the body while standing on a force plate³⁵. A possible explanation for the absence of an association of cognitive status with CoP movement, is that data on CoP movement is only available from patients who were able to maintain 10 s of standing balance, which may have led to an underestimation of the association between cognitive status and CoP movement. Another possible explanation is the heterogeneity of the study population, especially the presence of more than two diseases in more than 50% of the patients and the deterioration of multiple systems involved in standing balance⁴. As each underlying system could have a different effect on CoP movement, this may interfere with the association between cognition and CoP movement on population level³⁶. Further research into the assessment of CoP movement is still needed to get insight into the causal underlying mechanisms of impaired standing balance, which are yet unknown.

One of the strengths of this study is the study population consisting of community-dwelling elderly referred to a geriatric outpatient clinic. Because no exclusion criteria were used, the study population represents an average population encountered in common geriatric practice. This makes the results of this study highly relevant in clinical practice. Measuring standing balance in patients with low cognitive status and, the other way around, measuring cognitive status in patients with impaired standing balance will have an added value in clinical care. Furthermore, the combined assessment of the ability to maintain standing balance, as part of the SPPB, and CoP movement enables to get insight into the clinical utility of both measures. A limitation of the study is that CoP movement was measured during a relatively short time interval of 10 s and data of only one successful trial was available, while previous studies recommend to measure CoP movement more than once and during a longer time period^{35,37}. However, in clinical practice and in a population of elderly outpatients it is likely that this it is not feasible due to time limit and fatigue. The cross-sectional design of the present analysis prevents to study causality.

In conclusion, low cognitive status is associated with a lower ability to maintain balance for 10 s in more demanding standing conditions in elderly outpatients. This indicates the clinical relevance of measuring standing balance in patients encompassing those with low cognitive status in routine geriatric screening. Regarding interpretation, in patients with

impaired standing balance the possibility of low cognitive status must be considered and, the other way around, in case of poor performance on cognitive tests the possibility of impaired standing balance must be considered. We could not establish an additional value of assessment of CoP movement in routine geriatric assessment as we found low cognitive status not to be associated with CoP movement. A next step would be to focus on clustering of phenotypes and defining risk populations, which will be of clinical added value and will allow to investigating causality. This obviously requires large study sample sizes.

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Supplementary material

Supplementary Table 1 Center of Pressure (CoP) movement, represented by CoP parameters, within elderly outpatients able to maintain different standing positions with eyes open and eyes closed in medio-lateral direction.

	Side-by-side [*]	Semi-tandem [†]	Tandem [‡]
Eyes open			
Mean amplitude, cm	0.60 (0.02)	0.72 (0.03)	0.72 (0.03)
Range, cm	3.51 (0.13)	4.25 (0.18)	3.92 (0.17)
Mean velocity, cm/s	4.09 (0.10)	4.78 (0.13)	5.41 (0.21)
Amplitude variability, cm	0.75 (0.03)	0.91 (0.04)	0.88 (0.04)
Velocity variability, cm/s	5.70 (0.14)	6.76 (0.23)	7.55 (0.28)
Eyes closed			
Mean amplitude, cm	0.85 (0.03)	1.03 (0.04)	
Range, cm	4.86 (0.18)	5.64 (0.23)	
Mean velocity, cm/s	5.67 (0.15)	6.76 (0.26)	n.a.
Amplitude variability, cm	1.06 (0.04)	1.27 (0.05)	
Velocity variability, cm/s	7.88 (0.20)	9.33 (0.37)	

Data are given in mean with standard error. Abbreviations: n.a., not applicable, number of elderly outpatients able to maintain balance in the standing condition is <5. Data available in ^{*}n=136 and n=119 and [†]n=120 and n=75 for eyes open and closed, respectively and [‡]n=56 for eyes open.

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Walking speed in elderly outpatients depends on the assessment method

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Abstract

Background: Walking speed is shown to be an important indicator of health status and function in older adults and part of the comprehensive geriatric assessment in clinical practice. The present study aimed to assess the influence of different assessment methods on walking speed and its association with key aspects of poor health status, i.e. the presence of low cognitive performance and cardiopulmonary disease.

Methods: In 288 community-dwelling elderly (mean age 82.2 ± 7.1 years) referred to a geriatric outpatient clinic, walking speed was assessed with the 4-meter, 10-meter and 6-minute walking test.

Results: Mean walking speed assessed with the 10-meter walking test was higher compared to the 4-meter and 6-minute walking test (mean difference (95% CI) 0.11 (0.10; 0.13) m/s and 0.08 (0.04; 0.13) m/s, respectively). No significant difference was found in walking speed assessed with the 4-meter compared to the 6-minute walking test (mean difference (95% CI) -0.03 (-0.08; 0.03) m/s). ICCs showed excellent agreement of the 4-meter with the 10-meter walking test and fair to good agreement of the 6-minute with the 4-meter as well as 10-meter walking test. The presence of low cognitive performance was negatively associated with walking speed, with the highest effect size for the 4-meter walking test. The presence of cardiopulmonary disease was negatively associated with walking speed as well, with the highest effect size for the 6-minute walking test.

Conclusions: In the clinically relevant population of elderly outpatients, walking speed and its interpretation depends on assessment method, which therefore cannot be used interchangeably in clinical practice.

Introduction

Walking underlies many physical functions and reflects the interaction of several underlying systems, such as the central and peripheral nervous system, sensory systems, muscles, bones and joints, and the cardiopulmonary system¹. A dysfunction in any system may slow walking speed. Therefore, walking speed is an important indicator of health status and function and can be used as a ‘vital sign’²⁻⁴. It has been shown that walking speed associates with aspects of poor health status or outcomes in older adults, such as mortality⁵⁻⁸, mobility impairment^{7,9,10}, falls^{8,11}, presence of cognitive impairment^{2,13} and cardiopulmonary diseases^{7,14-16}, hospitalization and nursing home placement^{5,8,11,17}. Cut-off values for walking speed are used for prediction of aforementioned health outcomes and underpin clinical decision making.

Walking speed is often measured in clinical practice as part of a comprehensive geriatric assessment (CGA)¹⁸ and in clinical research¹⁹. It is a quick and easy measure and is not limited to specific equipment. Furthermore, it is a valid, sensitive and specific measure with high interrater and test-retest reliability²⁰⁻²³. Currently, there are many methods to assess walking speed varying in pace (i.e. normal or as fast as possible), static or dynamic start and walking distance or time. Previous research showed conflicting results regarding methodologically induced variance in assessed walking speed in elderly^{24,25}. This hampers comparison of different studies and may affect clinical interpretation of walking speed^{23,26}.

In this study, we assessed the influence of different assessment methods on walking speed in a clinically relevant population of community-dwelling elderly referred to a geriatric outpatient clinic. Walking tests varied in distance or time and static or dynamic start. Furthermore, we examined the association of walking speed assessed by different methods with the presence of low cognitive performance and cardiopulmonary disease as key aspects of poor health status influencing walking speed.

Methods

Setting

This cross-sectional study included 299 community-dwelling elderly referred to a geriatric outpatient clinic in a middle-sized teaching hospital (Bronovo Hospital, The Hague, the Netherlands) for a CGA between October 2010 and January 2012. CGA was performed during a 2-hour visit including questionnaires and measurements of physical and cognitive performance. Trained nurses or medical staff performed all tests. Medical charts were evaluated retrospectively. As this study is based on regular medical care, the need for individual informed consent was waived. In the present analyses, 11 (3.7%) patients were excluded due to missing data on all three walking tests (10 due to physical impairments and 1 due to time constraints), resulting in 288 patients.

Outpatient characteristics

Patients completed questionnaires, which provided information on age, gender, marital status, living arrangements, smoking and alcohol use. Body Mass Index (BMI) was calculated by dividing body weight in kilograms by the square of the height in meters. Medical charts were used to determine use of medication and presence of diseases, i.e. hypertension, myocardial infarction, chronic obstructive pulmonary disease (COPD), malignancy, diabetes mellitus, rheumatoid arthritis, (osteo)arthritis and Parkinson's disease. Multimorbidity was defined as having two or more diseases. The presence of cardiopulmonary disease was defined as having one or more diseases and risk factors relating to the cardiovascular and/or pulmonary system, i.e. hypertension, myocardial infarction and COPD. Depressive symptoms were assessed by the Hospital Anxiety and Depression Scale (HADS)²⁷; a depression subscore higher than 8 out of 21 points indicated depressive symptoms. Cognition was assessed through the Mini-Mental State Examination (MMSE)²⁸. A relative MMSE score was calculated by dividing the total MMSE score by the maximal possible MMSE score multiplied by 30. The presence of low cognitive performance was defined as scoring below the clinically used cut-off value of 24 points²⁹. Physical functioning was assessed by handgrip strength, the Short Physical Performance Battery (SPPB)³⁰ and questionnaires about walking difficulties and the use of a walking aid.

Walking speed

Walking speed was assessed with the 4-meter, 10-meter and 6-minute walking test. Patients wore non-slip socks during the 4- and 10-meter walking test and their regular shoes during the 6-minute walking test. The walking tests were performed without walking aid, unless the patients were not able to.

The 4-meter walking test was assessed as part of the SPPB and was performed twice. Patients started from standing position and were instructed to walk at their preferred speed over a length of 5 m, without slowing down before the 4-meter line. Time was measured using a hand-held stopwatch from the moment the first foot passed the starting line until the moment the first foot passed the 4-meter line completely. The shortest time was used for analysis.

The 10-meter walking test was performed twice and patients were instructed to walk at their preferred speed over a length of 15 m. Time was started at 2.5 m and stopped at 12.5 m, resulting in a steady state measurement over 10 m. Time was measured using a hand-held stopwatch and the shortest time was used for analysis.

The 6-minute walking test was performed once and patients were instructed to walk as far as possible, without running, for 6 min. The test started from standing position and stopped after 6 min or if patients could not walk further. Patients walked down a corridor of 15 m and the number of times patients walked down the corridor was recorded manually plus any

residual distance. A Dynaport Hybrid (McRoberts BV, The Hague, The Netherlands), a tri-axial accelerometer positioned on the lower back using an elastic strap at the height of the second lumbar vertebra, was used as a second measure of total walking distance. The number of turns was established off line by custom written software using Matlab (The MathWorks Inc., Natick, Massachusetts, U.S.A.). Subsequently, the counted turns were multiplied by 15 and the reported residual distance was added. For the current analysis, the total distance calculated using the Dynaport Hybrid was used for further analysis. As the 6-minute walking test was only performed between October 2010 and March 2011, data was available in 70 patients, of which 7 (12.9%) patients were not able to finish the test due to fatigue or shortness of breath.

Statistical analysis

Continuous variables with Gaussian distribution are presented as mean and standard deviation (SD), otherwise as median and interquartile range (IQR) or as number (n) and percentage (%). Paired samples t-tests were used to assess the systematic error, i.e. the mean difference, between the different methods to assess walking speed, i.e. 4- versus 10-meter, 4-meter versus 6-minute and 10-meter versus 6-minute walking test. Absolute agreement was assessed by the 95% limits of agreement (95% LOA), which were calculated by the mean difference ± 1.96 SD^{31,32} and visualized using Bland-Altman plots. Relative agreement was assessed by the Intraclass Correlation Coefficient (ICC_{3,1})³³. The ICC values were interpreted as excellent (0.75 or higher), fair to good (0.40 to 0.75) or poor (0.40 or lower)²⁵. The association of cognitive performance and cardiopulmonary diseases with walking speed assessed by three different walking tests was tested using linear regression analysis with adjustments for age and gender. Data was analysed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, USA). P-values below 0.05 were considered statistically significant.

Results

Outpatient characteristics

The characteristics of the elderly outpatients are shown in Table 1. Mean age (SD) was 82.2 (7.1) years and 35.1% were men.

Comparison of walking speed assessed with different methods

Mean differences between walking speed assessed with different walking tests are presented in Table 2 and visualized in Figure 1. Walking speed assessed with the 10-meter walking test was significantly higher compared to the walking speed assessed with the 4-meter and 6-minute walking test. Walking speed assessed with the 4-meter and 6-minute walking test were not significantly different. The 95% LOA of the comparison of the 4-meter and 10-meter walking test was lower than the 95% LOA of the comparison of the 6-minute walking test and the 4-meter walking test and the 95% LOA of the comparison of

the 6-minute walking test and the 10-meter waking test. The ICC between the 4- and the 10-meter walking test was excellent. The ICCs between the 4-meter and 6-minute walking test and between the 10-meter and 6-minute test were fair to good.

Table 1 Characteristics of elderly outpatients referred to a geriatric outpatient clinic.

