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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 people[1-3]. 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 performance[4].

The few longitudinal studies assessing the relationship between cognitive and physical performance in both directions, showed inconsistent results with uni- as well as bidirectional relationships[5-10]. Differences in findings between studies assessing different cognitive and physical domains might indicate dependence of the temporal relationship on these domains[4]. 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 older[11-13]. 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 population[14]. 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 Netherlands[15]. 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 status[16], comorbidity[17,18], depressive symptoms[19,20] and physical activity[21,22].

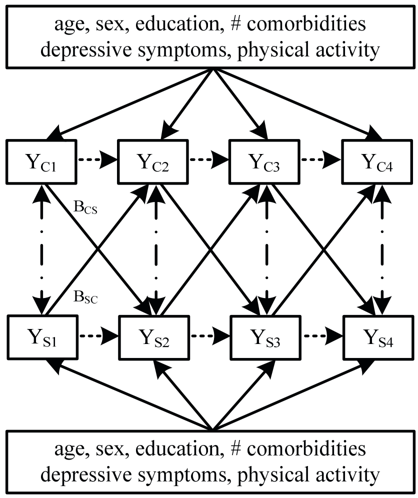

Figure 1 Cross-lagged panel model for estimation of the cross-lagged effects between cognitive and physical performance with confounding variables age, sex, education, number of comorbidities, depressive symptoms and physical activity. The model included synchronous and autoregressive correlations indicated 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.

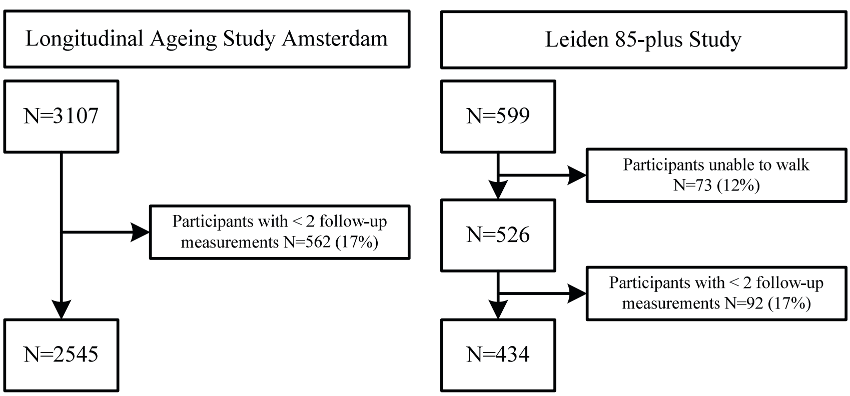

Figure 2 Flow chart of participants of the Longitudinal Ageing Study Amsterdam (LASA) and Leiden 85-plus Study included in the cross-lagged panel models. Abbreviations: N, number.

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 simultaneously[23]. 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 interest[24]. 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 variables[25]. 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 values[27]. 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^{2}[a]	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 [a]n=795, 730 and 658 for each of the age groups between 55 and 85 years, respectively; [b]n=390; [c]n=786 and 759 for each of the age groups between 65 and 85 years, respectively; [d]n=815, 735 and 665 for each of the age groups between 55 and 85 years, respectively; [e]n=377; [f]n=777 and 740 for each of the age groups between 65 and 85 years, respectively; and [g]n=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**	**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	0.029	0.99
Processing speed	0.051	0.038	0.98	0.039	0.034	0.99	0.036	0.028	0.99	0.042	0.032	0.99
Immediate recall	0.024	0.026	0.99	0.047	0.032	0.98	0.032	0.025	0.99	0.039	0.044	0.99
Delayed recall	0.019	0.028	1.0	0.034	0.031	0.99	0.008	0.024	1.0	0.042	0.040	0.99
Handgrip strength												
MMSE	0.039	0.070	0.99	0.068	0.039	0.99	0.070	0.040	0.98			
Processing speed	0.039	0.027	0.99	0.093	0.028	0.98	0.058	0.030	0.99		saturated model	
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.

