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Research Article

What Determines Cognitive Functioning in the Oldest-Old? The EMIF-AD 90+ Study

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Abstract

Objectives: Determinants of cognitive functioning in individuals aged 90 years and older, the oldest-old, remain poorly understood. We aimed to establish the association of risk factors, white matter hyperintensities (WMHs), hippocampal atrophy, and amyloid aggregation with cognition in the oldest-old.

Method: We included 84 individuals without cognitive impairment and 38 individuals with cognitive impairment from the EMIF-AD 90+ Study (mean age 92.4 years) and tested cross-sectional associations between risk factors (cognitive activity, physical parameters, nutritional status, inflammatory markers, and cardiovascular risk factors), brain pathology biomarkers (WMH and hippocampal volume on magnetic resonance imaging, and amyloid binding measured with positron emission tomography), and cognition. Additionally, we tested whether the brain pathology biomarkers were independently associated with cognition. When applicable, we tested whether the effect of risk factors on cognition was mediated by brain pathology.

Results: Lower values for handgrip strength, Short Physical Performance Battery (SPPB), nutritional status, HbA1c, and hippocampal volume, and higher values for WMH volume and amyloid binding were associated with worse cognition. Higher past cognitive activity and lower body mass index were associated with increased amyloid binding, lower muscle mass with more WMH, and lower SPPB scores with more WMH and hippocampal atrophy. The brain pathology

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markers were independently associated with cognition. The association of SPPB with cognition was partially mediated by hippocampal volume.

Discussion: In the oldest-old, physical parameters, nutritional status, HbA1c, WMH, hippocampal atrophy, and amyloid binding are associated with cognitive impairment. Physical performance may affect cognition through hippocampal atrophy. This study highlights the importance to consider multiple factors when assessing cognition in the oldest-old.

Keywords: Alzheimer's disease, Brain pathology biomarkers, Cognitive aging, Oldest-old, Risk factors

The number of individuals aged 90 years and older, the oldest-old, is estimated to increase fivefold, resulting in 77 million oldest-old individuals worldwide by 2050 (World Population Prospects, 2017). The prevalence of dementia in the oldest-old is 40% (Corrada et al., 2008). Despite this high prevalence, studies focusing on the underlying pathophysiology of cognitive impairment in the oldest-old are scarce (Legdeur, Badissi, et al., 2018). Worldwide there are two cohort studies specifically focusing on cognition in nonagenarians: The 90+ Study in the United States and the Danish Birth Cohort Studies. Besides these two, there are eight more studies that have a broader focus on successful aging or start inclusion from age 85 years: the H85 Gothenburg study, Leiden 85-plus Study, Newcastle 85+ Study, NonaSantfeliu study, Octabaix study, Project of Longevity and Aging in Dujangyan (PLAD), Umeå study, and Vantaa 85+ Study. These earlier studies have identified physical performance (Bullain et al., 2016) and nutritional status (Hai et al., 2017) as potential protective factors for cognitive impairment, while findings were conflicting for premorbid cognitive activity, inflammatory markers, and cardiovascular risk factors (Legdeur, Badissi, et al., 2018). Cognitive impairment is associated with white matter hyperintensity (WMH) volume, hippocampal atrophy, and amyloid aggregation in younger elderly (Petersen et al., 2000; Vemuri et al., 2015). It has been suggested that the association of brain pathologies with cognition weakens with older age (Savva et al., 2009), although WMH volume, hippocampal atrophy, and amyloid aggregation have also been related to lower cognitive performance in the oldest-old (Kawas et al., 2013; Legdeur et al., 2019).

In younger elderly, vascular risk factors for cognitive decline have also been identified as risk factors for brain pathologies (Debette et al., 2011; Rodrigue et al., 2013). Therefore, it has been suggested that brain pathologies might mediate the association between vascular risk factors and cognitive decline (Wang et al., 2017). Whether risk factors of cognitive impairment are also risk factors for brain pathology biomarkers in the oldest-old remains unknown and it is unclear whether the effect of risk factors on cognition is mediated by brain pathology biomarkers in this age group.

We aimed to determine the association of risk factors, WMH volume, hippocampal atrophy, and amyloid aggregation with cognition in the oldest-old using data from the EMIF-AD 90+ Study. Additionally, we determined the association of these risk factors with WMH volume, hippocampal atrophy, and amyloid aggregation and explored possible mediation between risk factors, brain pathology biomarkers, and cognition.