	All (N=288)
Demographics	
Age, years	82.2 (7.1)
Men, n (%)	101 (35.1)
Widowed, n (%)	117 (41.3)
Independent living, n (%) ^a	236 (83.1)
Current smoking, n (%) ^c	22 (16.1)
Excessive alcohol use, n (%) ^a	9 (3.2)
Health characteristics	
BMI, kg/m ^{2b}	25.9 (4.5)
Multimorbidity, n (%) ^{†b}	103 (37.5)
Cardiopulmonary disease, n (%) ^{§b}	169 (61.0)
Number of medication, median (IQR) ^a	5 (3-7)
HADS depression ^{‡c}	30 (23.4)
MMSE, points ^a	27 (24-29)
Physical functioning	
<i>Measured</i>	
Handgrip strength, kg	25.4 (8.0)
SPPB score, points; median (IQR) ^a	7 (5-9)
<i>Self-reported, n (%)</i>	
Walking difficulties	218 (76.8)
Use of walking aid	167 (58.6)
Walking speed	
4-meter walking speed, m/s ^a	0.72 (0.27)
10-meter walking speed, m/s ^b	0.84 (0.28)
6-minute walking speed, m/s ^d	0.75 (0.26)

Variables are presented as mean (standard deviation) unless indicated otherwise. Data available in ^an=280-283, ^bn=275-279, ^cn=137, ^dn=70. ^aDefined as >14 units per week for females or >21 units per week for males. [†]Defined as having ≥2 diseases, including hypertension, myocardial infarction, chronic obstructive pulmonary disease, malignancy, diabetes mellitus, rheumatoid arthritis, (osteo)arthritis and Parkinson's disease. [§]Defined as having ≥1 cardiopulmonary diseases; hypertension, myocardial infarction and chronic obstructive pulmonary disease. [‡]Present with a depression subscore >8 on the Hospital Anxiety and Depression Scale. Abbreviations: BMI, body mass index; IQR, interquartile range; SPPB, Short Physical Performance Battery; MMSE, Mini Mental State Examination.

Table 2 Comparison of walking speeds assessed with different walking tests.

Walking test	Mean difference, m/s	95% LOA	p value	ICC	95% CI
4 m – 10 m	-0.11	-0.13; -0.10	<0.001	0.79	0.44; 0.90
4 m – 6 min	-0.03	-0.08; 0.03	0.34	0.64	0.48; 0.76
10 m – 6 min	0.08	0.04; 0.13	<0.001	0.71	0.52; 0.82

Data is presented in intraclass correlation coefficients and mean differences obtained from paired samples t-tests. Abbreviations: LOA, limits of agreement; ICC, intraclass correlation coefficients; CI, confidence interval.

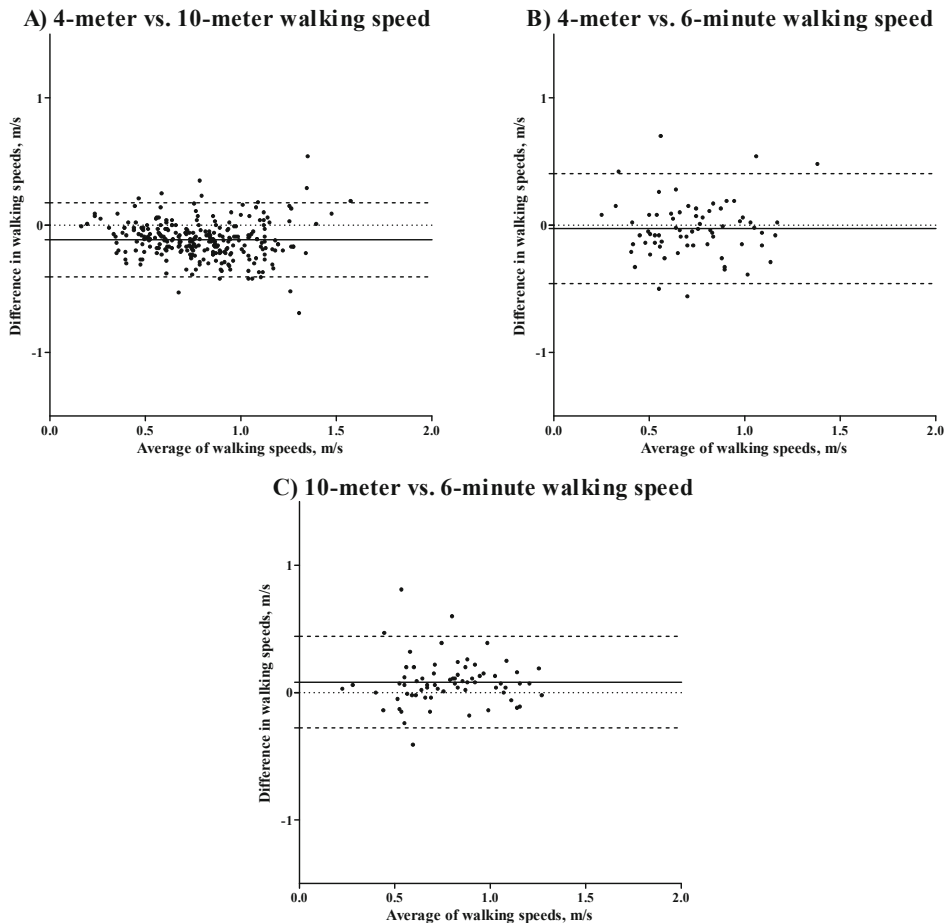


Figure 1 Bland-Altman plot representing the comparison between a) the 4-meter and 10-meter walking speeds, b) the 4-meter and 6-minute walking speeds and c) the 10-meter and 6-minute walking speeds. The solid line represents the mean difference in walking speed, while the dashed lines represent the upper and lower 95% limits of agreement (mean difference $\pm$ 1.96 SD).

Association of underlying systems with walking speed

Table 3 shows the association of the presence of low cognitive performance and cardiopulmonary disease with walking speed assessed with different walking tests. Presence of low cognitive performance was significantly associated with a lower 4-meter walking speed and 10-meter walking speed after adjustments for age and gender, of which the 4-meter walking speed showed the highest effect size. Presence of cardiopulmonary disease was significantly associated with a lower 4-meter, 10-meter and 6-minute walking speed after adjustments for age and gender, of which the 6-minute walking speed showed the highest effect size.

Table 3 Association between cognitive performance and cardiopulmonary disease with walking speed assessed with different walking tests.

	4-meter walking speed		10-meter walking speed		6-minute walking speed	
	Beta (SE)	p value	Beta (SE)	p value	Beta (SE)	p value
Cognitive performance						
unadjusted	-0.103 (0.038)	0.007	-0.091 (0.041)	0.027	0.032 (0.071)	0.66
adjusted*	-0.103 (0.035)	0.004	-0.095 (0.037)	0.012	0.018 (0.066)	0.79
Cardiopulmonary disease						
unadjusted	-0.069 (0.034)	0.039	-0.047 (0.035)	0.185	-0.107 (0.045)	0.088
adjusted*	-0.083 (0.031)	0.008	-0.064 (0.032)	0.047	-0.111 (0.055)	0.046

Data is presented in the effect size (Beta) and standard errors (SE). Low cognitive performance is defined as scoring below the clinically used cut-off value of 24 (0=normal, 1=low); Cardiopulmonary disease is defined as having 1 or more cardiopulmonary diseases (0=absent, 1=present). *adjusted for gender and age.

Discussion

In a population of community-dwelling elderly referred to a geriatric outpatient clinic, walking speed was assessed with three different methods, i.e. the 4-meter, the 10-meter and the 6-minute walking test. Walking speed assessed with the 10-meter walking test was significantly higher compared to walking speed assessed with the 4-meter and 6-minute walking test. ICC values indicated excellent agreement for the comparison between the 4-meter and 10-meter walking test and fair to good agreement for the 4-meter and 6-minute walking test and for the 10-meter and 6-minute walking test. The presence of low cognitive performance showed the strongest association with walking speed assessed with the 4-meter walking test, while presence of cardiopulmonary disease showed the strongest association with walking speed assessed with the 6-minute walking test.

No previous studies investigated the influence of different methods to assess walking speed in a clinically relevant population of elderly outpatients with comorbidities and mobility impairments. A previous study in a homogeneous population of healthy elderly showed an excellent agreement in walking speed assessed with the 4- and 10-meter walking test²⁵, which is comparable with our results. A lower ICC value with a larger 95% LOA compared with aforementioned study, can be explained by a difference in study population and sample size. In contrast to the present results, other previous studies performed in healthy older adults and older adults with neurologic conditions reported no effect of walking distance on walking speed^{24,26}. Apart from the differences in study population, it is difficult to compare aforementioned studies due to differences in test protocols, especially in pace and static or dynamic start of the walking test.

Walking speed assessed with the 10-meter walking test was significantly higher compared to walking speed assessed with the 4-meter walking test. The higher walking speed assessed with the 10-meter walking test can be explained by the exclusion of the acceleration phase, which is included in the 4-meter walking test, while the 10-meter

walking test measures only the steady state phase. The results showed an excellent relative agreement between the 4-meter and 10-meter walking tests by the ICC. This means a high consistency between tests, i.e. smaller difference between both assessed walking speeds compared with the differences between the patients within the group. A small range of the 95% LOA indicated a low random error and precise assessments of walking speeds.

A systematically lower walking speed assessed with the 6-minute walking test compared to the 10-meter walking test was found, which can be explained by the inclusion of the acceleration phase and the endurance needed to perform the 6-minute walking test. The difference between both assessed walking speeds is somewhat higher compared to the differences between the patients in the study population, as shown by the ICC values indicating fair to good agreement. The large range of the 95% LOA indicated a high random error and less precise assessments of walking speeds. This may be explained by the introduction of more variability due to differences in endurance between patients. Furthermore, data of the 6-minute walking tests was limited available.

We found no systematic difference between walking speed assessed with the 4-meter and the 6-minute walking test. Both tests include factors with a limiting effect on the assessed walking speed, i.e. an acceleration phase and endurance. The first factor has less effect on walking speed assessed with the 6-minute walking test, as the duration of the 6-minute walking test is longer compared with the 4-meter walking test. Endurance only has effect on the 6-minute walking test. The results showed a fair to good relative agreement between the tests, due to a somewhat higher difference between the tests compared with the differences within the group reflected by the ICC. A large range of the 95% LOA indicates a high random error and less precision between the two assessed walking speeds. An explanation for this may be the introduction of more variability due to differences in endurance as well as the lower number of patients who performed the 6-minute walking test compared to the 4-meter walking test.

The methodology to assess walking speed affects the association of cognitive performance with walking speed. In accordance with other studies performed in community-dwelling elderly and healthy elderly^{12,13,34-37}, we found an association between the presence of low cognitive performance and walking speed assessed by respectively the 4-meter and 10-meter walking test. The largest effect size was found for the walking speed assessed with the 4-meter walking test. This may be explained by the inclusion of the acceleration phase in the 4-meter walking test. Initiation of movement requires cognitive processes and therefore cognitive impairment slows walking^{13,37}, resulting in a larger effect size for the association between presence of low cognitive performance and walking speed assessed with the 4-meter walking test.

The methodology also affects the association between the presence of cardiopulmonary disease and walking speed. In accordance with previous studies showing a negative association between hypertension, myocardial infarction and COPD and walking speed^{7,14-16}, we found an association between presence of cardiopulmonary disease with a lower walking speed. The highest effect size was found for the walking speed assessed with the 6-minute walking test. This may be explained by the cardiovascular determined endurance factor, which is obviously more prominent in the 6-minute walking test.

The results found in this study are of high clinical relevance. Previous studies reported clinically meaningful changes in walking speed in community-dwelling older adults for the 4-meter walking test of 0.12 m/s³⁸. More in general, small and substantial clinically meaningful changes in walking speed were reported from 0.05 m/s and 0.10 m/s, respectively^{38,39}. In this study, we found differences in walking speeds of 0.11 m/s for the 10-meter compared to the 4-meter walking test and 0.06 m/s for the 10-meter compared to the 6-minute walking test. Especially for the 10-meter compared to the 4-meter walking test, the range of 95% LOA is small (0.10;0.13 m/s) indicating that for 95% of the patients the difference between the 10-meter and 4-meter walking test will be between these values. So, the difference between both walking tests is large and precise enough to measure clinically meaningful changes in walking speed over time at the individual level when these methods are used interchangeably, which will have direct influence on clinical decision making. Furthermore, this study emphasizes that when using cut-off values^{3,8,11,40} for clinical decision making, clinicians should be aware that they depend on the assessment method of walking speed.

The strength of this study is the large clinically relevant study population of elderly outpatients. No exclusion criteria were applied which further improves the generalizability of our results. Within the study population 64.9% were women, representing the geriatric outpatient population. Limitations were the limited availability of data on the 6-minute walking test. This could have influenced our results, as this reduces the power in the comparison of the 4- and 10-meter walking test with the 6-minute walking test and results in a methodologically induced enhancement of the 95% LOA and lower ICC values.

