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The Temporal Relation of Physical Function with Cognition and the Influence of Brain Health in the Oldest-Old

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Keywords
Cognition · Cognitive decline · Physical function · Physical decline · Neuroimaging · Oldest-old

Abstract
Introduction: Physical function and cognition seem to be interrelated, especially in the oldest-old. However, the temporal order in which they are related and the role of brain health remain uncertain. ***Methods:*** We included 338 participants (mean age 93.1 years) from two longitudinal cohorts: the UCI 90+ Study and EMIF-AD 90+ Study. We tested the association between physical function (Short Physical Performance Battery, gait speed, and handgrip strength) at baseline with cognitive decline (MMSE, memory tests, animal fluency, Trail Making Test (TMT-) A, and digit span backward) and the association between cognition at baseline with physical decline (mean follow-up 3.3 years). We also tested whether measures for brain health (hippocampal, white matter lesion, and gray matter volume) were related to physical function and cognition and whether brain health was a common driver of the association between physical function and cognition by adding it as confounder (if applicable). ***Results:*** Better performance on

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all physical tests at baseline was associated with less decline on MMSE, memory, and TMT-A. Conversely, fewer associations were significant, but better scores on memory, TMT-A, and digit span backward were associated with less physical decline. When adding measures for brain health as confounder, all associations stayed significant except for memory with gait speed decline. ***Conclusion:*** In the oldest-old, physical function and cognition are strongly related, independently of brain health. Also, the association between physical function and cognitive decline is more pronounced than the other way around, suggesting a potential for slowing cognitive decline by optimizing physical function.

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Introduction

Physical and cognitive impairment is highly prevalent in older individuals and has a major impact on quality of life and mortality. Previous studies have found that physical function and cognition are importantly intertwined [1–3]; however, the temporal order in which they are affected remains uncertain. Determining the temporal order of physical and cognitive decline is important as it will assist health care professionals in focusing screening and intervention programs and may help identifying causal pathways that are relevant for treatment and prevention. Earlier studies indicated that risk factors for cognitive decline may depend on age [4], indicating that results from studies in younger age-groups cannot be automatically extrapolated to the oldest-old. In addition, the prevalence of both physical and cognitive impairment strongly increases with age. For these two reasons, it is especially important and meaningful to study the association between physical and cognitive function in individuals aged 90 years and older (the oldest-old).

Several mechanisms have been suggested to explain the association between physical and cognitive functioning. First, brain pathologies may be a common underlying driver for both cognitive and physical decline as both physical and cognitive impairment is related to damage and atrophy of the gray and white matter (WM) of the brain [5, 6]. However, a recent postmortem study showed that only a minority of dual cognitive and physical decline is explained by brain pathologies [7] and that the association between physical function and cognition did not change when controlling for brain pathologies [8]. A second suggestion that has been made is that alternations in executive functioning and attention directly influence changes in gait [9]. This may implicate an important role for the frontal cortex, which is specifically affected by aging and emphasizes why it is important to study this association especially in the oldest-old [10]. Third, also mechanisms in the opposite direction have been proposed: training physical health would enhance cognitive performance [11], and physical impairment may be an early sign of cognitive impairment [3].

The aim of the present study was therefore to establish the temporal order in which physical and cognitive function decline in the oldest-old and to examine whether brain health assessed with MRI scans was a potential driving factor in the association between physical and cognitive functioning. We hypothesized that physical impairment would be associated with cognitive decline, but not the other way around, and that brain health would (partly) explain this association. To answer our research question, we combined data from the two largest brain imaging 90+ cohorts worldwide as the number of individuals aged 90 years and older included in neuroimaging studies is often limited [12].

Methods

Study Population

Participants were included from two cohorts: the 90+ Study at the University of California Irvine, CA, USA, and the European Medical Information Framework for Alzheimer's disease (EMIF-AD) 90+ Study in the Netherlands (for the characteristics and differences between the two cohorts, see online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000542395). The 90+ Study in Southern California (further described as the UCI 90+ Study) was initiated in 2003 and originally enrolled survivors from the Leisure World Cohort Study (LWCS) [13]. Over time, open recruitment beyond the LWCS was initiated, specifically focusing on brain imaging [14]. MRI scans were performed once at first opportunity beginning in 2014. Follow-up visits were performed every 6 months. In the present study, we included all participants from the UCI 90+ Study in whom physical and cognitive tests were performed and who had a brain MRI scan through November 2021.

The EMIF-AD 90+ Study was set up as a case-control study including cognitively normal and cognitively impaired participants [15]. Participants were recruited from June 2016 to July 2018 and the baseline of the study consisted of two home visits and two hospital visits including brain imaging. Follow-up visits were performed yearly in the participants who were cognitively normal at baseline. In the present study, we included all participants

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from the EMIF-AD 90+ Study in whom physical and cognitive tests were performed at baseline and who had a brain MRI scan. Both cohorts were approved by a local Medical Ethical Committee and all participants provided written informed consent.

Physical Function

The following three variables were included to describe physical functioning: the Short Physical Performance Battery (SPPB), gait speed, and handgrip strength. The SPPB includes tests for balance, gait speed, and a chair stand test (range 0–12 points, with higher scores representing better performance) [16]. Gait speed was included as part of the SPPB but also as separate variable and was measured in m/s by asking participants to walk 4 m at their usual pace with or without a walking aid. In the UCI 90+ Study, gait speed was measured once; in the EMIF-AD 90+ Study, the fastest gait speed of two attempts was used. Handgrip strength of the dominant hand was measured 3 times in the UCI 90+ Study with the Lafayette hand dynamometer (model 78,010) and 2 times in the EMIF-AD 90+ Study with the Jamar hand dynamometer (Sammons Preston, Inc., Bolingbrook, IL, USA). The highest score in kilograms was used in the analyses. If physical tests were not possible due to physical problems, a score of zero was used. In the UCI 90+ Study, all three physical function parameters were also measured during follow-up. In the EMIF-AD 90+ Study, only handgrip strength was measured during follow-up.