Method

Study Sample

Individuals were included from the European Medical Information Framework for Alzheimer's disease (EMIF-AD) 90+ Study, a case–control study including cognitively normal and cognitively impaired individuals (Legdeur, Badissi, et al., 2018). The inclusion and exclusion criteria and recruitment strategy described below were used in the EMIF-AD 90+ Study so also applied to the present study. Inclusion criteria for cognitively normal individuals were a global Clinical Dementia Rating (CDR) score of 0 and a score ≥26 points on the Mini-Mental State Examination (MMSE) (Melikyan et al., 2019). We also included three individuals with an MMSE <26 points, who were determined to be cognitively normal after extensive cognitive testing. Inclusion criteria for individuals with cognitive impairment were a diagnosis of amnestic mild cognitive impairment (aMCI) (Petersen, 2004) or a diagnosis of probable or possible Alzheimer's disease (AD) (McKhann et al., 1984), and a global CDR score ≥0.5 and a MMSE score of 20–28 points (inclusive). The overlap in MMSE score between the cognitively normal and impaired individuals is justified as CDR score and an aMCI or AD diagnosis was also used to make the distinction. Given a lower than expected enrolment rate, we also included six cognitively impaired individuals aged 85–89 and two cognitively normal individuals aged 88–89 years. Analyses without these individuals did not substantially change the findings. Exclusion criteria were physical inability to undergo the procedures, visual or hearing impairment interfering with neuropsychological testing, severe depression, and comorbidities or medications that could impair cognition, as judged by the investigator. We recruited individuals from June 2016 to July 2018 via advertisement, outreach to general practitioners (GPs), and the 100-plus Study (Holstege et al., 2018). The Medical Ethical Committee of the Amsterdam UMC approved this study. All individuals provided written informed consent.

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Clinical Characteristics

Data about the medical history, medication use, and education were collected through structured interview, in combination with information provided by the study partner (if available, this can either be a husband, wife, family member, friend, or caregiver), GP, and/or medical specialist. The presence of hypertension, diabetes mellitus (DM), and atrial fibrillation were based on a positive medical history or, in case of hypertension and DM, the use of antihypertensive or antidiabetic medication.

Cognitive Functioning

Cognitive tests were administered by a trained neuropsychologist. To reduce the number of outcome measures and thereby the chance of a type 1 error, we computed three cognitive composite scores by calculating *z*-scores and averaging them per cognitive domain. For memory, we included the immediate recall (range: 0–30 words) and 10-min delayed recall (range: 0–10) over three trials of the CERAD 10-word test (Morris et al., 1989), immediate recall (range: 0–23) and delayed recall after 20–30 min (range: 0–23) of the logical memory test (Abikoff et al., 1987), Rey Complex Figure Test delayed copy after 3 min (range: 0–36) corrected for the immediate copy (Meyers et al., 1996), Visual Association Test (range: 0–12) (Lindeboom et al., 2002), and the total adjusted errors on the Paired Associate Learning (PAL) test of the computerized Cambridge Neuropsychological Test Automated Battery (CANTAB) (range: 0–70) (Robbins et al., 1994). For executive functioning, we included Letter fluency (1 min per letter, letters D-A-T) (Tombaugh et al., 1999), Trail Making Test (TMT) B corrected for A (Reitan, 1958), and the Clock-Drawing Test (range: 0–14) (Royall et al., 1998). For processing speed, we included the Digit Symbol Substitution Test (DSST, range: 0–93 points) from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981), TMT A, and the median five-choice reaction time of the CANTAB. There was no time limit for the assessment of the TMT A and B. However, some individuals could not perform the TMT B due to cognitive problems. To minimize the number of missing values on the TMT B/A ratio, we assigned maximum scores to the TMT A and B if scores were missing due to cognitive problems. Maximum scores were based on the time 2 *SD* above the study sample mean. All scores higher than the maximum score were limited to the maximum score in order to avoid outliers influencing associations.

Risk Factors

Cognitive activity

Past cognitive activity was assessed with the Cognitive Activities Questionnaire (CAQ) (Wilson et al., 2003). Individuals were asked to rate how often they participated in cognitive activities, such as reading, writing, and playing board games (in total eight different activities), at age 6, 12, 18, and 40 years. Frequency of participation in each activity was rated on a 5-point scale. The mean score over the different activities and ages was calculated to determine past CAQ.

Physical parameters

Handgrip strength of the dominant hand was measured twice with a hand dynamometer (Jamar hand dynamometer; Sammons Preston, Inc., Bolingbrook, IL) and the highest score in kilograms was used in the analyses (Reijnierse et al., 2017). Skeletal muscle mass was measured in kilograms using a Bioelectrical Impedance Analyzer (BIA; InBody 770 or S10; Biospace Co., Ltd, Seoul, Korea) (Ling et al., 2011). We calculated the skeletal muscle mass index (further described as muscle mass) by dividing skeletal muscle mass by height (kg/m^2). The Short Physical Performance Battery (SPPB) included balance tests, a 4-m walk to measure walking speed and the chair stand test (range 0–12 points) (Guralnik et al., 1995).