This study showed that in the clinically relevant population of elderly outpatients, the walking test that has been used has direct influence on the assessed walking speed as well as its validity, illustrated by the association with two major underlying systems, i.e. cognition and the cardiopulmonary system. Walking speeds assessed by different walking tests are therefore not interchangeable in this population. Clinicians assessing elderly outpatients should be aware of the effect of the used walking test on the assessed walking speed and its consequences for clinical decision making.

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Temporal relationship between cognitive and physical performance in middle-aged to oldest old people

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Abstract

Background: Cognitive and physical impairment frequently co-occur in older people. The aim of this study was to assess the temporal order of these age-related changes in cognitive and physical performance and to assess whether a relationship was different across specific cognitive and physical domains and age groups.

Methods: Cognitive domains included global, executive and memory function; physical domains included gait speed and handgrip strength. These domains were assessed in two population-based longitudinal cohorts covering the age ranges of 55 – 64, 65 – 74, 75 – 85 and 85 – 90 years with a follow-up of five to twelve years. Cross-lagged panel models were applied to assess the temporal relationships between the different cognitive and physical domains adjusting for age, sex, education, comorbidity, depressive symptoms and physical activity.

Results: Over all age groups, poorer executive function was associated with a steeper decline in gait speed ($p < 0.05$). From the age of 85 years, this relationship was found across all cognitive and physical domains ($p < 0.02$). From the age of 65 years, slower gait speed and/or weaker handgrip strength were associated with steeper declines in global cognitive function ($p < 0.02$), with statistically significant results across all cognitive domains in the age group of 75 – 85 years ($p < 0.04$).

Conclusions: The temporal relationship between cognitive and physical performance differs across domains and age, suggesting a specific rather than a general relationship. This emphasizes the importance of repeated measurements on different domains and encourages future research to the development of domain and age specific interventions.

Introduction

Cognitive and physical performance are important determinants of independent living and quality of life. Deterioration of both frequently co-occurs in older people¹⁻³. The temporal order of age-related changes in cognitive and physical performance is largely unknown. Several longitudinal studies assessed the order of changes in only one of the possible directions; cognitive performance being associated with changes in physical performance or physical performance being associated with changes in cognitive performance⁴.

The few longitudinal studies assessing the relationship between cognitive and physical performance in both directions, showed inconsistent results with uni- as well as bidirectional relationships⁵⁻¹⁰. Differences in findings between studies assessing different cognitive and physical domains might indicate dependence of the temporal relationship on these domains⁴. Furthermore, it has become more and more evident in recent years that results might differ across different age ranges, especially for older populations aged 75 and older¹¹⁻¹³. Insight into whether the temporal relationship between cognitive and physical performance depends on age could provide important information for an effective clinical assessment, development and application of interventions.

The aim of this study was to assess the temporal relationship between cognitive and physical performance; whether poor cognitive performance is associated with a steeper decline in physical performance or poor physical performance with a steeper decline in cognitive performance; and to study whether a relationship was different across specific cognitive and physical domains and age groups.

Methods

Study design and populations

Two population-based longitudinal cohorts were included; the Longitudinal Aging Study Amsterdam (LASA) and the Leiden 85-plus Study. LASA is an ongoing study consisting of a nationally representative sample of the middle-aged to older Dutch population¹⁴. A random sample, stratified by age and gender, was drawn from the population registers of 11 municipalities in three culturally distinct geographical areas in the Netherlands. In total, 3107 participants aged 55 – 85 years (born between 1908 and 1937) were enrolled during the first data collection in 1992-1993 and have been followed up with a time interval of approximately three years. For the present study, data were used from the first four LASA cycles (1992-1993, 1995-1996, 1998-1999, and 2001-2002) in order to have the older ages sufficiently represented during the entire follow-up. The study was approved by the Ethical Review Board of the VU University Medical Center. Informed consent was obtained from all participants.

The Leiden 85-plus Study includes inhabitants of the city of Leiden, the Netherlands¹⁵. All inhabitants who reached the age of 85 years were eligible to participate. There were no selection criteria on health, functioning or demographic characteristics. In total 599 persons participated, which was 87% of all eligible inhabitants. Follow-up measurements were performed annually until the age of 90 years. The study was approved by the Medical Ethical Committee of the Leiden University Medical Center. All participants or guardians of the participants gave informed consent.

A full description of the cognitive and physical tests and the potential confounders is given in the Supplementary Methods section. A short explanation is given below.

Cognitive performance

Cognitive performance was assessed by three different measures: global cognitive function and the domain specific measures of executive and memory function. Global cognitive function was assessed by the Mini-Mental State Examination (MMSE). Information processing speed was used as measure of executive function, which was assessed by the Alphabet Coding Task-15 and the Letter Digit Substitution Task (LDST) in LASA and the Leiden 85-plus Study, respectively. Memory function was assessed with the 15-Words test in LASA and the 12-Picture Learning test in the Leiden 85-plus Study.

For all cognitive tests, a higher score indicates better cognitive performance. In LASA, cognitive performance was assessed in each LASA cycle. In the Leiden 85-plus Study, global cognitive function was assessed yearly. Executive and memory function were assessed yearly as well until MMSE score was below 19 points.

Physical performance

Physical performance was assessed by gait speed and handgrip strength. Gait speed was measured over a total distance of six meters (two times three meters with a turn), starting from standing position at maximal pace. Handgrip strength was measured by maximal squeeze using a hand held dynamometer. In LASA, gait speed was assessed in each cycle and handgrip strength from the second cycle. In the Leiden 85-plus Study, gait speed was assessed at the age of 85, 86, 87, and 89 years and handgrip strength at the age of 85 and 89 years.

Potential confounders

The following factors were included as potential confounding variables as these are found to be associated with both cognitive and physical performance: education to indicate participant's socio-economic status¹⁶, comorbidity^{17,18}, depressive symptoms^{19,20} and physical activity^{21,22}.

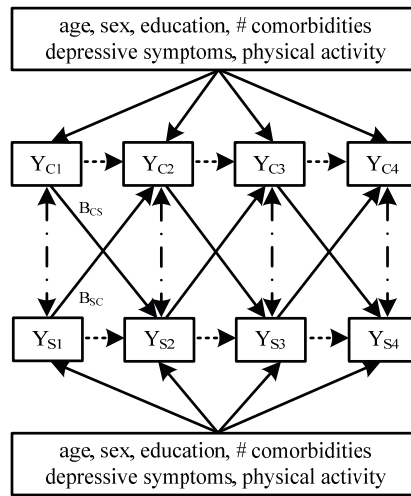


Figure 1 Cross-lagged panel model for estimation of the cross-lagged effects between cognitive and physical performance with confounding variables age, sex, education, number of comorbidities, depressive symptoms and physical activity. The model included synchronous and autoregressive correlations indicated by the semi-dotted and dotted arrows, respectively. Abbreviations: #, number; Y_{Cn} , measurements of cognitive performance at time point n ; Y_{Sn} , measurements of gait speed or handgrip strength at time point n ; B_{CS} , cross-lagged effect of different cognitive domains on gait speed/handgrip strength; B_{SC} , cross-lagged effect of gait speed/handgrip strength on different cognitive domains.

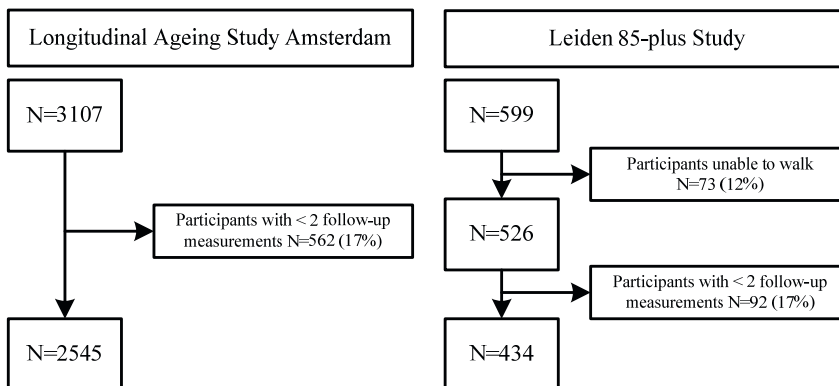


Figure 2 Flow chart of participants of the Longitudinal Ageing Study Amsterdam (LASA) and Leiden 85-plus Study included in the cross-lagged panel models. Abbreviations: N, number.

Statistical analyses

For descriptive reasons we provided means and standard deviations (SD) for normal distributed continuous variables, the median and interquartile range (IQR) for non-Gaussian distributed continuous variables, and the number per category and percentages for categorical variables.

Cross-lagged panel models (CLPM) were used to examine the cross-lagged effects of cognitive performance on changes in physical performance and of physical performance on changes in cognitive performance during follow-up adjusted for potential confounders (Figure 1). CLPMs are a specific type of structural equation models, i.e. models allowing to estimate a number of regression equations simultaneously²³. CLPMs allow simultaneous modelling of bidirectional, temporal relationships^{5,10}. This means that the variables of interest (cognitive and physical performance) are the dependent variable in one regression equation and the independent variable in another regression equation. Hypothesized causal associations can be tested if the assumptions of the models are met, which is when there is synchronicity, stationarity and stability within and between the variables of interest²⁴. Synchronicity means that cognitive and physical performance are measured at the same time, which is the case in both cohorts. Stationarity and stability presume that the causal process and autocorrelations do not change during follow-up, respectively. Therefore, effects in the CLPM were constrained to be equal, that is equal synchronous correlations, equal cross-lagged correlations and equal autocorrelations. Residuals of the variables for which synchronous correlation was estimated were allowed to correlate to take into account the effect of unknown third variables²⁵. Residuals were further allowed to correlate over time. The standardized cross-lagged effects, i.e. expressing the effect in standard deviations, were used to compare the strength of the cross-lagged effects of cognitive performance on physical performance with the cross-lagged effects of physical performance on cognitive performance. To compare the effects across LASA and the Leiden 85-plus Study, the unstandardized cross-lagged effects in the Leiden 85-plus Study were multiplied by three (for handgrip strength after division by four) to make them comparable to the three year unstandardized cross-lagged effects in LASA. The cross-lagged panel models were evaluated using MPlus (version 7)²⁶, which uses the Full Information Maximum Likelihood procedure for handling missing values²⁷. Model fit was evaluated on the following criteria: root mean square error of approximation (RMSEA) ≤ 0.06 , standardized root mean square residual (sRMR) ≤ 0.08 and comparative fit index (CFI) ≥ 0.95 ²⁸. If all degrees of freedom have been used to estimate the model, the model is saturated and thus perfectly fits the data.

Participants of the Leiden 85-plus Study not able to walk at baseline were excluded from the analyses leading to 526 (88%) participants (Figure 2). In both cohorts, the criterion of the presence of at least one follow-up measurement of gait speed was applied leading to 2545 (82%) participants in LASA and 434 (83% of the 526 participants able to walk) participants in the Leiden 85-plus Study. In order to get good model fits, gait speed values below 0.1 m/s were changed to missing data (7 and 13 measurements of all baseline and follow-up measurements in total in LASA and the Leiden 85-plus Study, respectively). In the Leiden 85-plus Study, executive and memory function were only assessed in participants with a MMSE score of 19 points or higher resulting in 392 out of the 434

(90%) participants for these cognitive tests at baseline. To get insight into the temporal relationship between cognitive and physical performance across age, the LASA cohort was stratified into three age groups: participants aged 55 – 64 years, 65 – 74 years and 75 – 85 years. P-values <0.05 were considered as statistically significant. Figures were made with GraphPad Prism 5 (GraphPad Software, Inc. La Jolla, USA).

Results

Baseline characteristics on demographics, health and cognitive and physical performance are shown in Table 1. Mean age (SD) for each of the different age groups of the LASA cohort was 60.2 (2.8), 69.8 (2.9) and 80.0 (2.9) years. Participants of the Leiden 85-plus Study were all 85 years of age at baseline. Table 2 shows the fit statistics for the cross-lagged panel models. The statistics indicate good model fits for all models.

Figure 3 shows the unstandardized cross-lagged effects of different cognitive domains on gait speed and handgrip strength during follow-up. For the age group of 55 – 64 years, poorer executive and memory function were associated with a steeper decline in gait speed. For the age groups of 65 – 74 and 75 – 85 years, poorer executive function was associated with a steeper decline in gait speed. Among the oldest age group of 85 – 90 years, poorer performance on each of the cognitive domains was associated with a steeper decline in gait speed and handgrip strength.