Cognition

The following cognitive tests were available in both cohorts and included in the present study: the Mini-Mental State Examination (MMSE) [17], animal fluency (in 1 min) [18], Trail Making Test (TMT-) A [19] (floored on 200 s in both cohorts), and the digit span backward [20]. For episodic memory, different list learning tests were used per cohort: the short 9-words version of the California Verbal Learning Test version II (CVLT-II) [21] in the UCI 90+ Study and the CERAD 10-words test [18] in the EMIF-AD 90+ Study. Immediate recall of the CVLT-II was the sum score over four trials. Immediate recall of the CERAD 10-words test was the sum over three trials. Delayed recall was administered after 10 min in both cohorts. Further details on the administration of these tests are described elsewhere [1, 22]. To combine the cognitive data, *z*-scores per cohort were calculated using the participants with a normal cognition at baseline as reference population (based on a method by Van der Elst et al. 2006). In this reference population, linear regression analyses were performed with the cognitive test as dependent variable and age, sex, and education (in three groups) as independent variables. The following formula was applied to calculate *z*-scores per cohort using the constant, betas, and standard deviation of the residuals from the linear regression: cognitive *z*-score = {raw score – [beta constant + (age × beta age) + (sex × beta sex) + (education low × beta education low) + (education high × beta education high)]}/standard deviation of the residuals.

Brain Imaging

In the UCI 90+ Study, all participants were scanned on a single GE Discovery 750W 3-T scanner (General Electric Healthcare, Milwaukee, WI, USA), and in the EMIF-AD 90+ Study, all participants were scanned on a single Philips 3T Achieva scanner. In both studies, volumetric segmentation of the 3D T1 images was performed using FreeSurfer v7.1 (https://surfer.nmr.mgh.harvard.edu) [23]. All FreeSurfer segmentations were visually inspected. In the UCI 90+ Study, segmentations of 14 scans failed and had to be excluded; in the EMIF-AD 90+ Study, segmentations failed in three that had to be excluded and an additional two scans, where gray matter volume measures were incorrect based on the visual inspection. The following segmentations were used as measures for brain health in the present study: hippocampal volume (the sum of left and right), WM lesion volume, and total gray matter volume. WM lesions were determined as hypointense lesions on T1 images rather than as hyperintensities on FLAIR as the FLAIR sequence (2D for UCI 90+ and 3D for EMIF-AD 90+) and WM hyperintensity methods differed substantially between the two studies. WM T1 hypointensities have been shown to strongly correlate with WM FLAIR hyperintensities [24]. MRI measures were corrected for head size by calculating the percentage of the MRI measure relative to intracranial volume. WM lesion volume was log transformed to normalize its distribution. To harmonize the MRI measures between the two cohorts, ComBat (the nonparametric version and without empirical Bayes) was used with adding age and sex as confounders [25].

Cognitive Status Evaluation

In both cohorts, cognitive status was based on clinical evaluation by a medical doctor and neuropsychologist, in combination with the MMSE score. In the UCI 90+ Study, criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), were applied [26] and participants who did not meet the DSM-IV criteria for dementia but had some cognitive or functional loss were diagnosed with cognitive impairment no

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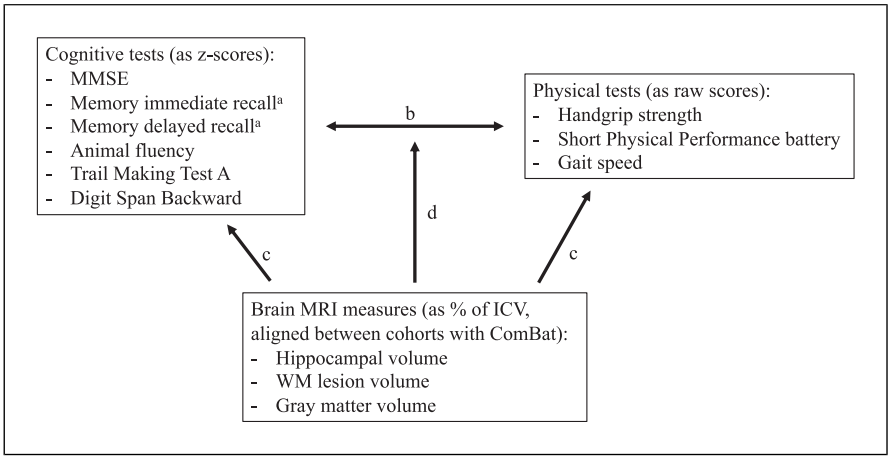

Fig. 1. Graphical depiction of the associations tested. [a]Assessed by the 9-words version of the California Verbal Learning Test version II (CVLT-II) in UCI 90+ and by the CERAD 10-words test in EMIF-AD 90+; [b]Cross-sectional and longitudinal associations, tested in both directions; [c]Cross-sectional and longitudinal associations with the brain MRI measures as independent variables; [d]Brain MRI measures were added as confounder to the significant associations between cognition and physical function. ICV, intracranial volume; MMSE, Mini-Mental State Examination (only cognitive test for which the raw score was used in the analyses); WM, white matter.

dementia (CIND) [27]. In the EMIF-AD 90+ Study, criteria for a diagnosis of amnestic mild cognitive impairment (MCI) [28] or a diagnosis of probable or possible Alzheimer's disease [29] were used. During follow-up, the Clinical Dementia Rating (CDR) score was used to determine whether a participant cognitively deteriorated toward MCI (CDR = 0.5) or dementia (CDR >0.5).

Comorbidity Variables

In both cohorts, data about education and medical history were based on self-report. Medication use was based on medication container inspection in the UCI 90+ Study and on self-report in the EMIF-AD 90+ Study. If needed, information on medical history and medication use was complemented with information by study partner in the UCI 90+ Study, and by study partner and GP and/or medical specialist in the EMIF-AD 90+ Study. The following comorbidities were considered as potential confounders when present at baseline (based on medical history and medication use): hypertension, diabetes mellitus, hypercholesterolemia, stroke/transient ischemia attack, heart disease (including coronary artery disease, myocardial infarction, atrial fibrillation or other arrhythmias, heart valve disease, congestive heart failure, or coronary artery bypass). In addition, the Geriatric Depression Scale (GDS) was administered in both cohorts at baseline and considered as potential confounder [30].