Nutritional status

We used the Mini-Nutritional Assessment (MNA) and the body mass index (BMI) to measure nutritional status. The MNA consists of a screening and assessment score (Isautier et al., 2019). For the present analyses, we used the assessment score (range 0–16 points).

Inflammatory markers

We included the acute-phase protein C-reactive protein (CRP) level in mg/L and number of leukocytes in $10^{\wedge}9$/L measured in serum as inflammatory markers. Blood samples were collected after approximately 2 hr of fasting (Reijs et al., 2015). CRP was measured with an immunoturbidimetric assay on a Roche/Hitachi cobas c system. The lower detection limit of the assay is 2.5 mg/L. The number of leukocytes was determined using the Fluorocell WPC channel on a Sysmex XN hematology analyzer (Sysmex, Kobe, Japan). Individuals with a CRP >15 mg/L were excluded from the analyses, as such CRP levels primarily reflect acute infection. All CRP levels <2.5 mg/L were set at 1.0 mg/L in the analyses and CRP levels were log transformed because of a skewed distribution.

Cardiovascular risk factors

Mean systolic and diastolic blood pressure (BP) were calculated over three measurements performed in lying position (eight individuals had only one BP measurement and one individual had two BP measurements due to logistic reasons, we did not exclude these individuals). Total cholesterol in mmol/L was determined in serum by an enzymatic test on a Roche/Hitachi cobas c system. Levels of hemoglobin A1c (HbA1c), as a measure of average glucose levels over the past weeks, were determined with the HA-8160 (Menarini).

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Brain Pathology Biomarkers

WMH and hippocampal volume

Brain magnetic resonance imaging (MRI) scans were performed on a Philips 3T Achieva scanner and structural three-dimensional (3D) T1-weighted images and 3D sagittal fluid-attenuated inversion recovery (FLAIR) sequences were acquired with isotropic 1 mm resolution (Konijnenberg et al., 2018). A neuroradiologist visually inspected the MRI scans for incidental findings. WMH segmentation was performed by using an algorithm based on a three-level Gaussian mixture model to model healthy tissues and lesions (Sudre et al., 2015). Volumetric segmentation of the 3D T1 images was performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). The automated procedure includes motion correction, removal of non-brain tissue, automated Talairach transformation, and segmentation of the white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002). Hippocampal volume was computed from the segmented images in native space and mean hippocampal volume was calculated by averaging the left and right side. Both the WMH and FreeSurfer segmentations were visually inspected. In the present analyses, we computed the percentage of WMH and hippocampal volume relative to total intracranial volume (TIV, which is the sum of gray matter, white matter, and cerebrospinal fluid), in order to correct for head size. Because of a skewed distribution, WMH volume was log transformed in the analyses.

Amyloid binding

Individuals underwent amyloid positron emission tomography (PET) imaging using a specific fibrillary amyloid β radiotracer, [^{18}F]flutemetamol, which was produced by General Electric (GE) Healthcare at the Cyclotron Research Centre of the University of Liège (Liège, Belgium). PET scans were performed on a Philips Ingenuity TF PET-MRI. The emission scan was performed in two parts starting with a 30-min dynamic scan simultaneously with the bolus intravenous injection of 185 MBq [^{18}F]flutemetamol, followed by a 20-min scan performed 90–110 min after the injection. A T1-weighted gradient echo pulse MRI scan was obtained for attenuation correction. The dynamic data were analyzed on a voxel-by-voxel level using the basis function approach of the Simplified Reference Tissue Model (SRTM) with cerebellar gray matter as reference tissue to determine amyloid non-displaceable binding potential (BP_{ND}) (Wu & Carson, 2002). Global amyloid BP_{ND} was determined by determining the volume-weighted average BP_{ND} of the frontal (superior, middle, and inferior frontal gyrus), parietal (posterior cingulate, superior parietal gyrus, postcentral gyrus, and inferolateral remainder of parietal lobe), and temporal regions (parahippocampal gyrus, hippocampus, medial temporal lobe, superior, middle, and inferior temporal gyrus). The distribution volume ratio (DVR) was calculated using global amyloid BP_{ND} + 1. For the analyses, DVR was log transformed because of a skewed distribution.