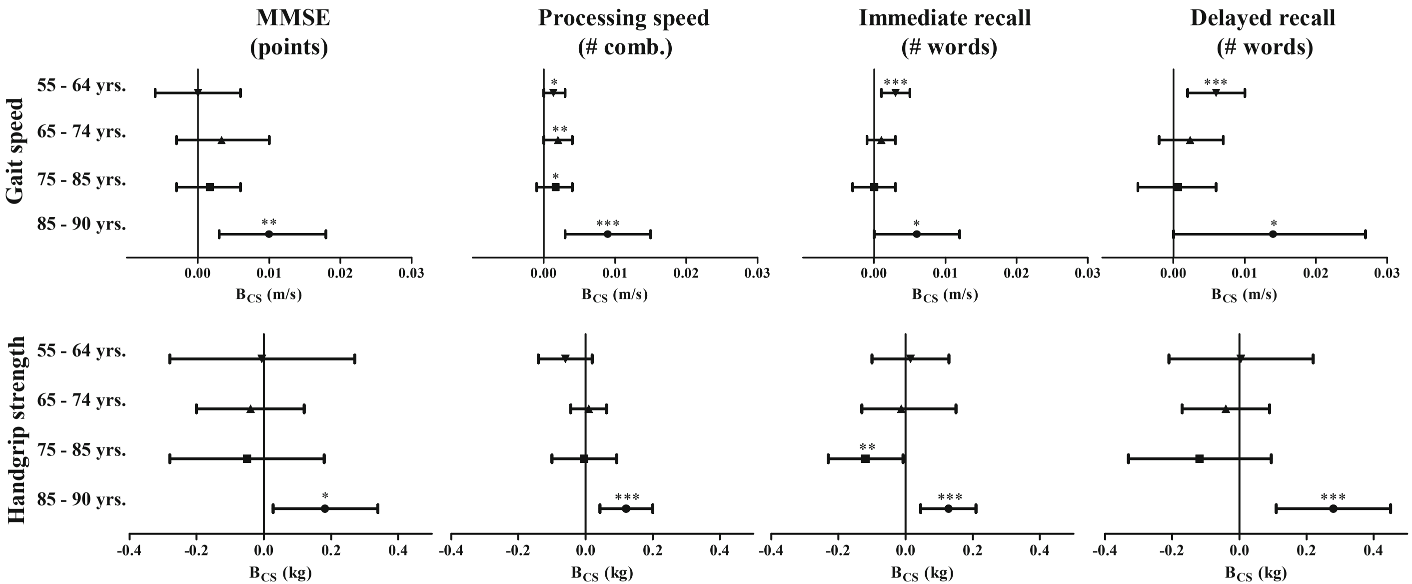

Figure 3 Unstandardized cross-lagged effects and 95% confidence intervals of different cognitive domains on gait speed and handgrip strength during follow-up. Cross-lagged panel models were adjusted for age, sex, education, number of comorbidities, depressive symptoms and physical activity. Abbreviations: 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.