Statistical Analyses

Differences between the participants from the UCI and EMIF-AD 90+ Study were investigated using *t* tests, chi-square tests, or Wilcoxon tests where appropriate. To assess the temporal order of the association between physical function and cognition, two sets of associations were performed: (1) the association between physical function at baseline with cognition at baseline and during follow-up, (2) the association between cognition at baseline with physical function at baseline and during follow-up (Fig. 1). Baseline (time = 0) in the UCI 90+ Study was defined as the visit closest to the MRI scan and in the EMIF-AD 90+ Study as the first home visit. From the UCI 90+ Study, all visits within 1 year before the MRI scan and all visits after the scan were included, whereas from the EMIF-AD 90+ Study all visits were included. Linear mixed models were used including the following variables: (1) one cognitive test as dependent variable and one physical function test, time (in years), and the interaction between the physical function test and time as independent variables, (2) one physical function test as dependent variable and one cognitive test, time (in years), and the interaction between the cognitive test and time as independent variables. Subject-specific intercepts and linear change with time (the slope) were added to all models as random effects. Furthermore, models were adjusted for the fixed effects of age at baseline, sex, education, and the significant comorbidity variables (defined as significant when there was an association at

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baseline of the comorbidity with physical function and of the same comorbidity with cognition). The estimate of the physical function or cognitive test reflects the baseline effect, whereas the interaction between the physical functioning or cognition test with time reflects the longitudinal effect. Separate analyses were performed for each combination of physical and cognitive test.

To assess the association between brain health at baseline with physical function or cognition at baseline and during follow-up, linear mixed models were used including the following variables: one physical function or cognitive test as dependent variable and one measure for brain health, time (in years), and the interaction between the brain health measure and time as independent variables (Fig. 1). Models were adjusted for a random subject-specific intercept, a random slope, and fixed effects for age at baseline, sex, and education. If one of the measures for brain health was associated with both physical function and cognition, it was added to the linear mixed model described above to assess it as a potential common driver.

The following sensitivity analyses were performed: (1) to assess the influence of cognitive diagnosis on the association between physical function and cognition, cognitive diagnosis (normal vs. CIND/MCI/dementia) was added to the above described linear mixed models as interaction term with the independent physical or cognitive variable. If significant, analyses were repeated separately for the cognitively normal and impaired (CIND/MCI/dementia) participants. (2) To assess whether the association between physical function and cognition differed per cohort, cohort type (UCI or EMIF-AD) was added to the above-described linear mixed models as interaction term with the independent physical or cognitive variable. If significant, analyses were repeated for the two cohorts separately.

The p value threshold for significance was set at 0.05. In the tables, we additionally indicated significance after Holm's sequential Bonferroni correction [31]. The n (number of tests) in the Holm-Bonferroni formula (target p value/[n – rank +1]) was based on the number of outcome measures (so "6" when cognition was the outcome and "3" when physical function was the outcome). Statistical analyses were performed in RStudio version 2023.06.0 + 421 with R version 4.3.1 [32]. The lmerTest package was used for the linear mixed models [33].

Results

Baseline characteristics of the total study population and per cohort are shown in Table 1, and the number of individuals for each variable (at baseline, during follow-up and per cohort) is shown in online supplementary Table S2 (which indicates the lost to follow-up during the study). In total, 338 participants (62.7% female) were included who were on average 93.1 (interquartile range 91.0–94.4) years old. At baseline, 226 (66.9%) participants were cognitively normal and the mean follow-up time was 3.3 (interquartile range 1.9–4.6) years. The two cohorts significantly differed by age, cognitive status at baseline, number of follow-up visits, raw scores on the animal fluency and TMT-A, SPPB, gait speed, hippocampal volume, and gray matter volume.

Evaluation of the comorbidities (hypertension, diabetes mellitus, hypercholesterolemia, stroke/transient ischemia attack, and heart disease) showed that none were associated with physical function and therefore they were not included as confounders in the analyses. However, GDS was associated with the SPPB, gait speed, handgrip strength, memory immediate recall, memory delayed recall, and TMT-A. Therefore, GDS was added as confounder to all analyses.

Association of Physical Function at Baseline with Cognition at Baseline and during Follow-Up

At baseline, a higher score on the SPPB was associated with better scores on all cognitive tests (p values ranging from <0.01 to 0.04; Table 2; Fig. 2; online suppl. Fig. S1). Faster gait speed was associated with better scores on all cognitive tests (p values <0.01), except for the digit span backward (p value = 0.07), and a stronger handgrip was associated only with a faster TMT-A (p value = 0.01).

Better scores on all physical function parameters at baseline were associated with slower decline on the MMSE, memory, and TMT-A (p values ranging from <0.01 to 0.02; Table 2; Fig. 2; online suppl. Fig. S1). In addition, gait speed was associated with slower decline on animal fluency (p value <0.01).

Association of Cognition at Baseline with Physical Function at Baseline and during Follow-Up

At baseline, better scores on all cognitive tests except for the digit span backward, were associated with better scores on the SPPB and faster gait speed (p values ranging from <0.01 to 0.02; Table 3; Fig. 3; online suppl. Fig. S2). In addition, better animal fluency and a faster TMT-A were associated with a stronger handgrip (both p values <0.01).