Statistical Analyses

Differences between the cognitively normal and cognitively impaired individuals were investigated using *t* tests, chi-squared tests, or Wilcoxon tests. First, we performed linear regression analyses in the total sample to investigate associations between the cognitive composite scores as dependent variables and the risk factors and brain pathology biomarkers as independent variables. To test the independent effect of the brain pathology biomarkers on the cognitive composite scores, we performed multivariate linear regression analyses including the significant brain pathology biomarkers in the same model and we tested whether the brain pathology biomarkers were mutually associated. Secondly, we performed linear regression analyses to investigate associations between the brain pathology biomarkers as dependent variables and the risk factors as independent variables in the total sample. To test whether results were driven by the cognitively impaired individuals, we repeated the linear regression analyses separately in the cognitively normal and impaired individuals for the variables that showed a significant association in the total sample. All linear regression analyses were adjusted for age, sex, and years of education. If a risk factor was both significantly associated with a cognitive composite score and a brain pathology biomarker, mediation analyses were performed to test whether the brain pathology biomarker mediated the effect of the risk factors on the cognitive composite. For these mediation analyses, we first tested whether the brain pathology biomarker was significantly associated with the cognitive composite score in the presence of the risk factor. If so, we calculated the direct, indirect, and total effect (direct + indirect effect) of the risk factor on the cognitive composite score by using structural equation modeling of the Lavaan package in R (Rosseel, 2002). The proportion mediated was determined as the indirect effect divided by the total effect and all mediation analyses were adjusted for age, sex, and years of education. The *p*-value threshold for significance was set at .05 and additionally we indicated significance after Bonferroni correction (*p*-value < .05/3). Analyses were performed in R-Studio version 1.1.414 with R version 3.4.3.

Results

Characteristics of the 122 individuals included in the EMIF-AD 90+ Study are shown in Table 1. Individuals were on average 92.4 years (*SD* 2.8, IQR: 90.5–93.5 years), 70 (57.4%) were female, and their mean years of education was 11.4 (*SD* 3.4). We included 84 cognitively normal and 38 cognitively impaired individuals. The individuals with cognitive impairment scored lower on the three cognitive composite scores (see Supplementary Table 1 for scores on individual tests). The three cognitive composite scores were significantly correlated with each other in the total sample (*p*-values < .05). Individuals with cognitive impairment

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had a lower handgrip strength, a lower score on the SPPB, a lower score on the MNA, a lower level of leukocytes, more hippocampal atrophy, and a higher amyloid binding (Table 1).

Associations of Risk Factors and Brain Pathology Biomarkers With Cognition

Lower values for handgrip strength, SPPB, MNA, HbA1c, and hippocampal volume, and higher values for WMH volume and amyloid binding were associated with worse scores on all three cognitive composites (Table 2).

In order to test the independent effect of brain pathology biomarkers on memory and processing speed, we analyzed hippocampal volume, WMH, and amyloid binding together in a multivariate model. These analyses showed that WMH volume (memory: β = −.25, *p*-value < .01; processing speed: β = −.21, *p*-value = .02), hippocampal volume (memory: β = .47, *p*-value < .01; processing speed: β = .22, *p*-value = .03), and amyloid binding (memory: β = −.28, *p*-value < .01; processing

Table 1. Clinical Characteristics and Correlates of Cognition in the Total Sample and Separately for the Cognitively Normal (CN) and Impaired (CI) Individuals