Figure 4 shows the unstandardized cross-lagged effects of gait speed and handgrip strength on different cognitive domains during follow-up. No association was found for the youngest age group of 55 – 64 years. For the age group of 65 – 74 years, slower gait speed and weaker handgrip strength were associated with a steeper decline in global cognitive function. Among the age group of 75 – 85 years, slower gait speed was associated with a steeper decline on each of the cognitive domains. For the age group of 85 – 90 years, weaker handgrip strength was associated with a steeper decline in global cognitive function.

Supplementary Tables 1 and 2 present the standardized cross-lagged effects of different cognitive domains on gait speed and handgrip strength during follow-up and of gait speed and handgrip strength on different cognitive domains during follow-up, respectively. Comparing the standardized cross-lagged effects of the temporal relationships that were statistically significant in both directions, similar effect sizes were found.

Table 1 Baseline characteristics of the participants of the two study cohorts stratified for age.

	LASA			Leiden 85+ Study
	55 – 64 yrs. (N=887)	65 – 74 yrs. (N=831)	75 – 85 yrs. (N=827)	85 – 90 yrs. (N=434)
Demographics				
Age, years	60.2 (2.8)	69.8 (2.9)	80.0 (2.9)	85
Females, n (%)	462 (52.1)	451 (54.3)	445 (53.8)	289 (66.6)
Education				
Years*	9.0 (6.0 - 11.0)	9.0 (6.0 - 11.0)	6.0 (6.0 - 10.0)	-
Lower education, n (%)	-	-	-	167 (38.5)
Health characteristics				
BMI, kg/m ^{2a}	26.7 (3.7)	26.8 (4.0)	27.1 (4.5)	27.3 (4.4)
Comorbidities*	0.0 (0.0 - 1.0)	1.0 (0.0 - 1.0)	1.0 (0.0 - 2.0)	2.0 (1.0 - 3.0)
Depressive symptoms, points				
CES-D score*	5.0 (2.0 - 9.0)	5.0 (2.0 - 11.0)	7.0 (3.0 - 12.0)	-
15-item GDS score ^{b*}	-	-	-	1.0 (1.0 - 3.0)
Physical activity				
LASA quest. ^{c*} , hrs./day	2.9 (1.8 - 4.4)	2.7 (1.6 - 4.0)	2.0 (1.2 - 3.1)	-
TSP quest. [*] , points	-	-	-	7.0 (5.0 - 9.0)
Cognitive performance				
MMSE*, points	28.0 (27.0 - 29.0)	28.0 (27.0 - 29.0)	27.0 (25.0 - 28.0)	27.0 (24.0 - 28.0)
Processing speed, # comb.				
adj. Alphabet Coding Task ^d	28.2 (6.5)	25.0 (6.5)	19.5 (6.6)	-
LDST ^{e*}	-	-	-	17.0 (13.0 - 22.0)
Immediate recall				
15 Words Test, # words ^{d*}	21.0 (18.0 - 25.0)	19.0 (15.0 - 23.0)	16.0 (12.0 - 19.0)	-
12-PLT, # pictures ^{b*}	-	-	-	25.0 (21.0 - 29.0)
Delayed recall				
15 Words Test, # words ^{d*}	6.0 (4.0 - 8.0)	5.0 (3.0 - 7.0)	4.0 (2.0 - 5.0)	-
12-PLT, # pictures ^{b*}	-	-	-	9.0 (7.0 - 11.0)
Physical performance				
Gait speed, m/s ^f	0.96 (0.28)	0.86 (0.28)	0.69 (0.24)	0.55 (0.22)
Handgrip strength*, kg ^g	30.5 (23.5 - 40.0)	27.0 (21.0 - 37.5)	22.0 (17.5 - 30.0)	22.0 (18.0 - 28.0)

Variables are expressed as mean (standard deviation) unless indicated otherwise.

Abbreviations: N, number; BMI, body mass index; CES-D, Centre for Epidemiologic Studies Depression Scale; GDS, Geriatric Depression Scale; quest., questionnaire; hrs., hours; TSP, Time Spending Patterns; MMSE, Mini-Mental State Examination; comb., combinations; LDST, Letter Digit Substitution Test; 12-PLT, 12 Picture Learning Test; #, number. *Values expressed as median (interquartile range). Data are available in ^an=795, 730 and 658 for each of the age groups between 55 and 85 years, respectively; ^bn=390; ^cn=786 and 759 for each of the age groups between 65 and 85 years, respectively; ^dn=815, 735 and 665 for each of the age groups between 55 and 85 years, respectively; ^en=377; ^fn=777 and 740 for each of the age groups between 65 and 85 years, respectively; and ^gn=237, 668 and 596 for each of the age groups between 55 and 85 years, respectively.

Table 2 Fit statistics of the cross-lagged panel models between cognitive and physical performance for each age group.

	LASA						Leiden 85-plus Study			
	55 - 64 yrs.			65 - 74 yrs.			75 - 85 yrs.			85 - 90 yrs.
	RMSEA	sRMR	CFI	RMSEA	sRMR	CFI	RMSEA	sRMR	CFI	
Gait speed										
MMSE	0.012	0.064	1.0	0.030	0.035	0.99	0.033	0.067	0.99	0.049
Processing speed	0.051	0.038	0.98	0.039	0.034	0.99	0.036	0.028	0.99	0.042
Immediate recall	0.024	0.026	0.99	0.047	0.032	0.98	0.032	0.025	0.99	0.039
Delayed recall	0.019	0.028	1.0	0.034	0.031	0.99	0.008	0.024	1.0	0.042
Handgrip strength										
MMSE	0.039	0.070	0.99	0.068	0.039	0.99	0.070	0.040	0.98	saturated model
Processing speed	0.039	0.027	0.99	0.093	0.028	0.98	0.058	0.030	0.99	
Immediate recall	0.054	0.035	0.99	0.095	0.027	0.97	0.061	0.031	0.98	
Delayed recall	0.046	0.019	0.99	0.092	0.026	0.98	0.066	0.033	0.98	

Abbreviations: RMSEA, root mean square error of approximation; sRMR, standardized root mean square residual; CFI, comparative fit index.

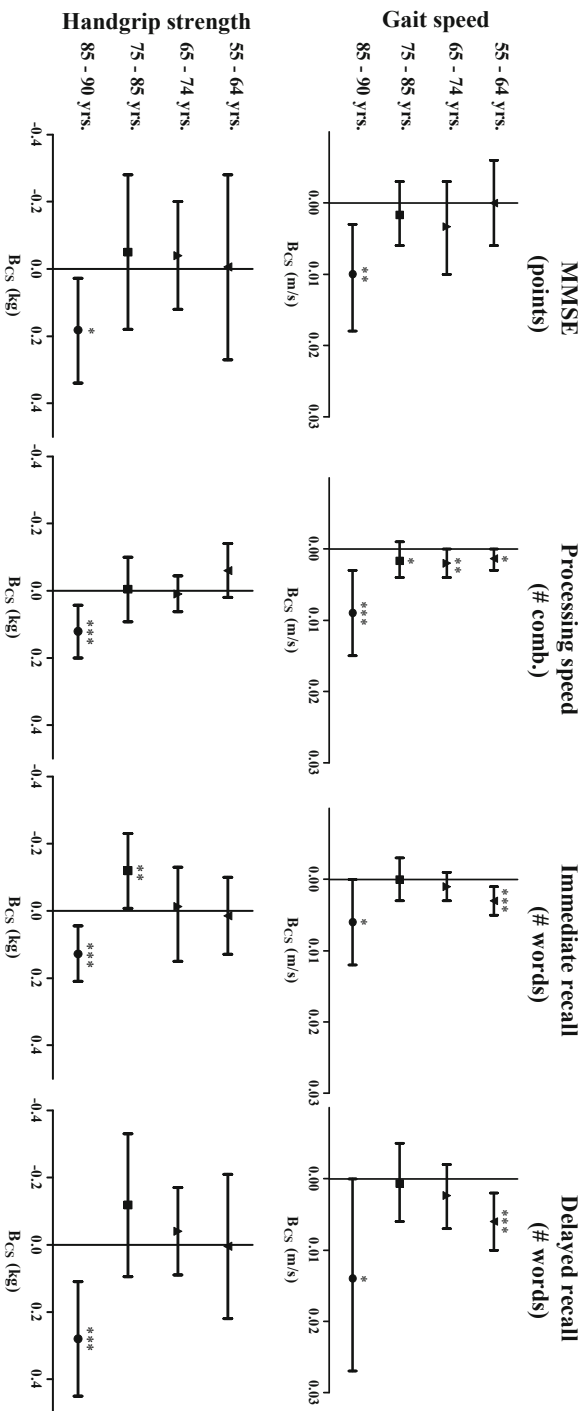


Figure 3 Unstandardized cross-lagged effects and 95% confidence intervals of different cognitive domains on gait speed and handgrip strength during follow-up. Cross-lagged panel models were adjusted for age, sex, education, number of comorbidities, depressive symptoms and physical activity. Abbreviations: B_{CS} (unstandardized) cross-lagged effect of different cognitive domains on gait speed/handgrip strength; MMSE, Mini-Mental State Examination; #, number. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ An explanatory note for interpretation of the results in this figure is given in the Supplementary results section.

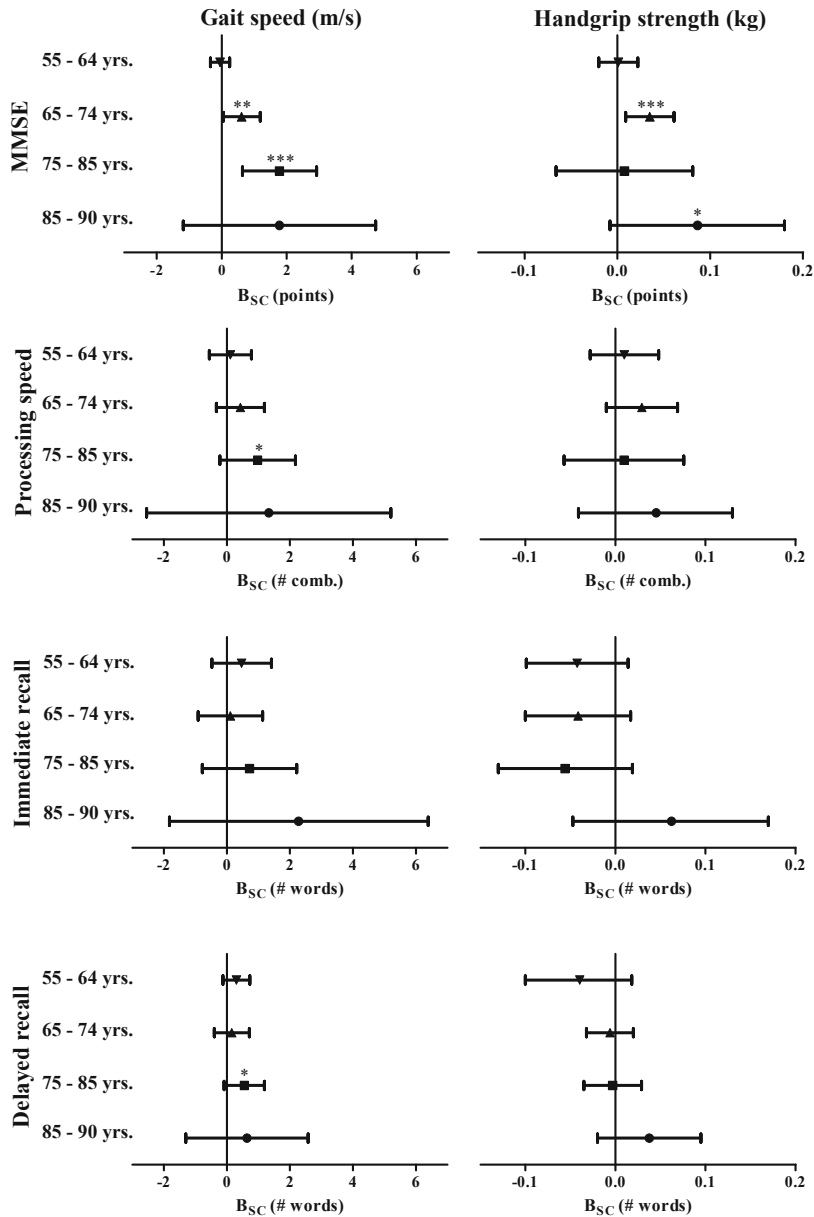


Figure 4 Unstandardized cross-lagged effects and 95% confidence intervals of gait speed and handgrip strength on different cognitive domains during follow-up. Cross-lagged panel models were adjusted for age, sex, education, number of comorbidities, depressive symptoms and physical activity. Abbreviations: B_{SC}, (unstandardized) cross-lagged effect of gait speed/handgrip strength on different cognitive domains; MMSE, Mini-Mental State Examination; #, number. *p<0.05, **p<0.01, ***p<0.001 An explanatory note for interpretation of the results in this figure is given in the Supplementary results section.