Better memory and a faster TMT-A at baseline were associated with less decline of gait speed (p values ranging from 0.01 to 0.03; Table 3; Fig. 3; online suppl. Fig. S2). In addition, better performance on the digit span backward

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Table 1. Baseline characteristics of the total study population and per cohort

	Total	UCI 90+	EMIF-AD 90+	*p* value[a]
Sample size, *N*	338	249	89	N/A
Age, y	93.1 (2.9)	93.4 (2.9)	92.4 (2.7)	<**0.01**
Females, *N* (%)	212 (62.7)	162 (65.1)	50 (56.2)	0.17
Education[b]				N/A[c]
Low	68 (20.1)	56 (22.5)	12 (13.5)	
Average	146 (43.2)	105 (42.2)	41 (46.1)	
High	124 (36.7)	88 (35.3)	36 (40.4)	
GDS, points	2.1 (2.1)	2.2 (2.2)	1.9 (1.6)	1.00
Cognitive status at baseline				<**0.01**
Normal	226 (66.9)	159 (63.9)	67 (75.3)	
CIND/MCI[d]	81 (24.0)	76 (30.5)	5 (5.6)	
Dementia	31 (9.2)	14 (5.6)	17 (19.1)	
Follow-up time (IQR), y	3.3 (1.9–4.6)	3.3 (1.7–4.6)	3.3 (2.5–4.0)	0.98
Number of follow-up visits	5.1 (3.4)	7.9 (3.5)	3.1 (1.2)	<**0.01**
MMSE, points	27.3 (2.7)	27.2 (2.7)	27.4 (2.9)	0.18
Memory immediate recall, *z*-score[e]	−0.5 (1.2)	−0.5 (1.2)	−0.5 (1.2)	0.89
Memory delayed recall, *z*-score[e]	−0.5 (1.3)	−0.5 (1.4)	−0.4 (1.2)	0.70
Animal fluency, words[f]	15.2 (4.9)	14.9 (4.8)	16.3 (5.2)	**0.03**
TMT-A, sec[f]	72.8 (38.5)	64.7 (33.8)	93.8 (42)	<**0.01**
Digit span backward, digits[f]	5.5 (1.9)	5.5 (2.0)	5.5 (1.7)	0.96
Handgrip strength females, kg	11.8 (5.1)	11.6 (5.3)	12.1 (4.6)	0.53
Handgrip strength males, kg	21.4 (7.4)	21.1 (7.7)	21.9 (7.0)	0.55
SPPB, points	7.0 (2.9)	6.8 (2.9)	7.7 (2.8)	**0.01**
Gait speed, m/s	0.7 (0.3)	0.6 (0.3)	0.8 (0.3)	<**0.01**
Hippocampal volume, % ICV[g]	0.43 (0.1)	0.43 (0.1)	0.42 (0.1)	**0.04**
WM lesion volume, % ICV[g]	0.9 (0.7)	0.9 (0.7)	0.9 (0.6)	0.94
Gray matter volume, % ICV[g]	36.6 (2.9)	37.1 (2.6)	35.3 (3.3)	<**0.01**

Values are presented as mean (SD), unless stated otherwise. CIND, cognitive impairment no dementia; EMIF-AD, European Medical Information Framework for Alzheimer's disease; ICV, intracranial volume; IQR, interquartile range; m/s, meter per second; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; *N*, number; N/A, not applicable; SPPB, Short Physical Performance Battery; TMT, Trail Making Test; UCI, University of California, Irvine; WM, white matter; y, years. [a]*p* values compare the UCI 90+ participants with the EMIF-AD 90+ participants and are determined using *t*-tests, chi-square tests, or Wilcoxon tests where appropriate. [b]UCI 90+ low = less than college, average = some college or college degree, high = beyond college; EMIF-AD 90+ low = at most primary school, average = junior vocational training, high = senior vocational or academic training. [c]Difference in educational level was not assessed as school systems differ too much to give a relevant result. [d]Clinical diagnosis, in the UCI 90+ Study described as CIND, in the EMIF-AD 90+ Study as MCI. [e]Assessed by the 9-words version of the California Verbal Learning Test version II (CVLT-II) in UCI 90+ and by the CERAD 10-words test in EMIF-AD 90+. [f]In the analyses, *z*-scores are used. [g]These are the MRI measures before applying ComBat.

at baseline was associated with less decline of the SPPB and handgrip strength (both *p* values = 0.01) and a faster TMT-A at baseline with less decline of handgrip strength (*p* value = 0.02). Of the 18 associations tested longitudinally (three physical tests times the six cognitive tests), 13 showed a significant association between physical

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Table 2. Association of baseline physical function with cognition[a]

Physical function at baseline	Cross-sectional effect											
	MMSE		memory immediate recall		memory delayed recall		animal fluency		TMT-A[b]		digit span backward	
	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
SPPB	**0.16 (0.06–0.27)**	**<0.01[c]**	**0.11 (0.06–0.16)**	**<0.01[c]**	**0.09 (0.04–0.15)**	**<0.01[c]**	**0.08 (0.04–0.12)**	**<0.01[c]**	**−0.12 (−0.17 to −0.08)**	**<0.01[c]**	**0.04 (0.00–0.08)**	**0.04**
Gait speed	**1.96 (0.85–3.0′7)**	**<0.01[c]**	**1.35 (0.81–1.89)**	**<0.01[c]**	**0.94 (0.35–1.54)**	**<0.01[c]**	**0.65 (0.22–1.07)**	**<0.01[c]**	**−1.42 (−1.94 to −0.89)**	**<0.01[c]**	0.40 (−0.03 to 0.82)	0.07
Handgrip strength	0.02 (−0.03 to 0.06)	0.52	0.01 (−0.01 to 0.04)	0.23	0.02 (0.00–0.05)	0.10	0.02 (0.00–0.04)	0.06	**−0.03 (−0.05 to −0.01)**	**0.01**	0.01 (−0.01 to 0.03)	0.29
	Longitudinal effect											
	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
SPPB	**0.09 (0.04–0.15)**	**<0.01[c]**	**0.02 (0.00–0.04)**	**0.01[c]**	**0.02 (0.00–0.04)**	**0.01[c]**	0.01 (0.00–0.02)	0.05	**−0.03 (−0.05 to −0.02)**	**<0.01[c]**	−0.01 (−0.02 to 0.00)	0.22
Gait speed	**0.99 (0.42–1.57)**	**<0.01[c]**	**0.23 (0.05–0.40)**	**0.01[c]**	**0.21 (0.04–0.39)**	**0.01[c]**	**0.18 (0.06–0.30)**	**<0.01[c]**	**−0.35 (−0.51 to −0.19)**	**<0.01[c]**	−0.03 (−0.14 to 0.08)	0.59
Handgrip strength	**0.02 (0.00–0.05)**	**0.02**	**0.01 (0.00–0.02)**	**<0.01[c]**	**0.01 (0.00–0.01)**	**0.02**	0.00 (0.00–0.01)	0.38	**−0.01 (−0.01 to 0.00)**	**<0.01[c]**	0.00 (0.00–0.00)	0.66