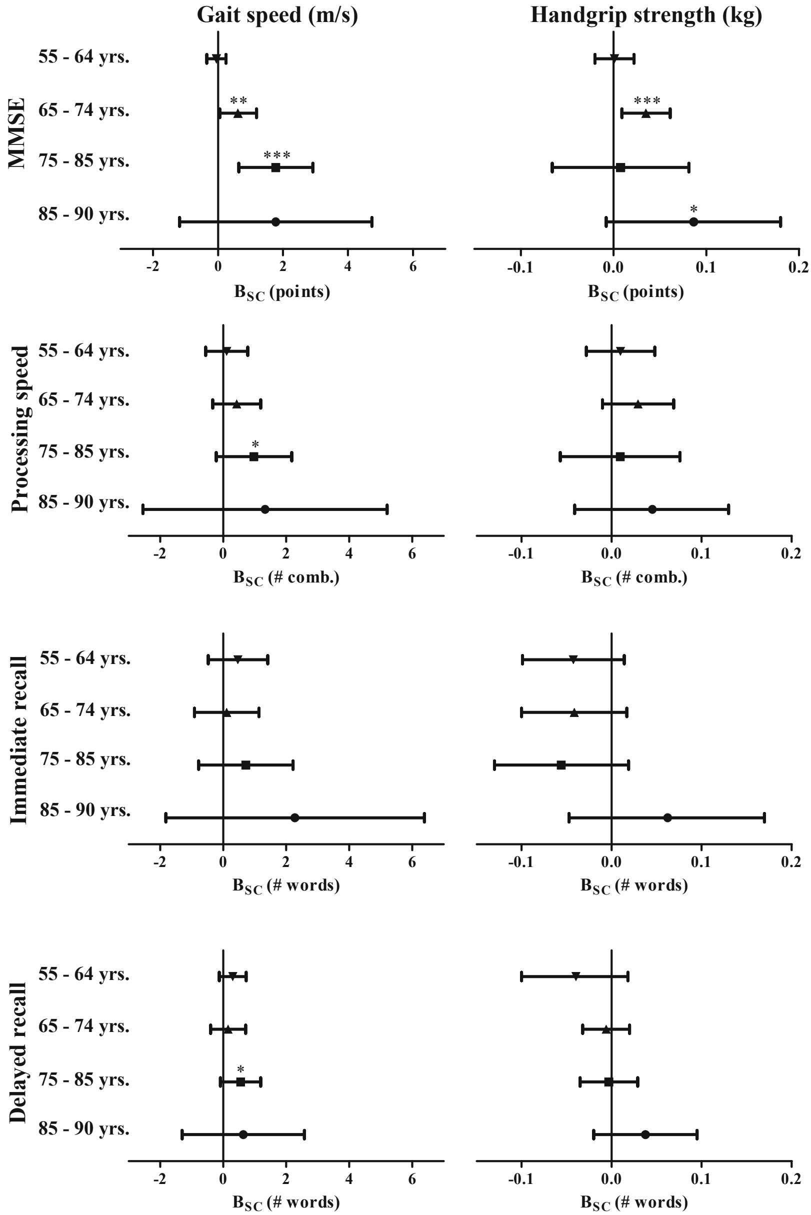

Figure 4 Unstandardized cross-lagged effects and 95% confidence intervals of gait speed and handgrip strength on different cognitive domains during follow-up. Cross-lagged panel models were adjusted for age, sex, education, number of comorbidities, depressive symptoms and physical activity. Abbreviations: 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 used[6] and unidirectional relationships in study populations consisting of more specific age ranges and health status[7-9]. 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 function[10], 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 performance[40-42]. Common biological processes throughout the entire human body, like cellular senescence, are suggested as well[43]. 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-15[45]. 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 Test[46]. 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 test[47] and 12-Picture Learning test[48] in LASA and the Leiden 85-plus Study, respectively. In the 15-Words test, which is the Dutch version of the Auditory Verbal Learning Test[49], 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 status[16]; 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 population[53]. Physical activity was assessed by the LASA physical activity questionnaire[54], 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, osteoarthrosis and malignancies[15]. 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 activity[56]. 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									Leiden 85-plus Study		
	55 - 64 yrs.			65 - 74 yrs.			75 - 85 yrs.			85 - 90 yrs.		
Model variables	**Beta$_{CS}$**	**95% CI**	**p**	**Beta$_{CS}$**	**95% CI**	**p**	**Beta$_{CS}$**	**95% CI**	**p**	**Beta$_{CS}$**	**95% CI**	**p**
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: Beta$_{CS}$, 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.

	LASA									Leiden 85-plus Study		
	55 - 64 yrs.			65 - 74 yrs.			75 - 85 yrs.			85 - 90 yrs.		
Model variables	**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: Beta$_{SC}$, 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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