Discussion

In two large population-based longitudinal cohorts, the temporal relationship between cognitive and physical performance differed across specific cognitive and physical domains and across age groups. The temporal relationship was most prominent from the age of 75 years. Thereby, an inversed temporal order was found comparing the age groups of 75 – 85 years and 85 – 90 years. Slower gait speed was associated with steeper declines on each of the cognitive domains in the age group of 75 – 85 years, while poorer performance on each of the cognitive domains was associated with steeper declines in gait speed and handgrip strength in the age group of 85 – 90 years. Across all age groups, poorer executive function was associated with a steeper decline in gait speed.

Our specific findings across the different age groups might explain the inconsistent findings in the current literature. They support the findings of bidirectional relationships when broad age ranges are used⁶ and unidirectional relationships in study populations consisting of more specific age ranges and health status⁷⁻⁹. Furthermore, our results are in accordance with the results of the few studies that used cross-lagged modelling as well instead of regression modelling. These studies, consisting of 70 to 79 years old participants, indicated the presence of bidirectional relationships^{5,10} and a predominance of the relationship in the temporal order of slow gait speed being associated with steeper declines in global and executive function¹⁰, which supports our findings in the age group of 75 to 85 years.

The temporal relationship between cognitive and physical performance was most prominent from the age of 75 years. From this age, deterioration of underlying systems such as the central and peripheral nervous, musculoskeletal and cardiovascular system^{29,30}, is generally more substantial, which might lead to a more significant role of cognitive and physical performance as compensating mechanisms for each other. Thereby, the potential influence of physical performance on cognitive performance especially reached the level of significance in the age range of 75 – 85 years. This was particularly shown in gait speed, which emphasizes the role of gait speed as important indicator of health status^{31,32}. The influence of cognitive performance on physical performance was found across the entire age range for executive function and gait speed, with consistent findings across all cognitive and physical domains for participants aged 85 years and older. This more elaborate influence of cognitive performance on physical tasks with advancing age is supported by previous studies showing that already from middle age several additional brain areas are recruited as compensating mechanism during the performance of physical tasks when compared to younger adults^{33,34}. Thereby, the findings of a temporal relationship of executive function with gait speed across all age groups emphasize the important role of this cognitive domain in the performance of physical tasks^{35,36}. The presence of the temporal relationships also in the younger age groups indicates the potential

role of these measures of cognitive and physical performance as early markers for the identification of physical and cognitive impairments, respectively. Based on the results in this study, poor executive function below the age of 75 years might be an early marker for physical impairments and slow gait speed and weak handgrip strength for cognitive impairments.

The strength of the temporal relationships between cognitive and physical performance for each of the two different directions was similar. These findings indicate the potential effectiveness of cognitive and physical interventions to delay physical and cognitive impairment, respectively^{22,37,38}. Especially on the effectiveness of physical interventions several studies have been performed showing reduced risks on cognitive decline and dementia^{22,37,39}. Based on the results in this study, these effects might be most effective in the age range of 75 – 85 years. Future studies investigating the possible dependence of these interactions on age and the effectiveness of cognitive interventions especially from the age of 85 years are needed. Furthermore, the bidirectionality of the temporal relationship and similar strength of the effect sizes makes involvement of common underlying pathologies of age-related changes in cognitive and physical performance likely. One of the potential mechanisms that have been suggested is the presence of brain pathologies as common underlying etiology, which is supported by several cross-sectional and longitudinal studies showing the association between brain pathology and cognitive and physical performance⁴⁰⁻⁴². Common biological processes throughout the entire human body, like cellular senescence, are suggested as well⁴³. The results of this study encourage further research to possible common underlying determinants of cognitive and physical decline.

One of the strengths of this study is the large sample size and availability of repeated measurements of the same cognitive and physical domains. Additional to the current literature, the temporal relationship between cognitive and physical performance was assessed by cross-lagged panel models enabling to get insight into the temporal order of age-related changes in cognitive and physical performance. The large age range of 55 – 90 years and assessment of different cognitive and physical domains enhanced our understanding of how the relationship between cognitive and physical performance changes with age. A limitation is the population existing of two different longitudinal cohorts. Although both cohorts consisted of community-dwelling participants and the assessments of the cognitive and physical domains and potential confounders were comparable, differences might have influenced the results. Thereby, the selection of comparable cognitive tests resulted in a restricted battery, especially according to the assessment of the complex domain of executive function. According to the Leiden 85-plus Study, executive and memory function (as well as the GDS) were only assessed in participants with an MMSE score of 19 points or higher in order to get valid results. This loss of power might

have resulted in an underestimation of the temporal relationships between cognitive and physical performance. The exclusion of participants unable to walk and with less than one follow-up measurement has probably led to an underestimation of the results as well.

In conclusion, the temporal relationship between cognitive and physical performance differs across domains and age, suggesting a specific rather than a general relationship. Especially from the age of 75 years, consistent temporal relationships of gait speed with different cognitive domains during follow-up were found, with an inversed temporal order from the age of 85 years. This emphasizes the importance of repeated measurements of cognitive and physical performance on different domains and the need for future studies investigating the potential dependency of cognitive and physical interventions based on these domain and age specific findings.

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Supplementary material

Methods

Cognitive performance

Cognitive performance was assessed by three different measures: global cognitive function, information processing speed as measure of executive function and memory function. In both studies, global cognitive function was assessed by the Mini-Mental State Examination (MMSE)⁴⁴. The MMSE consists of 20 items and scores range from 0 to 30 points, with higher scores indicating better cognitive performance. In LASA, cognitive performance was assessed in each LASA cycle. Among the participants of the Leiden 85-plus Study, global cognitive function was assessed yearly. Executive and memory function were assessed yearly as well until MMSE score was below 19 points.

In LASA, information processing speed was assessed by an adjusted version of the Alphabet Coding Task-15⁴⁵. In this task, a row of characters is shown to the participant with an empty row below it. The participant is asked to name the correct corresponding characters based on the character combinations given at the top of the sheet and to work as quickly and accurately as possible. Three consecutive trials of one minute each were performed. The number of completed character combinations made up the score of each trial. The mean score of the three trials was used for statistical analyses. In the Leiden 85-plus Study, the Letter Digit Substitution Task (LDST) was used to assess information processing speed. The LDST is a modified version of the Symbol Digit Modalities Test⁴⁶. During this test, the participant is asked to make as many letter-digit combinations as possible according to a given key. Outcome parameter is the number of correct combinations within 60 seconds. For both tests, a higher score indicates better cognitive performance.

Memory function was assessed with the 15-Words test⁴⁷ and 12-Picture Learning test⁴⁸ in LASA and the Leiden 85-plus Study, respectively. In the 15-Words test, which is the Dutch version of the Auditory Verbal Learning Test⁴⁹, 15 words are presented verbally by the interviewer. Outcome parameters were the immediate and delayed recall, defined as total number of correct words during three consecutive trials and number of correct words after a distraction period of 20 minutes, respectively. Higher scores on both outcome parameters indicate better cognitive performance. Two versions of the 15 Words Test were used in consecutive LASA cycles in order to reduce a possible practice effect. The 12-Picture Learning Test consists of 12 pictures of different objects that are shown to the participant. Outcome parameters are again the immediate recall and delayed recall after 20 minutes.

Physical performance

Physical performance was assessed by gait speed and handgrip strength. Gait speed was measured over a 3-meter course created with a measuring line at the participant's home. Participants were asked to walk to the other end of the course, to turn around and walk back as fast as possible. The use of an assistive device was allowed when needed. The test started from a standing position and total time was measured by use of a stopwatch. Gait speed was assessed in each LASA cycle and at the age of 85, 86, 87 and 89 years in the Leiden 85-plus Study.

Handgrip strength was measured to the nearest kilogram using a hand held dynamometer (Takei Scientific Instruments CO. Ltd., Tokyo, Japan in LASA and Sammons Preston Inc, Bolingbrook, IL in the Leiden 85-plus Study). The width of the dynamometer's handle was adjusted to hand size. Participants were instructed to squeeze with maximal strength. In LASA, handgrip strength was measured twice for each hand. Outcome parameter was the mean of the highest values on each hand. If only one value was available (e.g. only one trial for left or right hand or only measurements of one hand), this value was used. Handgrip strength was measured from the second LASA cycle onwards. In the Leiden 85-plus Study, handgrip strength was defined as the highest value during three trials measured on the dominant hand. Handgrip strength was measured at age 85 and 89 years.

Potential confounders

The following factors were included as potential confounding variables as these are found to be associated with both cognitive and physical performance: education to indicate participant's socio-economic status¹⁶; comorbidity^{17,18,29}, depressive symptoms^{19,20,50} and physical activity^{21,22,51,52}.

In LASA, education was expressed in years. Comorbidity was defined as the number of chronic diseases, including chronic non-specific lung disease, cardiac disease, peripheral arterial disease, stroke, diabetes mellitus, arthritis and malignancies. Depressive symptoms were assessed with the Dutch translation of the Centre for Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report scale (ranging from 0 to 60) designed to measure depressive symptoms in the general population⁵³. Physical activity was assessed by the LASA physical activity questionnaire⁵⁴, a questionnaire in which frequency and duration of walking outside, cycling, light and heavy household activities and a maximum of two sports during the past two weeks are estimated. Scores were converted to total time spent on physical activities in hours per day.

In the Leiden 85-plus Study, education was divided into low education level, including participants without schooling or primary school only, and high education level, equivalent to more than six years of schooling. Chronic diseases included chronic obstructive pulmonary disease, myocardial infarction, hypertension, stroke, diabetes mellitus,

rheumatoid arthritis, osteoarthritis and malignancies¹⁵. Depressive symptoms were assessed by the 15-item Geriatric Depression Scale (GDS)⁵⁵ and was restricted to participants with an MMSE score of 19 points or higher. Physical activity was measured with the Time Spending Pattern questionnaire, scoring on four items of physical exercise above routine daily physical activity⁵⁶. Physical activity scores range from 0 to 16 points with lower scores indicating lower physical activity.

Results

Explanatory note by figure 3

B_{CS} in this figure can be interpreted as the unstandardized cross-lagged effect of each of the different cognitive domains on gait speed or handgrip strength. For example, $B_{CS}=0.01$ m/s in the left upper panel for the age group of 85 – 90 years means that a 1 point lower MMSE score at time point n is associated with a 0.01 m/s steeper decline in gait speed at time point $n+1$ (which is for the Leiden 85-plus Study one year, but is in this figure recalculated to a three year cross-lagged effect to be comparable with LASA).

Explanatory note by figure 4

B_{SC} in this figure can be interpreted as the unstandardized cross-lagged effect of gait speed or handgrip strength on each of the cognitive domains. For example, $B_{SC}=0.6$ points in the left upper panel for the age group of 65 – 74 years means that a 1 m/s slower gait speed at time point n is associated with a 0.6 points steeper decline in MMSE score at time point $n+1$ (which is for LASA three years).

Supplementary Table 1 Standardized cross-lagged effects of different cognitive domains on gait speed and handgrip strength during follow-up.

LASA												
55 - 64 yrs.				65 - 74 yrs.				75 - 85 yrs.				
Betas				Betas				Betas				
95% CI				95% CI				95% CI				
p				p				p				
Leiden 85-plus Study												
85 - 90 yrs.												
Betas				Betas								
95% CI				95% CI								
p				p								
Model variables												
Gait speed, m/s												
MMSE, points	0.000	-0.043;0.044	0.99	0.030	-0.026;0.085	0.17	0.020	-0.039;0.079	0.38	0.060	0.014;0.11	0.001
Processing speed*, # comb.	0.032	-0.007;0.071	0.034	0.050	0.005;0.095	0.004	0.044	-0.013;0.10	0.049	0.089	0.034;0.015	<0.001
Immediate recall†, # words	0.066	0.024;0.11	<0.001	0.030	-0.016;0.076	0.095	0.000	-0.058;0.058	0.99	0.042	-0.004;0.087	0.018
Delayed recall‡, # words	0.056	0.019;0.092	<0.001	0.023	-0.022;0.068	0.18	0.005	-0.049;0.059	0.80	0.051	0.002;0.099	0.007
Handgrip strength, kg												
MMSE, points	-0.001	-0.051;0.048	0.95	-0.010	-0.055;0.034	0.54	-0.024	-0.14;0.090	0.59	0.14	0.022;0.26	0.002
Processing speed*, # comb.	-0.037	-0.086;0.012	0.053	0.006	-0.032;0.045	0.67	-0.004	-0.076;0.068	0.89	0.16	0.055;0.26	<0.001
Immediate recall†, # words	0.007	-0.056;0.071	0.77	-0.036	-0.080;0.009	0.039	-0.080	-0.15;-0.006	0.006	0.13	0.045;0.22	<0.001
Delayed recall‡, # words	0.000	-0.055;0.056	0.98	-0.012	-0.050;0.027	0.44	-0.036	-0.10;0.029	0.15	0.13	0.051;0.21	<0.001

Abbreviations: Betas, standardized cross-lagged effects of cognitive performance on gait speed/handgrip strength; CI, confidence interval; p, p-value; MMSE, Mini-Mental State Examination; #, number. Cross-lagged panel models were adjusted for age, sex, education, number of comorbidities, depressive symptoms and physical activity. Assessed with ^{*}an adjusted version of the Alphabet Coding Task and the Letter Digit Substitution Task and with [†]the 15-Words test and 12 Picture Learning Test for LASA and the Leiden 85-plus Study, respectively.