βs and 95% CIs of each cognitive test are determined in a linear mixed model that includes the following variables: one of the physical function parameters at baseline, time, the interaction between the physical function parameter and time, the confounders age at baseline, sex, education, cohort type (UCI or EMIF-AD 90+ Study), and the score on the GDS at baseline as fixed effects and subject-specific intercepts and linear change with time (the slope) as random effects. The β for the cross-sectional effect shows the change in cognitive *z*-score at baseline per unit increase in physical function parameter at baseline. The β for the longitudinal effect shows the annual change in cognitive *z*-score per unit increase in physical function parameter at baseline. CI, confidence interval; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery; TMT, Trail Making Test. The bold values are the significant *p* values (before Holm's sequential Bonferroni procedure). [a]Cognitive tests are analyzed as *z*-scores, except for the MMSE, which is the raw score. [b]For the TMT-A, higher scores represent worse performance; for all other cognitive tests, higher scores represent better performance. [c]*p* value significant after correcting for the number of outcome measures using the Holm's sequential Bonferroni procedure.

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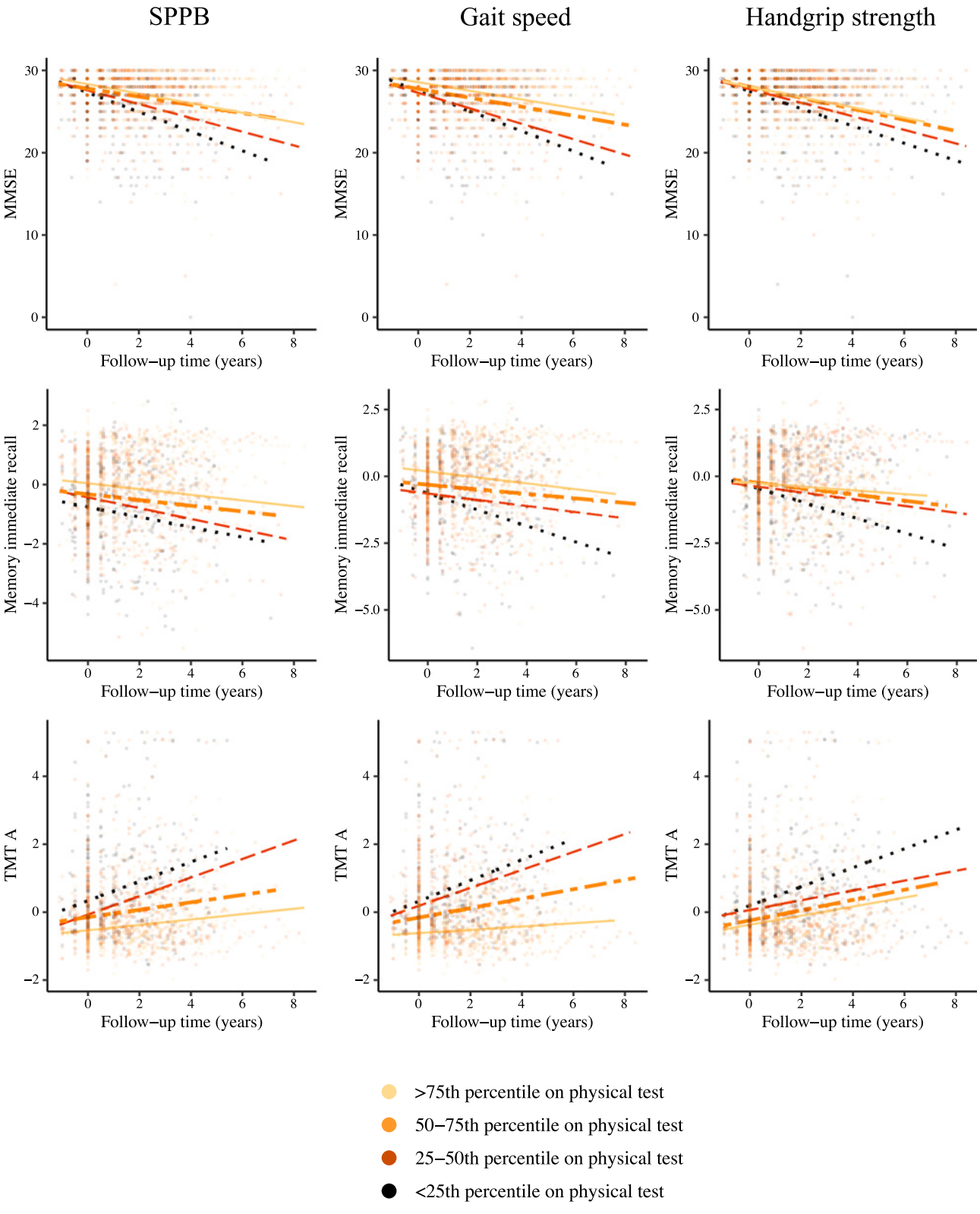

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function at baseline and cognitive decline (Tables 2) and 6 showed a significant association between cognition at baseline and physical decline (Table 3).

Association of Brain MRI Measures with Cognition and Physical Function

Better brain health (defined as greater hippocampal or gray matter volume or fewer WM lesions) was associated with better cognitive functioning and less cognitive decline on all cognitive tests (p values ranging from <0.01 to 0.05), except for the digit span backward (p values ranging from 0.09 to 0.97; online suppl. Table S3). In addition, better brain health was associated with better performance on all physical function parameters (p values ranging from <0.01 to 0.02; online suppl. Table S4). Also, hippocampal and gray matter volume were associated with less decline on the SPPB and/or gait speed (p values ranging from <0.01 to 0.02). All significant associations between cognition and physical function remained significant after adding hippocampal volume, WM lesions, or gray matter volume as confounder in the analyses. The only exception was the association between memory delayed recall and decline in gait speed, which became borderline significant when adding hippocampal or gray matter volume as confounder to the analyses (with hippocampal volume as confounder: $\beta = 0.01$, p value = 0.07; with gray matter volume as confounder: $\beta = 0.01$, p value = 0.07).