			Cognitive group				
	N	Total	*N*	CN	*N*	CI	*p*-value
Clinical characteristics							
Age, years	122	92.4 (2.8)	84	92.8 (2.9)	38	91.6 (2.4)	**.02**[e]
Sex, female[a]	122	70 (57.4)	84	45 (53.6)	38	25 (65.8)	.29[f]
Education, years	122	11.4 (3.4)	84	11.2 (3.4)	38	11.9 (3.3)	.32[g]
MMSE, points	122	27.1 (3.1)	84	28.5 (1.5)	38	23.8 (3.3)	**<.01**[g]
CERAD memory test, words	114	15.6 (4.8)	79	17.6 (3.8)	35	11.2 (3.5)	**<.01**[e]
Hypertension[b]	122	84 (69.0)	84	58 (69.0)	38	26 (68.4)	1.00[f]
Diabetes mellitus[b]	122	8 (7.0)	84	5 (6.0)	38	3 (7.9)	.70[h]
Atrial fibrillation[b]	122	21 (17.0)	84	11 (13.1)	38	10 (26.3)	.13[f]
Infarction on MRI	92	7 (8.0)	67	6 (9.0)	25	1 (4.0)	.67[h]
Visual read amyloid, pos[a,c]	84	33 (39.3)	63	20 (31.7)	21	13 (61.9)	**.03**[f]
Cognitive activity							
Past CAQ, points	100	2.6 (0.6)	70	2.5 (0.5)	30	2.6 (0.7)	.53[e]
Physical parameters							
Handgrip strength males, kg	50	21.3 (7.0)	38	22.5 (6.7)	12	17.5 (6.8)	**.04**[e]
Handgrip strength females, kg	66	11.5 (4.6)	44	12.3 (4.0)	22	9.9 (5.4)	.08[e]
Muscle mass index, kg/m^2	95	9.0 (1.0)	66	9.2 (1.0)	29	8.8 (1.0)	.09[e]
SPPB, points	103	7.5 (2.8)	70	8.0 (2.7)	33	6.2 (2.6)	**<.01**[e]
Nutritional status							
MNA, points	102	12.7 (1.3)	72	12.8 (1.4)	30	12.2 (1.1)	**.02**[e]
BMI, kg/m^2	108	25.7 (3.8)	75	26.0 (3.8)	33	24.9 (3.7)	.17[e]
Inflammatory markers							
CRP, mg/L	100	3.0 (3.1)	67	2.9 (2.9)	33	3.2 (3.5)	.85[e,i]
Leukocytes, 10^9/L	104	7.0 (2.4)	71	7.4 (2.6)	33	6.3 (1.7)	**.01**[e]
Cardiovascular risk factors							
Systolic BP, mm Hg	109	151.9 (24.3)	76	152.0 (26.2)	33	151.6 (19.6)	.93[e]
Diastolic BP, mm Hg	109	78.0 (11.8)	76	77.9 (11.9)	33	78.4 (11.8)	.85[e]
HbA1c, %	104	5.8 (0.4)	71	5.8 (0.4)	33	5.7 (0.4)	.22[e]
Total cholesterol, mmol/L	104	5.0 (1.3)	71	5.0 (1.3)	33	5.1 (1.3)	.62[e]
Brain pathology biomarkers							
WMH volume, % ICV	90	1.5 (1.0)	64	1.4 (1.0)	26	1.7 (1.1)	.26[e,i]
Hippocampal volume, % ICV	91	0.19 (0.03)	65	0.19 (0.03)	26	0.17 (0.03)	**<.01**[e]
Amyloid binding[d]	84	1.3 (0.3)	63	1.3 (0.3)	21	1.5 (0.3)	**.03**[e,i]

Notes: BMI = body mass index; BP = blood pressure; CAQ = Cognitive Activities Questionnaire; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CRP = C-reactive protein; HbA1c = hemoglobin A1c; ICV = intracranial volume; MMSE = Mini-Mental State Examination; MNA = Mini-Nutritional Assessment; MRI = magnetic resonance imaging; *N* = sample size per variable; pos = positive; SPPB = Short Physical Performance Battery; WMH = white matter hyperintensity. Values are presented as mean (*SD*), unless stated otherwise. *p*-Values compare the CN with the CI individuals. The bold values are the *p*-values which are ≤.05.

[a]Presented as number (%). [b]Based on medical history and/or medication use. [c]Visual read based on amyloid non-displaceable binding potential (BP_{ND}) images. [d]Numbers are the distribution volume ratio (DVR). [e]Tested using *t* test. [f]Tested using chi-squared test. [g]Tested using Wilcoxon test. [h]Tested using Fisher's exact test. [i]These values are log transformed in the analyses.

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Table 2. Associations of Risk Factors and Brain Pathology Biomarkers With Cognitive Composite Scores[a]

	Memory		Executive functioning		Processing speed	
	β[b]	*p*-value	β[b]	*p*-value	β[b]	*p*-value
Cognitive activity						
Past CAQ, points	.05	.67	−.14	.17	−.13	.28
Physical parameters						
Handgrip strength, kg	.53	**<.01**[c]	.21	.06	.45	**<.01**[c]
Muscle mass, kg/m²	.20	.12	.21	.07	.22	.10
SPPB, points	.43	**<.01**[c]	.24	**<.01**[c]	.42	**<.01**[c]
Nutritional status						
MNA, points	.23	**.02**	.20	**.02**[c]	.24	**.02**[c]
BMI, kg/m²	.19	.06	.10	.25	.18	.07
Inflammatory markers						
CRP, mg/L	−.15	.15	−.05	.61	−.05	.61
Leukocytes, 10⁹/L	.10	.31	.09	.30	.11	.28
Cardiovascular risk factors						
Systolic BP, mm Hg	.11	.30	−.03	.77	.04	.72
Diastolic BP, mm Hg	.00	1.00	−.05	.58	−.02	.86
HbA1c, %	.25	**.01**[c]	.19	**.02**[c]	.02	.84
Total cholesterol, mmol/L	.06	.56	.05	.62	−.02	.86
Brain pathology biomarkers						
WMH volume, % ICV	−.25	**.02**	−.18	.06	−.27	**.02**[c]
Hippocampal volume, % ICV	.48	**<.01**[c]	.23	**.02**[c]	.30	**<.01**[c]
Amyloid binding[d]	−.23	**.05**	−.08	.44	−.27	**<.01**[c]