Supplementary Table 2 Standardized cross-lagged effects of baseline gait speed/handgrip strength on different cognitive domains during follow-up

Model variables	LASA						Leiden 85-plus Study					
	55 - 64 yrs.			65 - 74 yrs.			75 - 85 yrs.			85 - 90 yrs.		
	Beta _{SC}	95% CI	p	Beta _{SC}	95% CI	p	Beta _{SC}	95% CI	p	Beta _{SC}	95% CI	p
MMSE, points												
Gait speed, m/s	-0.006	-0.047;0.034	0.69	0.066	0.007;0.13	0.004	0.10	0.038;0.16	<0.001	0.027	-0.018;0.073	0.12
Handgrip strength, kg	0.005	-0.11;-0.12	0.90	0.11	0.031;-0.19	<0.001	0.014	-0.12;0.15	0.79	0.16	-0.013;0.33	0.017
Processing speed*, # comb.												
Gait speed, m/s	0.005	-0.023;0.033	0.065	0.017	-0.013;-0.048	0.14	0.035	-0.008;0.078	0.036	0.014	-0.026;0.053	0.38
Handgrip strength, kg	0.016	-0.047;0.079	0.51	0.042	-0.015;-0.099	0.057	0.012	-0.074;0.099	0.71	0.076	-0.065;0.22	0.17
Immediate recall†, # words												
Gait speed, m/s	0.023	-0.023;0.069	0.20	0.005	-0.041;-0.051	0.78	0.029	-0.031;0.090	0.21	0.028	-0.023;0.078	0.16
Handgrip strength, kg	-0.078	-0.18;0.026	0.053	-0.067	-0.16;0.027	0.065	-0.080	-0.19;0.026	0.052	0.10	-0.074;0.27	0.14
Delayed recall†, # words												
Gait speed, m/s	0.029	-0.011;-0.070	0.064	0.016	-0.038;-0.069	0.45	0.049	-0.008;0.11	0.026	0.016	-0.033;0.066	0.40
Handgrip strength, kg	-0.038	-0.14;0.067	0.35	-0.021	-0.11;0.068	0.55	-0.011	-0.11;0.091	0.79	0.12	-0.068;0.31	0.10

Abbreviations: Betas_c, standardized cross-lagged effect of gait speed/handgrip strength on cognitive performance; CI, confidence interval; p, p-value; MMSE, Mini-Mental State Examination; #, number. Cross-lagged panel models were adjusted for age, sex, education, number of comorbidities, depressive symptoms and physical activity. Assessed with *an adjusted version of the Alphabet Coding Task and the Letter Digit Substitution Task and with †the 15-Words test and 12 Picture Learning Test for LASA and the Leiden 85-plus Study, respectively.

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Summary and general discussion

8

Human ageing is characterized by a gradual decline in cognitive and physical performance strongly determining someone's functional abilities and quality of life. Insights into these age-related changes and most importantly their interactions might be suggestive for potential causal mechanisms, which is required for an effective clinical assessment, development and application of interventions. The aim of this thesis was to enhance this understanding by assessing the interactions of cognitive and physical performance across different groups of calendar and biological age, i.e. the person's rate of ageing, which might deviate from its calendar age. Therefore, four different study populations were included: three large population based longitudinal cohorts and one cross-sectional study of elderly outpatients. The interactions were assessed across global measures representing functioning on several cognitive or physical domains and domain specific measures. Furthermore, the sensitivity of these measures to calendar and biological age were assessed. For the assessment of physical performance, instrumented measures were introduced to assess their additional value for the identification of age-related changes in physical performance and understanding of the influence of underlying determinants.

Main findings

In the **chapters two and three** we showed that the association of calendar age with domain specific measures of cognitive and physical performance is already observable from middle age, supporting the current literature¹⁻⁴. Higher calendar age was associated with worse performances on memory and executive tasks, sit-to-stand transfers and steady-state 25-meter walking speed. More complex cognitive tasks were sensitive for biological age, which was indicated by a better performance of offspring of nonagenarian siblings, who are enriched for familial factors of longevity, compared to their partners of similar calendar age. The assumed younger biological age of the offspring of nonagenarian siblings could not be detected by differences in physical performance. These findings indicate the early onset of age-related changes in cognitive and physical performance and the role cognitive performance might have in healthy ageing.

Furthermore, we showed in **chapter three** that instrumented measures of physical performance have similar sensitivity to calendar age as standard clinical measures. Instrumented measures showed strongest associations with calendar age for physical tasks requiring a good balance control; the extension and flexion phase of sit-to-stand and stand-to-sit transfers, respectively, and gait stability and symmetry in especially mediolateral direction during walking across a steady-state 25-meter course. These results indicate that instrumented measures can be used for the identification of age-related changes in physical performance from middle age and may be of additional value in getting insight into the influence of potential underlying determinants.

In the **chapters four to six** we showed that across two populations of different calendar and biological age, i.e. healthy middle-aged to older adults and elderly outpatients, a consistent cross-sectional relationship was found of poor global cognitive function and memory function with low 4-meter walking speed. For other physical domains such as standing balance and steady-state longer distance walks, associations were only found in the population of elderly outpatients. These findings suggest that independent of calendar and biological age, especially the initiation of movements, i.e. the start from standing position in the 4-meter walk, requires cognitive control, with memory function more in specific.

Moreover, we showed in **chapter four** that the presence of cerebral microbleeds and lacunar infarcts, as potential common underlying determinant of cognitive and physical performance, was associated with lower steady-state 25-meter walking speed independent of cognitive performance at middle age. These findings suggest that the influence of brain structure and cognitive performance on physical performance are two independent processes and emphasize the clinical relevance of identifying each of these possible underlying determinants of physical performance in order to develop targeted therapies.

In **chapter seven**, we showed that the temporal relationship between cognitive and physical performance differs across domains and calendar age, suggesting a specific rather than a general relationship. Across the age range of 55 to 90 years, lower executive function was associated with a stronger decline in 6-meter walking speed. From the age of 85 years, this relationship was found for the different measures of cognitive and physical performance that were tested, i.e. global cognitive function, memory and executive function, 6-meter walking speed and handgrip strength. An inverse relationship was found from the age of 65 years, with lower 6-meter walking speed being associated with a stronger decline in global cognitive function and across all measures of cognitive performance in the age range of 75 to 85 years. The findings in this study emphasize the importance of repeated measurements on different cognitive and physical domains and encourage further research to the development of domain and age specific interventions.

Reflection

Interactions between cognitive and physical performance

According to the influence of calendar age, consistent interactions between cognitive and physical performance were found across the entire age range of 45 to 90 years covered by the four study populations that were included. The influence of cognitive performance on physical tasks was found from the age of 55 years, supporting the findings of functional imaging studies showing that already from middle age, several additional brain areas are recruited during the performance of physical tasks when compared to younger adults^{5,6}. In the age range of 75 to 85 years, there seems to be a window with influences of physical performance on cognitive performance, while from the age of 85 years the influence of

cognitive performance is more prominent again with more elaborate interactions between different cognitive and physical domains compared to younger age groups. From the age of 85 years, associations with both low and high complex tasks, i.e. handgrip strength and walking, respectively, were found, while in younger age groups only associations with high complex tasks were observed. These more consistent interactions between different cognitive and physical domains above the age of 75 years might indicate a more significant role of cognitive and physical performance as compensating mechanisms of each other. A possible explanation for that might be the deterioration of other underlying systems such as the central and peripheral nervous, musculoskeletal and cardiovascular system, which are likely to be more affected in higher age groups^{7,8}.

Our specific findings for calendar age on the temporal relationship between cognitive and physical performance in chapter seven, might explain the inconsistent results according to the direction of this relationship in the current literature. They support the findings of longitudinal studies on broad age ranges showing bidirectional relationships and the findings of unidirectional relationships of longitudinal studies including a specific age range⁹⁻¹². The dependence of the interaction between cognitive and physical performance on specific domains, which was observed for both cross-sectional and temporal relationships, might explain the inconsistencies between studies even more. Furthermore, these findings indicate that different cognitive domains are incorporated in the performance of physical tasks instead of one in particular. Our results support the important role of executive function in walking, which has been frequently reported in literature, and also the less frequently studied influence of memory function¹³⁻¹⁵. Thereby, we showed that memory function might especially be of influence on the initiation of movements. However, future studies focusing on the role of different cognitive domains on these specific phases of physical tasks are needed to further explore this.

With respect to the effect of biological age, the association of cognitive performance with both low and high complex physical tasks was also found for a clinically relevant population of elderly outpatients (mean age (standard deviation) 82 (7) years). In this population, poor global cognitive function was associated with a lower ability to maintain standing balance and 4-meter walking speed, representing physical tasks of low and high complexity, respectively. These findings underpin the idea of cognitive performance as compensating mechanism for the deterioration of several other underlying determinants of physical performance^{8,16}.

For the assessment of physical performance, we showed that instrumented measures can be used for the identification of age-related changes in physical performance from middle age and may be of additional value in getting insights into the influence of underlying determinants. In addition to our findings of standard clinical measures showing longer durations on the performances of sit-to-stand transfers and a steady-state 25-meter walk at

higher calendar age, the findings of instrumented measures suggested that this might especially be the influence of balance control as one of the underlying determinants of these tasks. These more refined observations of performances on physical tasks using instrumented measures might provide insights into the relation with specific cognitive domains as well. Some studies already showed that more specific instrumented measures of walking, instead of walking speed as standard clinical measure, are associated with particular cognitive domains such as executive function^{17,18}. It was not possible to further explore this with the available data in this thesis, due to the minimal number of strides which is required for a reliable determination of instrumented measures of walking¹⁹. Within the study populations with available instrumented measures, only associations of cognitive performance with relatively short distance walks were found. This also shows a limitation of the use of instrumented measures, especially in clinical settings, where the practical realization of longer distance walks is sometimes difficult. More elaborate research on different and long enough physical tasks for a reliable estimation of instrumented measures across a wide range of calendar and biological age is needed to further investigate their additional value as sensitive marker of age-related changes and influence of underlying determinants in particular.

Potential causal mechanisms

One of the hypotheses for the co-occurrence of age-related changes in cognitive and physical performance is the presence of common underlying causes^{9,20}. The findings in chapter seven showing that age-related changes in cognitive and physical performance are present in both directions at the same time, whereby the effect sizes were similar, support this hypothesis. Brain pathology, at least at middle age, as a common underlying cause is less likely due to the independence of the association between brain structure and physical performance on cognitive performance we showed in chapter four. However, longitudinal studies covering a broader age range and including repeated measures of brain structure are needed to get more insight into this.

Besides brain pathology, other biological aspects of ageing have been suggested as common underlying causes of age-related changes in cognitive and physical performance. For example, an increased number of senescent cells, i.e. cells with a permanently arrested cell cycle, has been shown to be associated with age-related pathologies including decline in both cognitive and physical performance²¹. Furthermore, the potential role of metabolites, i.e. the intermediate and endpoint products of metabolism, in the ageing process has been shown by the age-dependence of metabolic profiles^{22,23}. Differences according to these important indicators of biological age have been shown between offspring of nonagenarian siblings and their partners, indicating a younger biological age of the offspring²⁴⁻²⁶. The better cognitive performance which was found for the offspring of nonagenarian siblings compared to their partners in this thesis encourage the idea of the

potential role of these biological aspects as underlying causal mechanisms. Together with the findings of a bidirectional temporal relationship between cognitive and physical performance, the findings in this thesis emphasize the need for ongoing research on these more general aspects of ageing.

Clinical implications and future directions

The interactions between cognitive and physical performance shown in this thesis support the potential effectiveness of cognitive and physical interventions to delay physical and cognitive decline, respectively. Especially on the effectiveness of physical interventions several studies have been performed showing reduced risks on cognitive decline and dementia²⁷⁻²⁹. Because the relationship of baseline physical performance on cognitive performance was found in particular between 75 and 85 years, interventions might be most effective in this age range. In the age range of 85 to 90 years, future studies on the effectiveness of cognitive interventions may be interesting because of the more prominent role of cognitive performance indicated in this thesis.