Sensitivity Analyses

One cross-sectional and two longitudinal associations showed a significant interaction with cognitive diagnosis: gait speed with TMT-A, handgrip strength with decline on memory immediate recall, and gait speed with decline on MMSE. When performing these analyses separately in the cognitively normal and impaired group, both groups showed significant results, but estimates were higher in the cognitively impaired group (data not shown).

One cross-sectional and two longitudinal associations showed a significant interaction with cohort: memory delayed recall with gait speed and SPPB and gait speed with animal fluency decline. When performing these analyses separately per cohort, the cross-sectional association of memory delayed recall with gait speed was present in both cohorts, but the estimate was higher in the EMIF-AD 90+ Study. The two longitudinal associations were only present in the UCI 90+ Study (data not shown).

Discussion

Overall Findings

In individuals aged 90 years and older (the oldest-old), this study showed that physical function and cognition are inherently intertwined. The association of better physical function at baseline with less cognitive decline was more pronounced than the association between better cognition at baseline with less physical decline. Of the different cognitive tests, slower performance on the TMT-A was most evident associated with physical impairment and decline. Of the tests for physical function, the SPPB and gait speed showed more associations with cognition at baseline than handgrip strength. All measures for brain health (hippocampal, WM lesion, and gray matter volume) were related to physical and cognitive functioning at baseline and during follow-up. However, when controlling for brain health in the significant associations between physical and cognitive function, these associations did not change. This suggests that the associations between cognition and physical function were independent of brain health.

(Temporal Order of the) Association between Physical Function and Cognition

Most prior studies assessing physical functioning in relation to cognition were performed in groups aged 65–80 years [34]. A few studies focused on older individuals, but studies in individuals aged 90 years and older remain scarce [15, 35]. It has been suggested that the association between physical function and cognition is especially present and more pronounced in the oldest-old, highlighting the importance of the present study [2]. Our study confirmed the strong interrelation between physical function and cognition in this age-group. Results about the temporal order in which physical function and cognition were related vary and might depend on the age-group in which it has been studied [2, 36]. However, mixed results have also been found in individuals aged 85 and older. In the Leiden 85-plus Study, better baseline

Fig. 2. Association of physical function with cognitive decline. Lines are the predicted trajectories for a participant with the most common characteristics: women, age 92.2 years (median age of study population), from the UCI 90+ Study, with an average education level and a GDS score of 2 (median of study population). The cognitive scores are Z-scores except for MMSE. For all physical and cognitive tests, higher scores represent better performance, except for the TMT-A (for which lower scores are better). MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery; TMT, Trail Making Test.

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Table 3. Association of baseline cognition[a] with physical function

Cognition at baseline	Cross-sectional effect						Longitudinal effect					
	SPPB		gait speed		handgrip strength		SPPB		gait speed		handgrip strength	
	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
MMSE	**0.13 (0.02–0.24)**	**0.02[b]**	**0.01 (0.00–0.02)**	**0.01[b]**	0.04 (–0.18 to 0.27)	0.72	0.03 (–0.01 to 0.07)	0.13	0.00 (0.00–0.01)	0.11	0.03 (–0.07 to 0.13)	0.54
Memory immediate recall	**0.48 (0.25–0.70)**	**<0.01[b]**	**0.05 (0.03–0.07)**	**<0.01[b]**	0.24 (–0.22 to 0.71)	0.30	0.05 (–0.01 to 0.12)	0.12	**0.01 (0.00–0.01)**	**0.02**	0.16 (–0.01 to 0.33)	0.07
Memory delayed recall	**0.35 (0.14–0.56)**	**<0.01[b]**	**0.03 (0.01–0.05)**	**<0.01[b]**	0.42 (–0.01 to 0.85)	0.06	0.02 (–0.05 to 0.09)	0.58	**0.01 (0.00–0.01)**	**0.01[b]**	0.10 (–0.06 to 0.27)	0.22
Animal fluency	**0.54 (0.27–0.80)**	**<0.01[b]**	**0.04 (0.02–0.07)**	**<0.01[b]**	**0.82 (0.27–1.36)**	**<0.01[b]**	–0.01 (–0.09 to 0.07)	0.87	0.00 (–0.01 to 0.01)	0.92	0.13 (–0.07 to 0.32)	0.20
TMT-A[c]	**–0.73 (–0.96 to –0.50)**	**<0.01[b]**	**–0.06 (–0.08 to –0.04)**	**<0.01[b]**	**–1.06 (–1.56 to –0.56)**	**<0.01[b]**	–0.04 (–0.13 to 0.05)	0.39	**–0.01 (–0.02 to 0.00)**	**0.03**	**–0.25 (–0.46 to –0.04)**	**0.02**
Digit span backward	0.14 (–0.14 to 0.43)	0.33	0.02 (0.00–0.05)	0.11	–0.10 (–0.68 to 0.48)	0.75	**0.10 (0.03–0.18)**	**0.01[b]**	0.01 (0.00–0.01)	0.14	**0.24 (0.06–0.43)**	**0.01[b]**

βs and 95% CIs of each physical function parameter are determined in a linear mixed model that includes the following variables: one of the cognitive *z*-scores (except for MMSE, which is the raw score) at baseline, time, the interaction between the cognitive *z*-score and time, the confounders age at baseline, sex, education, cohort type (UCI or EMIF-AD 90+ Study), and the score on the GDS at baseline as fixed effects and subject-specific intercepts and linear change with time (the slope) as random effects. The β for the cross-sectional effect shows the change in physical function parameter at baseline per unit increase in cognitive *z*-score at baseline. The β for the longitudinal effect shows the annual change in physical function parameter per unit increase in cognitive *z*-score at baseline. The bold values are the significant *p* values (before Holm's sequential Bonferroni procedure). CI, confidence interval; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery; TMT, Trail Making Test. [a]Cognitive tests are analyzed as *z*-scores, except for the MMSE, which is the raw score. [b]*p* value significant after correcting for the number of outcome measures using the Holm's sequential Bonferroni procedure. [c]For the TMT-A, higher scores represent worse performance; for all other cognitive tests, higher scores represent better performance.