Notes: BMI = body mass index; BP = blood pressure; CAQ = Cognitive Activities Questionnaire; CRP = C-reactive protein; HbA1c = hemoglobin A1c; ICV = intracranial volume; MNA = Mini-Nutritional Assessment; SPPB = Short Physical Performance Battery; WMH = white matter hyperintensity. The bold values are the *p*-values which are ≤.05.

[a]The cognitive composite score are *z*-scores. [b]Standardized regression coefficient from linear regression analysis adjusted for age, sex, and years of education. [c]*p*-Value is significant after correcting for the three cognitive outcomes using Bonferroni correction (0.05/3). [d]Determined with the distribution volume ratio (DVR).

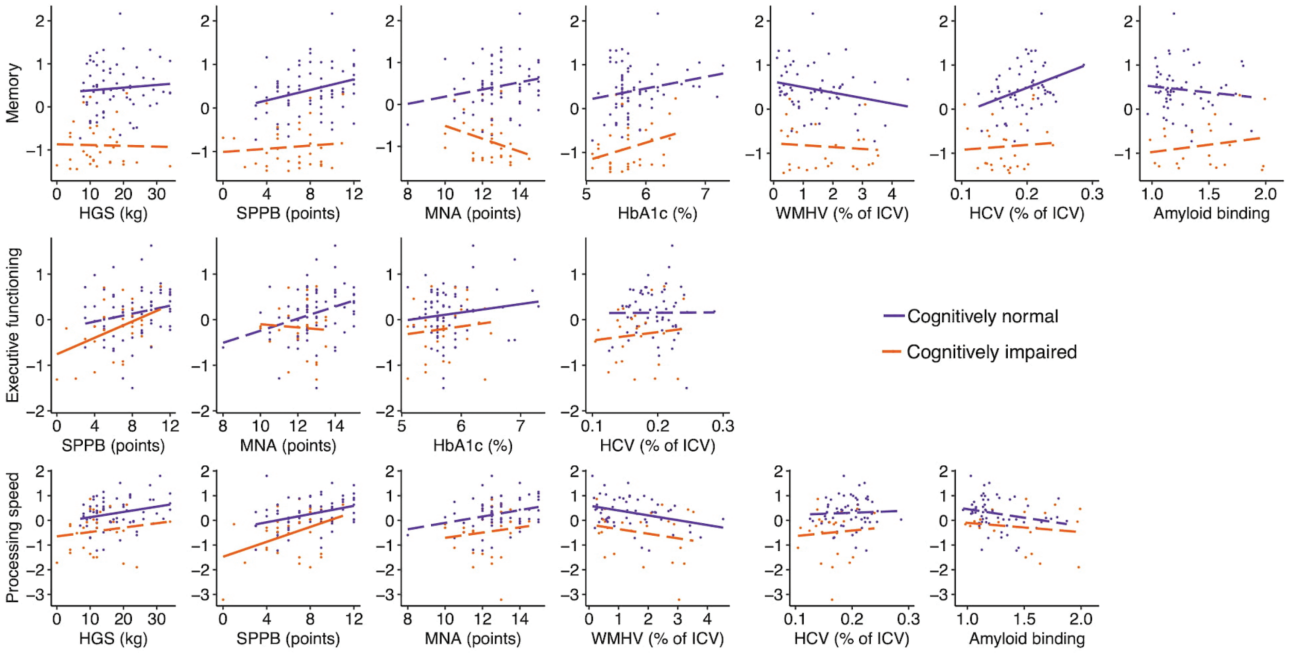

Figure 1. Associations of risk factors and brain pathology biomarkers with cognitive composite scores separately for the cognitively normal and impaired individuals. Scatterplots depict raw values for ease of interpretation and are not corrected for age, sex, and education as presented in Supplementary Tables 2 and 3. Only the significant associations from Table 2 are visualized. Solid lines indicate a significant (*p*-value < .05) association within that specific cognitive group. Amyloid binding is represented by the distribution volume ratio. BMI = body mass index; HCV = hippocampal volume; HGS = handgrip strength; ICV = intracranial volume; MNA = Mini-Nutritional Assessment; SPPB = Short Physical Performance Battery; WMHV = white matter hyperintensity volume. Full color version is available within the online issue.