The already available interventions and promising results for the development of more specific ones encourages the early assessment of cognitive and physical performance. Based on the results in this thesis, we showed that age-related changes in cognitive and physical performance are already observable from middle age in the absence of overt diseases. Thereby, the presence of temporal relationships between cognitive and physical performance in each of the directions indicates the clinical relevance of measuring both; in patients with poor cognitive performance, a poor and faster change in physical performance should be considered and vice versa, in patients with poor physical performance a poor and faster change in cognitive performance should be considered. Because of the dependence of the interaction between cognitive and physical performance on specific domains, inclusion of these domain specific measures besides global measures is recommended.

According to the assessment of physical performance, instrumented measures can be used for the identification of age-related changes and thereby showed promising results in giving additional insights into potential underlying determinants. Moreover, some instrumented measures have the advantage of enabling measurements outside clinical settings providing a more complete observation of the patient. Future studies are however needed to investigate the potential of instrumented measures in characterizing groups of individuals based on deterioration of specific underlying determinants, like deterioration of the sensory system (including vision and the vestibular and proprioceptive systems), low muscle mass or strength and cognitive impairment. This will enable the development of more refined and patient specific interventions.

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Nederlandse samenvatting
– Summary in Dutch –

9

Introductie

Zelfredzaamheid van ouderen en daarmee ook de kwaliteit van leven wordt in belangrijke mate bepaald door zowel het cognitief als fysiek functioneren^{1,2}. Bij het verouderen van de mens gaan het cognitief en fysiek functioneren geleidelijk achteruit^{3,4}. Het doel van dit proefschrift was het inzicht in deze leeftijdsgerelateerde veranderingen in het cognitief en fysiek functioneren, en met name ook het inzicht in de interacties tussen beide, te vergroten. Dit met het uiteindelijke perspectief preventieve en therapeutische interventies te kunnen ontwikkelen die gericht zijn op een zo lang mogelijk behoud van de kwaliteit van leven.

Het cognitief en fysiek functioneren en de interactie tussen beide is onderzocht binnen vier studiepopulaties van verschillende kalender- en biologische leeftijd. Hierbij is de biologische leeftijd een indicatie van de snelheid van het verouderingsproces. Deze leeftijd kan dus lager of hoger liggen dan de kalenderleeftijd – ook wel chronologische leeftijd genoemd –, die het daadwerkelijke aantal levensjaren weergeeft. Binnen elke populatie is naar globale en domeinspecifieke maten van het cognitief en fysiek functioneren gekeken, waarbij globale maten een weerspiegeling zijn van het functioneren over meerdere cognitieve dan wel fysieke domeinen. De gevoeligheid van deze maten voor kalender- en biologische leeftijd is onderzocht, alsook de interacties tussen deze cognitieve en fysieke maten. Voor het beoordelen van het fysiek functioneren is daarnaast voor een aantal domeinen gekeken naar de toegevoegde waarde van het gebruik van instrumentele maten – verkregen met bewegingssensoren – voor de identificatie van leeftijdsgerelateerde veranderingen en voor het mogelijk geven van inzicht in de invloed van onderliggende systemen.

Studiepopulaties

De Leiden Langleven Studie

De Leiden Langleven Studie (LLS) is een longitudinaal cohort van 420 families bestaande uit minimaal twee langlevende broers en/of zussen van caucasische afkomst⁵. Mannen worden hierbij als langlevend beschouwd als zij 89 jaar of ouder zijn en vrouwen als zij 91 jaar of ouder zijn. In dit proefschrift is cross-sectioneel onderzoek gedaan naar het cognitief en fysiek functioneren van de nakomelingen van deze langlevende broers en zussen en de partners van deze nakomelingen. In deze studiepopulatie zijn de nakomelingen en hun partners van vergelijkbare middelbare leeftijd ($n=500$, gemiddelde leeftijd (standaarddeviatie) 66 (6) jaar) en kunnen voor onderzoek verstorende omgevingsfactoren als gelijk worden beschouwd, doordat zij al gedurende lange tijd samenleven. Op basis van de resultaten van eerdere studies – waarin onder andere een lagere prevalentie van leeftijdsgerelateerde ziektebeelden van de nakomelingen ten opzichte van hun partners is gevonden – wordt verondersteld dat de biologische leeftijd van de nakomelingen lager is

dan die van hun partners⁶⁻⁹. Voor verschillende domeinspecifieke maten van het cognitief en fysiek functioneren is dan ook onderzocht wat naast de relatie met kalenderleeftijd de relatie met biologische leeftijd is, door het vergelijken van de nakomelingen uit de langlevende families met hun partners. Daarnaast is het cross-sectionele verband tussen de verschillende cognitieve en fysieke domeinen onderzocht en de relatie met mogelijke onderliggende breinschade.

De Longitudinal Aging Study Amsterdam

De Longitudinal Aging Study Amsterdam (LASA) is een longitudinaal cohort bestaande uit een willekeurige steekproef van deelnemers tussen de 55 en 85 jaar ($n=3107$, gemiddelde leeftijd (standaarddeviatie) 71 (9) jaar) uit drie verschillende regio's in Nederland, die samen representatief zijn voor de Nederlandse bevolking¹⁰. Deze deelnemers worden elke drie jaar opnieuw onderzocht, waarbij ook het cognitief en fysiek functioneren wordt bepaald aan de hand van globale en domeinspecifieke maten. De data van de eerste vier herhaalde metingen zijn in dit proefschrift gebruikt om inzicht te krijgen in de relatie in de tijd – de temporele relatie – tussen het cognitief en fysiek functioneren; gaat een achteruitgang in het cognitief functioneren vooraf aan een achteruitgang in het fysiek functioneren, gaat deze relatie de andere kant op of komen de relaties in beide richtingen tegelijkertijd voor? Daarnaast is gekeken of deze relatie afhangt van het cognitieve en fysieke domein en van kalenderleeftijd.

De Leiden 85-plus Studie

De Leiden 85-plus Studie is een longitudinaal cohort van inwoners uit de stad Leiden (Nederland) met als inclusie criterium het bereikt hebben van een leeftijd van 85 jaar in het jaar van inclusie¹¹. Deze deelnemers ($n=599$) zijn jaarlijks gevolgd tot aan de leeftijd van 90 jaar. Voor het bepalen van het cognitief en fysiek functioneren zijn vergelijkbare testen gebruikt als binnen LASA, waardoor samen met die studiebevolking de relatie in de tijd over een leeftijdsrange van 55 tot 90 jaar is onderzocht.

Poliklinische ouderen

Om inzicht te krijgen in de mogelijke invloed van de gezondheidstoestand of biologische leeftijd op de interactie tussen het cognitief en fysiek functioneren, is cross-sectioneel onderzoek gedaan binnen een populatie van poliklinische ouderen. Deze studiebevolking ($n=299$, gemiddelde leeftijd (standaarddeviatie) 82 (7) jaar) bestaat uit thuiswonende ouderen die werden verwezen naar het Behandeladviescentrum Ouderengeneeskunde van een middelgroot opleidingsziekenhuis (Bronovo ziekenhuis, Den Haag, Nederland) voor een uitgebreid geriatrisch onderzoek, het comprehensive geriatric assessment (CGA). Onderdeel van het CGA is de beoordeling van het cognitief en fysiek functioneren aan de hand van globale en domeinspecifieke maten.

Hoofdbevindingen

In **hoofdstuk 2 en 3** wordt beschreven dat het cross-sectionele verband tussen kalenderleeftijd en domeinspecifieke maten van het cognitief en fysiek functioneren al waarneembaar is vanaf middelbare leeftijd, wat in overeenstemming is met de huidige literatuur^{3,4,12,13}. Deelnemers uit de LLS met een hogere kalenderleeftijd scoorden lager op geheugen- en executieve taken – uitvoerende taken die onder andere het vermogen om de aandacht te richten en de snelheid waarmee informatie verwerkt kan worden meten – en deden langer over het verrichten van vijf herhaalde bewegingen van zittende naar staande positie – de Chair Stand Test (CST) – en het afleggen van een 25-meter loop, gemeten op voorkeurssnelheid en in steady-state, dat wil zeggen zonder de versnellings- en vertragingssfase aan het begin en einde van looptest. De meest complexe cognitieve taken binnen zowel het geheugen als het executief functioneren waren daarbij ook gevoelig voor biologische leeftijdsverschillen, wat zichtbaar is door het verschil in prestaties tussen de nakomelingen uit langlevende families en hun partners. De nakomelingen scoorden hoger op deze complexe cognitieve taken vergeleken met hun partners (*hoofdstuk 2*). Dit verschil werd niet waargenomen voor het fysiek functioneren (*hoofdstuk 3*). De bevindingen in de hoofdstukken 2 en 3 benadrukken daarmee de vroege aanvang van leeftijdsgerelateerde veranderingen in het cognitief en fysiek functioneren en de rol die met name het cognitief functioneren zou kunnen hebben in succesvolle veroudering.

In **hoofdstuk 3** wordt daarnaast beschreven dat voor het detecteren van leeftijdsgerelateerde verschillen in het fysiek functioneren op middelbare leeftijd zowel standaard klinische als instrumentele maten kunnen worden gebruikt. Voorbeelden van standaard klinische maten zijn uitkomstmaten als de mogelijkheid om een test wel/niet succesvol te kunnen uitvoeren en de duur van een test. Onder instrumentele maten worden in dit hoofdstuk de uitkomstmaten bedoeld die zijn verkregen met een bewegingssensor gepositioneerd op de onderrug. Voor de eerder genoemde CST en 25-meter looptest was de effectgrootte van deze instrumentele maten voor het detecteren van leeftijdsgerelateerde verschillen gelijk aan die van de standaard klinische maten. De instrumentele maten die het sterkst geassocieerd waren met kalenderleeftijd hadden daarbij betrekking op de fasen die een goede controle van het evenwicht vereisen; de fase waarin de rug wordt gestrekt en gebogen gedurende de beweging van zittende naar staande positie en van staande naar zittende positie, respectievelijk, en de stabiliteit en symmetrie van het lopen in met name de zijwaartse richting. Deze resultaten tonen aan dat instrumentele maten gebruikt kunnen worden voor het detecteren van leeftijdsgerelateerde verschillen op middelbare leeftijd en daarnaast van toegevoegde waarde kunnen zijn in het verkrijgen van inzicht in de invloed van mogelijke onderliggende systemen.

In de **hoofdstukken 4 tot en met 6** wordt de interactie tussen het cognitief en fysiek functioneren op cross-sectioneel niveau beschreven. Hierbij werd binnen twee verschillende studiepopulaties, de nakomelingen en partners uit de LLS en poliklinische ouderen, een consistent cross-sectioneel verband gevonden tussen het globaal cognitief functioneren, het geheugen en de 4-meter loopsnelheid, gemeten op voorkeurssnelheid en startend vanuit stand. Voor andere fysieke domeinen zoals het evenwicht in staande positie en het lopen over langere loopafstanden gemeten in steady-state conditie, werd alleen een verband gevonden met het cognitief functioneren binnen de poliklinische ouderen. Deze resultaten suggereren dat onafhankelijk van kalender- en biologische leeftijd, met name de initiatie van bewegingen – de start vanuit stand bij de 4-meter looptest – cognitieve aansturing vereist met het geheugen in het bijzonder.

In **hoofdstuk 4** is daarnaast gekeken naar het verband tussen verschillende maten van subklinische breinschade – breinschade die (nog) geen klinisch zichtbare symptomen geeft – en het cognitief en fysiek functioneren, om zicht te krijgen op de invloed van dit mogelijke (gemeenschappelijke) onderliggende mechanisme. Hierbij werd gevonden dat de aanwezigheid van kleine bloedingen en infarcten in de hersenen – cerebrale microbloedingen en lacunaire infarcten – geassocieerd is met een lagere loopsnelheid op de 25-meter looptest, onafhankelijk van het cognitief functioneren. Deze bevindingen suggereren dat de invloed van deze subklinische vasculaire pathologie van het brein en het cognitief functioneren twee onafhankelijke mechanismen zijn die het fysiek functioneren beïnvloeden. Daarmee wordt tevens het klinische belang benadrukt van het identificeren van elk van deze mogelijke onderliggende systemen om tot doelgerichte behandelingen te kunnen komen.