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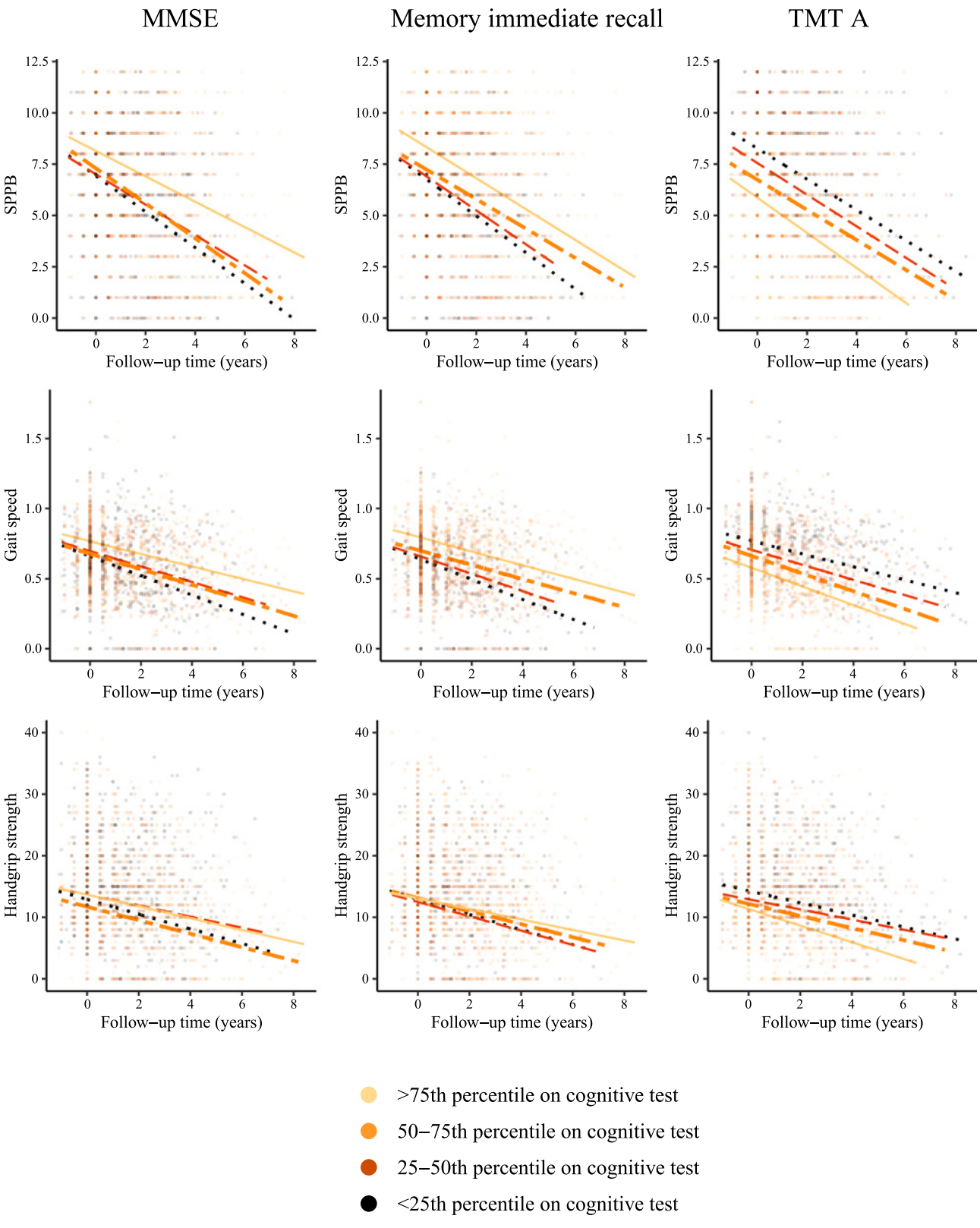

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cognition was associated with slower decline in handgrip strength and gait speed, whereas baseline handgrip strength and gait speed were not associated with cognitive decline, except for handgrip strength with MMSE [2, 35]. In a former study performed in the UCI 90+ Study, poor physical performance was associated with greater risk of incident dementia [3]. The present study found associations in both directions; however, the association between physical function at baseline with cognitive decline seemed to be more pronounced than the other way around. A possible explanation for the difference in results between our study and the Leiden 85-plus study is that our range of follow-up was larger, which might correlate with more cognitive decline in our study population and therefore more chance to find an association with cognitive decline. Our results are in line with studies indicating that physical exercise may improve cognition (through both biological and psychological effects) and suggest that this may also be true for the oldest-old [11].

Differences between the Physical and Cognitive Domains

Of the different cognitive tests included in our study, TMT-A showed the most consistent association with physical function. This is in line with earlier studies indicating that processing speed and attention, two cognitive domains assessed with TMT-A, are important cognitive abilities in relation to physical function [2, 9]. With regard to the different tests used for physical function, handgrip strength showed the fewest associations with cognition at baseline. Mainly the absence of a cross-sectional association between global cognition (as assessed with the MMSE) and memory with handgrip strength does not seem to be in line with earlier studies [37]. If we compare the mean handgrip strength in our study (11.8 kg for female and 21.4 kg for men) with that in individuals aged 85 years old in another study (22.0 kg for females and men together), our values were lower [2]. Potentially, loss of muscle strength at the age of 90 years and older is rather inevitable and therefore less discriminating between individuals with a normal or impaired cognition. This is line with research showing that, when using an arbitrary cutoff point for handgrip strength, most individuals aged 90 years and older perform below this cutoff point [38]. In addition, physical performance (as measured by gait speed or the SPPB) seems to decline later in life and might therefore discriminate better at an older age [38]. This may indicate that gait speed and SPPB are more relevant measures to use in clinical practice for the oldest-old than handgrip strength.