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Table 3. Associations of Risk Factors With Brain Pathology Biomarkers

	WMH volume, % ICV		Hippocampal volume, % ICV		Amyloid binding[a]	
	β[b]	*p*-value	β[b]	*p*-value	β[b]	*p*-value
Cognitive activity						
Past CAQ, points	.10	.43	.04	.75	.26	**.05**
Physical parameters						
Handgrip strength, kg	−.26	.07	.18	.18	.08	.58
Muscle mass, kg/m^2	−.35	**.01**[c]	−.04	.75	−.25	.11
SPPB, points	−.32	**.01**[c]	.37	**<.01**[c]	.10	.44
Nutritional status						
MNA, points	−.18	.10	.20	.07	.07	.54
BMI, kg/m^2	−.06	.58	.10	.36	−.29	**.02**[c]
Inflammatory markers						
CRP, mg/L	.17	.17	.13	.27	−.11	.37
Leukocytes, 10^9/L	−.00	.99	.11	.29	−.06	.61
Cardiovascular risk factors						
Systolic BP, mm Hg	−.01	.91	.16	.11	.06	.57
Diastolic BP, mm Hg	.08	.46	.12	.26	−.15	.20
HbA1c, %	.02	.85	.08	.43	.06	.66
Total cholesterol, mmol/L	−.01	.96	.10	.36	−.17	.17

Notes: BMI = body mass index; BP = blood pressure; CAQ = Cognitive Activities Questionnaire; CRP = C-reactive protein; HbA1c = hemoglobin A1c; ICV = intracranial volume; MNA = Mini-Nutritional Assessment; SPPB = Short Physical Performance Battery; WMH = white matter hyperintensity. The bold values are the *p*-values which are ≤.05.

[a]Determined with the distribution volume ratio (DVR). [b]Standardized regression coefficient from linear regression analysis adjusted for age, sex, and years of education. [c]*p*-Value is significant after correcting for the three cognitive outcomes using Bonferroni correction (0.05/3).

speed: β = −.31, *p*-value < .01) were all independently associated with memory and processing speed. In line with this, WMH, hippocampal volume, and amyloid binding did not correlate with each other.

Analyses of the significant associations in the total sample were repeated separately for the cognitively normal and impaired individuals (Figure 1; Supplementary Tables 2 and 3). In the cognitively normal individuals, 12 out of 17 associations of risk factors and brain pathology biomarkers with cognition were statistically significant (n = 8) or tended to be significant (n = 4) while in the cognitively impaired individuals, there was only one association with cognition statistically significant.

Associations of Risk Factors With Brain Pathology Biomarkers

Lower muscle mass and a lower score on the SPPB were associated with higher WMH volume (Table 3). A lower score on the SPPB was also associated with hippocampal atrophy. Higher past cognitive activity and lower BMI were associated with higher amyloid binding.

Analyses of the significant associations were repeated separately for the cognitively normal and impaired individuals and showed that associations were present in the cognitively normal individuals, except for muscle mass with WMH volume, but not in the cognitively impaired individuals (Figure 2; Supplementary Tables 4 and 5).

Mediation Analyses

The SPPB score was the only correlate of cognition that was also associated with brain pathology biomarkers. Criteria for mediation analyses were met for the association between hippocampal volume with memory and executive functioning. Mediation analyses showed that hippocampal volume mediated 38.5% of the effect of SPPB on memory and 33.3% of the effect of SPPB on executive functioning (Figure 3).

Discussion

In this unique, extensively tested population of oldest-old individuals, physical parameters and brain pathology biomarkers were the most important factors to be associated with cognition. The three brain pathology biomarkers, WMH, hippocampal volume, and amyloid aggregation, were all independently related to cognition. We also found an association between the physical parameters and brain pathology biomarkers. The association between cognition and physical performance was partly mediated by