De bevindingen in **hoofdstuk 7** beschrijven de relaties in de tijd tussen het cognitief en fysiek functioneren, waarbij werd gevonden dat deze relatie afhangt van het cognitieve en fysieke domein waarnaar wordt gekeken en de kalenderleeftijd. Over de gehele leeftijdsrange van 55 tot 90 jaar is een laag executief functioneren geassocieerd met een sterkere afname in de 6-meter loopsnelheid, gemeten op maximale snelheid en startend vanuit stand. Vanaf 85-jarige leeftijd werd deze relatie gevonden voor elk van de onderzochte cognitieve en fysieke maten: het globaal cognitief functioneren, het geheugen en executief functioneren, de 6-meter loopsnelheid en handknijpkracht. Vanaf 65-jarige leeftijd werd daarnaast een relatie in de andere richting gevonden: een lage 6-meter loopsnelheid is dan tevens geassocieerd met een sterkere afname in het globaal cognitief functioneren. In de leeftijdsrange van 75 tot 85 jaar gold dit voor alle cognitieve maten. De bevindingen van deze studie benadrukken het belang van het uitvoeren van herhaalde metingen over verschillende cognitieve en fysieke domeinen met toenemende leeftijd en onderschrijven daarnaast het belang van nader onderzoek naar de ontwikkeling van domein en leeftijdsspecifieke interventies.

Reflectie

Interactie tussen het cognitief en fysiek functioneren

De interactie tussen het cognitief en fysiek functioneren werd in dit proefschrift consistent aangetoond over de vier verschillende studiepopulaties die gezamenlijk een leeftijdsrange beslaan van 45 tot 90 jaar met variërende biologische leeftijd. De invloed van het cognitief functioneren op het fysiek functioneren werd daarbij gevonden vanaf een leeftijd van 55 jaar. Deze bevindingen worden ondersteund door de bevindingen van functionele MRI studies – een speciale MRI-techniek waarmee de activiteit van de hersenen wordt gemeten –, waarin is aangetoond dat, in vergelijking met jongvolwassenen, reeds vanaf middelbare leeftijd verscheidene extra hersengebieden worden geactiveerd gedurende het uitvoeren van fysieke taken^{14,15}. De leeftijdsrange van 75 tot 85 jaar lijkt een periode te zijn waarin er meer ruimte is voor invloed van het fysiek functioneren op het cognitief functioneren, terwijl vanaf 85-jarige leeftijd de invloed van het cognitief functioneren weer belangrijker lijkt te worden. Dit is onder meer zichtbaar door de verschillende cognitieve domeinen waarvoor een relatie in de tijd met het fysiek functioneren werden gevonden, in tegenstelling tot de bevindingen voor slechts één cognitief domein in jongere leeftijdsgroepen. Bovendien werden de interacties vanaf 85-jarige leeftijd gevonden voor zowel laag als hoog complexe taken – handknijpkracht en de 6-meter loopsnelheid, respectievelijk – terwijl in de leeftijdsrange van 55 tot 85 jaar dit verband alleen voor de hoog complexe taak werd gevonden. Het consistentere aanwezig zijn van de interacties tussen verschillende cognitieve en fysieke domeinen vanaf de leeftijd van 75 jaar zou erop kunnen wijzen dat het cognitief en fysiek functioneren twee belangrijke compenserende mechanismen voor elkaar zijn. Hieraan zou de verslechtering van onderliggende systemen zoals het centraal en perifeer zenuwstelsel, het musculoskeletaal systeem en het cardiovasculair systeem – die op hogere leeftijd meer zullen zijn aangetast^{16,17} – kunnen liggen.

Deze kalenderspecifieke relatie in de tijd tussen het cognitief en fysiek functioneren zou een verklaring kunnen zijn voor de ogenschijnlijk tegenstrijdige resultaten wat betreft de richting van deze relatie in de huidige literatuur. De resultaten in dit proefschrift ondersteunen de bevindingen van longitudinale studies die een relatie in beide richtingen aantonen binnen studiepopulaties die een brede leeftijdsrange beslaan, alsook de bevindingen van longitudinale studies die een relatie in slechts één richting vinden binnen een specifieke leeftijdsgroep¹⁸⁻²¹. De afhankelijkheid van de interactie tussen het cognitief en fysiek functioneren van het specifieke domein dat is gemeten, wat in dit proefschrift binnen zowel het cross-sectioneel als longitudinaal onderzoek is waargenomen, zou de tegenstrijdige bevindingen nog verder kunnen verklaren. De resultaten bevestigen daarnaast de bevindingen van eerdere studies die wijzen op de betrokkenheid van meerdere cognitieve domeinen in het uitvoeren van fysieke taken in plaats van één in het bijzonder;

de frequent beschreven rol van het executief functioneren bij lopen werd ook in dit proefschrift gevonden, alsook de minder frequent aangetoonde invloed van het geheugen²²⁻²⁴. Daarbij lijkt het geheugen met name van invloed op de initiatie van de beweging. Nader onderzoek is echter nodig om zicht te krijgen op deze meer specifieke relaties tussen cognitieve domeinen en de verschillende fasen waaruit een fysieke taak is opgebouwd.

Wat betreft het effect van biologische leeftijd werd de interactie tussen het cognitief en fysiek functioneren tevens gevonden binnen de populatie van poliklinische ouderen. In deze populatie was een laag globaal cognitief functioneren geassocieerd met een kleinere mogelijkheid om het evenwicht te bewaren bij verschillende manieren van staan en de 4-meter loopsnelheid, die respectievelijk een laag en hoog complexe taak representeren. Deze bevindingen onderbouwen de hypothese van het cognitief functioneren als compenserend mechanisme voor de verslechtering van verscheidene onderliggende systemen van het fysiek functioneren.

Voor het fysiek functioneren werd gevonden dat instrumentele maten gebruikt kunnen worden voor het detecteren van verschillen op middelbare leeftijd en dat ze van toegevoegde waarde zouden kunnen zijn om inzicht te krijgen in de invloed van onderliggende systemen. In aanvulling op de resultaten verkregen met standaard klinische maten – die op hogere leeftijd een langere duur van de CST en 25-meter loop lieten zien –, lijkt op basis van de instrumentele maten met name de controle van het evenwicht een belangrijk onderliggend systeem te zijn. Deze meer verfijnde observatie van het fysiek functioneren door gebruik te maken van instrumentele maten zou wellicht ook inzicht kunnen geven in de relatie van het fysiek functioneren met specifieke cognitieve domeinen. Enkele studies hebben reeds specifieke relaties van instrumentele maten van het lopen met domeinspecifieke maten van het cognitief functioneren beschreven^{25,26}. Wegens het minimaal aantal stappen dat nodig is voor een betrouwbare bepaling van instrumentele maten van het lopen, is het niet mogelijk geweest deze interactie met domeinspecifieke maten van het cognitief functioneren in dit proefschrift verder te onderzoeken²⁷. Binnen de onderzochte studiep populatie met beschikbare instrumentele maten zijn immers alleen interacties van het cognitief functioneren met de korte 4-meter loopafstand gevonden en niet met de langere 25-meter loopafstand. Dit toont tevens de beperking van het gebruik van instrumentele maten in klinische settingen aan, waarin het meten over langere loopafstanden soms lastig te realiseren is. Nader onderzoek naar het gebruik van instrumentele maten voor het beoordelen van verschillende fysieke domeinen, die zijn gemeten over een traject van voldoende lengte dan wel duur en over een breed spectrum wat betreft kalender- en biologische leeftijd, is dan ook nodig om de toegevoegde waarde hiervan als gevoelige marker voor leeftijdsgerelateerde verschillen verder te onderzoeken en zicht te krijgen op de relaties met specifieke cognitieve domeinen en op de invloed van mogelijke onderliggende systemen.

Mogelijke causale mechanismen

Een van de mogelijke verklaringen voor het tegelijkertijd voorkomen van leeftijdsgerelateerde veranderingen in het cognitief en fysiek functioneren is de aanwezigheid van een gemeenschappelijke onderliggende oorzaak^{18,28}. Deze hypothese wordt ondersteund door de bevindingen in hoofdstuk 7, waarin een bidirectionele interactie tussen het cognitief en fysiek functioneren werd gevonden met vergelijkbare effectgroottes in beide richtingen. Daarbij werd in hoofdstuk 4 gevonden dat subklinische vasculaire pathologie van het brein als gemeenschappelijke onderliggende oorzaak niet waarschijnlijk lijkt op middelbare leeftijd. Longitudinale studies met herhaalde metingen wat betreft de aanwezigheid van breinschade en het cognitief en fysiek functioneren, en die een bredere range beslaan wat betreft kalender- en biologisch leeftijd, zijn echter nodig om hier meer zicht op te krijgen.

Naast breinschade zijn andere biologische processen van veroudering gesuggereerd als mogelijke gemeenschappelijke onderliggende oorzaak voor leeftijdsgerelateerde veranderingen in het cognitief en fysiek functioneren. Zo is aangetoond dat de aanwezigheid van een verhoogd aantal senescente cellen – zogenaamde verouderde cellen die niet meer delen, maar waarvan de stofwisseling nog wel (op een verlaagd niveau) actief is – geassocieerd is met verscheidene leeftijdsgerelateerde ziektebeelden, waaronder ook een verminderd cognitief en fysiek functioneren²⁹. Daarnaast lijken metabolieten – de tussen- en eindproducten van de stofwisseling – een mogelijke rol te spelen in het verouderingsproces, wegens de leeftijdsafhankelijkheid van metabole profielen^{30,31}. Verschillen met betrekking tot bovenstaande belangrijke indicatoren van biologische leeftijd zijn tevens aangetoond in de LLS tussen de nakomelingen uit langlevende families en hun partners⁷⁻⁹. Deze verschillen wijzen op een jongere biologische leeftijd van de nakomelingen uit de langlevende families ten opzichte van hun partners. De bevindingen in dit proefschrift die een beter cognitief functioneren van de nakomelingen laten zien, ondersteunen de hypothese van de mogelijke rol van deze biologische processen als onderliggend causaal mechanisme. Samen met de bevindingen van de bidirectionele relatie tussen het cognitief en fysiek functioneren, onderstrepen de resultaten in dit proefschrift de behoefte aan verdergaand onderzoek naar deze meer algemene aspecten van veroudering.

Klinische implicaties en toekomstperspectieven

De interacties tussen het cognitief en fysiek functioneren zoals beschreven in dit proefschrift onderschrijven de potentiële effectiviteit van zowel cognitieve als fysieke interventies om achteruitgang in respectievelijk het fysiek en cognitief functioneren te vertragen. Met name wat betreft de effectiviteit van fysieke interventies hebben verscheidene studies laten zien dat deze kunnen leiden tot een verlaagd risico op cognitieve achteruitgang en dementie³²⁻³⁴. Omdat de relatie in de tijd van het fysiek functioneren op

het cognitief functioneren met name werd gevonden in de leeftijd van 75 tot 85 jaar, zijn deze fysieke interventies mogelijk het meest effectief in deze leeftijdsrange. Nader onderzoek naar de effectiviteit van cognitieve interventies in de leeftijdsrange van 85 tot 90-jarigen is van belang, vanwege de prominentere rol die het cognitief functioneren lijkt in te nemen vanaf deze leeftijd.

Het reeds beschikbaar zijn van interventies en de stimulerende resultaten voor de ontwikkeling van domeinspecifieke en leeftijdsgelateerde interventies, moedigen een vroege beoordeling van het cognitief en fysiek functioneren aan. In dit proefschrift hebben we laten zien dat leeftijdsrelateerde veranderingen in het cognitief en fysiek functioneren reeds zichtbaar zijn in een relatief gezonde populatie van middelbare leeftijd. De aanwezigheid van de relaties in de tijd tussen het cognitief en fysiek functioneren in beide richtingen benadrukt daarnaast het belang van het meten van beide aspecten; in patiënten met een laag cognitief functioneren dient rekening te worden gehouden met een verminderd en snellere achteruitgang in het fysiek functioneren en vice versa, in patiënten met een laag fysiek functioneren dient rekening te worden gehouden met een verminderd en snellere achteruitgang in het cognitief functioneren. Vanwege de afhankelijkheid van de interacties tussen het cognitief en fysiek functioneren van het specifieke domein, dienen bij de klinische beoordeling naast globale ook domeinspecifieke maten te worden meegenomen.

Met betrekking tot de beoordeling van het fysiek functioneren kunnen instrumentele maten worden gebruikt voor het detecteren van leeftijdsgelateerde verschillen. Daarnaast tonen deze maten verwachtingsvolle resultaten in het geven van inzicht in de invloed van mogelijke onderliggende systemen. Bovendien bieden instrumentele maten zoals verkregen met bewegingssensoren het voordeel dat zij het meten buiten de klinische setting mogelijk maken, wat een completere observatie van de patiënt geeft. Toekomstig onderzoek is echter nodig om zicht te krijgen op de mogelijkheid van het gebruik van instrumentele maten voor het karakteriseren van groepen van individuen op basis van de achteruitgang in specifieke onderliggende systemen, zoals een verslechtering van het sensorische systeem – die zintuigelijke informatie als zicht, evenwicht en tast omvat –, een lage spiermassa of spierkracht, dan wel cognitieve beperkingen. Dit zal uiteindelijk de ontwikkeling van meer verfijnde en patiëntspecifieke interventies mogelijk maken.

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