Brain Pathology as Potential Common Underlying Driver

Although most associations we found were between physical function at baseline and cognitive decline, there were also some associations in the opposite direction. This bidirectional association between cognitive and physical function suggests a common underlying driver [39]. Several studies suggest that brain pathology may be this common underlying etiology, driving both physical and cognitive impairment and decline [2, 5]. In the present study, MRI measures for brain health were related to both physical function and cognition; however, they were not identified as common drivers. This is in line with postmortem studies showing that the association between physical function and cognition did not change when controlling for brain pathologies and that only a minority of dual cognitive and physical decline was explained by brain pathologies [7, 8]. Perhaps, volume loss in more specific brain regions (and other than the hippocampus) underlies both physical and cognitive impairment, for example, the frontal area, which is specifically affected by aging and an important structure for processing speed and attention [6, 9, 39]. Or a common driving factor needs to be found in different research areas, for example, in genetics (apolipoprotein E ε4 carriership has been found to be more present in individuals who experience both physical and cognitive decline) or in metabolics (alterations in lipid metabolites were more extensively present in individuals with both physical and cognitive decline) [40]. Additionally, inflammation and mitochondrial dysfunction have been suggested as potential contributing factors [40].

Strengths and Limitations

The most important strength of the present study is the large number of oldest-old individuals included, which is achieved by combining the two largest imaging cohort

Fig. 3. Association of cognition with physical decline. Lines are the predicted trajectories for a participant with the most common characteristics: women, age 92.2 years (median age of study population), from the UCI 90+ Study, with an average education level and a GDS score of 2 (median of study population). The cognitive scores are *Z*-scores except for MMSE. For all physical and cognitive tests, higher scores represent better performance, except for the TMT-A (for which lower scores are better). MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery; TMT, Trail Making Test.

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studies worldwide that specifically focus on cognition in individuals aged 90 years and older. Most of the cognitive tests and all physical parameters and brain measures were derived in the same manner in both cohorts. To allow pooling of the data of the two cohorts, *z*-scores of the cognitive data were calculated per cohort by using the cognitively normal individuals of each cohort as reference population. For the MRI data, only FreeSurfer segmentations of the T1 sequences were used to optimize comparison and the MRI data were harmonized with ComBat, which has shown satisfactory results in earlier papers [25]. However, the limitations of the present study are also related to the fact that we combined data of two different cohorts as these two cohorts differ on the following aspects (Table 1): the percentage of participants with dementia at baseline, the frequency of follow-up visits (every 6 months in the UCI 90+ Study and yearly in the EMIF-AD 90+ Study), raw scores on animal fluency and TMT-A, the SPPB and gait speed at baseline (both higher in the EMIF-AD 90+ Study), and the level of brain health (higher hippocampal and gray matter volume in the UCI 90+ Study). The difference in physical function at baseline may be explained by the more demanding study protocol of the EMIF-AD 90+ Study than that of the UCI 90+ Study potentially leading to the selection of physical healthier participants and that the faster gait speed of two attempts was used in the EMIF-AD 90+ Study whereas it was measured only once in the UCI 90+ Study (online suppl. Table S1) [14, 15]. It is important to take these differences into account when interpreting our results. However, when performing separate analyses per cohort (when appropriate according to a significant interaction with cohort) only two of all the associations tested showed differences per cohort. In our opinion, this does not outweigh the advantage of the large number of individuals by combining the two cohorts and therefore justifies our approach. In addition, due to differences in the protocols of the UCI and EMIF-AD 90+ Study, we were not able to include measures for physical activity, nutrition, and quality-of-life in our study. Another limitation is that study samples of both cohorts were mostly white, highly educated, and probably physically healthier than the average 90+ year old due to demanding study protocols. This limits the generalizability of our results. Last, we explicitly decided to not make composite scores of the cognitive and physical tests as each measures a different aspect of someone's cognitive and physical functioning. Consequently, we performed a substantial number of tests, for which we corrected by indicating the significant results after Holm's sequential Bonferroni correction in Tables 2 and 3. Given the explorative nature of this study, we described the uncorrected results. In line with this, we focused in the Discussion on the direction of the significant associations and not on the magnitude of the regression coefficients.

Conclusion and Implications

In the present study, we showed that physical and cognitive function is strongly related in the oldest-old and that this association is independent of brain health. Also, the association between physical function and cognitive decline was more pronounced than the other way around, which suggests there may be the potential for restraining cognitive decline by optimizing physical function. As diminished brain health was not found to be a common driving factor for physical and cognitive impairment in the present study, future research should focus on the identification of other possible common underlying etiologies, which will aid in finding modifiable factors to preserve physical and cognitive function in the oldest-old.

Acknowledgments

The authors thank all study participants.

Statement of Ethics

The study protocol of the UCI 90+ Study was reviewed and approved by the Institutional Review Board at the University of California, Irvine (registration No. 2001–2029). The study protocol of the EMIF-AD 90+ Study was reviewed and approved by the Medical Ethical Committee of the Amsterdam UMC (registration No. 2015.374). All participants provided written informed consent.

Conflict of Interest Statement

HR performs contract research for Combinostics; all funding is paid to her institution. The other authors declare no conflicts of interest.

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Author Contributions

All authors have made substantial contributions to the manuscript and contributed to and approved the final version. C.K., P.J.V., M.C., M.M., H.R., and N.L. created the design and concept of the study. N.L., J.S.V., and H.R. performed or supervised the data analyses. V.V., D.W., F.O., and F.B. performed or supervised the MRI analyses. M.B. made a substantial contribution to the data collection. N.L. drafted the first and final versions of the manuscript.

Data Availability Statement

The data of the EMIF-AD 90+ Study are available for reuse through the EPND portal (https://discover.epnd.org). The data of the UCI 90+ Study that support the findings of this study are not publicly available as this could compromise the privacy of the participants; however, the data are available from M.C. upon reasonable request.

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