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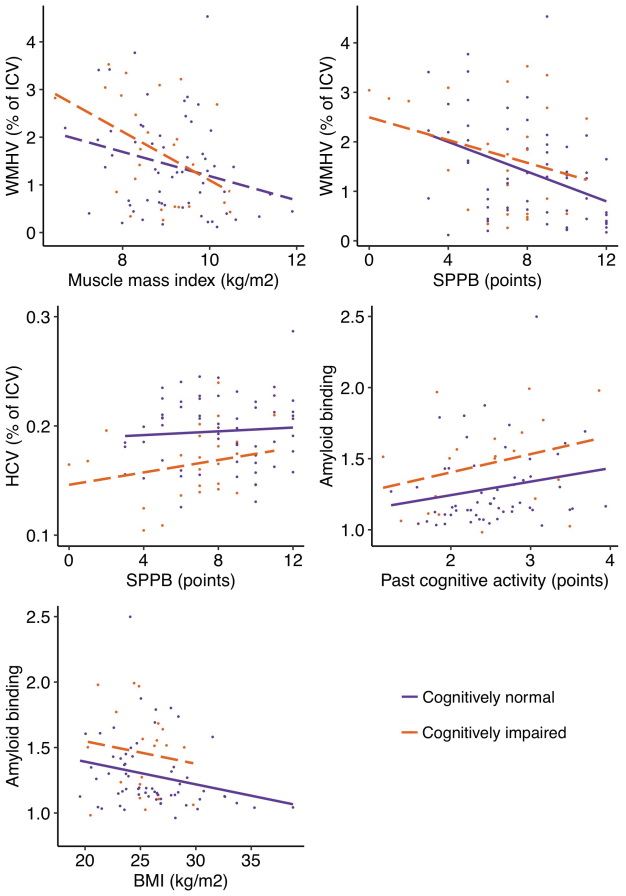

Figure 2. Associations of risk factors with brain pathology biomarkers separately for the cognitively normal and impaired individuals. Scatterplots depict raw values for ease of interpretation and are not corrected for age, sex, and education as presented in Table 3. Only the significant associations from Table 3 are visualized. Solid lines indicate a significant (p-value < .05) association within that specific cognitive group. Amyloid binding is represented by the distribution volume ratio. BMI = body mass index; HCV = hippocampal volume; ICV = intracranial volume; SPPB = Short Physical Performance Battery; WMHV = white matter hyperintensity volume. Full color version is available within the online issue.

hippocampal volume. In the following paragraphs, we will discuss our findings more specifically per risk factor group.

Cognitive Activity

Most longitudinal studies in younger elderly have associated higher cognitive activity with reduced cognitive decline (Vemuri et al., 2014; Wilson et al., 2013). We did not find an association between past cognitive activity at the ages 6, 12, 18, and 40 years, and cognitive functioning after age 90 years indicating that the protective effect of cognitive activity at these ages may not persist in the oldest-old. This is in line with another study that did not find an association between lifestyle factors, including cognitive activities, at age 70 years and incident dementia after age 90 years (Paganini-Hill et al., 2016). Surprisingly, higher past cognitive activity was related to more amyloid aggregation which is in contrast to previous studies in younger cognitively normal elderly (Landau et al., 2012; Wirth et al., 2014). A possible explanation for this association in the cognitively normal oldest-old individuals might be that high past cognitive activity leads to more cognitive reserve which may protect against the negative effect of amyloid aggregation on cognition. In line with this explanation, we did not find a significant association between past cognitive activity and amyloid aggregation in the cognitively impaired individuals.

Physical Parameters

Of all risk factors tested, handgrip strength and physical performance showed the strongest association with cognition. The associations of higher handgrip strength and physical performance with better cognition have been shown before in populations over the age of 40 years (Clouston et al., 2013) and also in populations aged 85 years and older (Bullain et al., 2016; Taekema et al., 2010). Different mechanisms may explain the association between physical parameters and cognition. Physical activity has been shown to increase hippocampal volume, potentially by increasing the secretion of myokines and subsequently the level of brain-derived neurotrophic factor (BDNF), and thereby improving cognitive performance (Delezie & Handschin, 2018). Our study showed that the association between physical performance and cognition was partially mediated by hippocampal volume. This indicates that the mechanism described for physical activity might also apply to physical performance. Another explanation for the association between physical parameters and cognition includes the possibility of a common driving factor, for example WMH or other vascular brain pathologies (Guttmann et al., 2000). Furthermore, poor physical function can also be a consequence of cognitive impairment rather than a cause (Taekema et al., 2012). However, due to the cross-sectional nature of this study, we can only speculate about possible mechanisms without making any statements about potential causalities.

Nutritional Status

In line with our findings, malnutrition has been associated with lower cognitive performance in the oldest-old (Hai et al., 2017) and with brain pathology in individuals who were on average 80 years old (de van der Schueren et al., 2016). Most likely, malnutrition is a consequence of worse cognitive functioning, which also explains the lack of an association in cognitively normal individuals. The association between lower BMI and more amyloid aggregation has been shown before in younger elderly with normal cognition or MCI (Vidoni et al., 2011). This association might be explained by neuropathological changes in brain areas that are important for metabolism regulation or by

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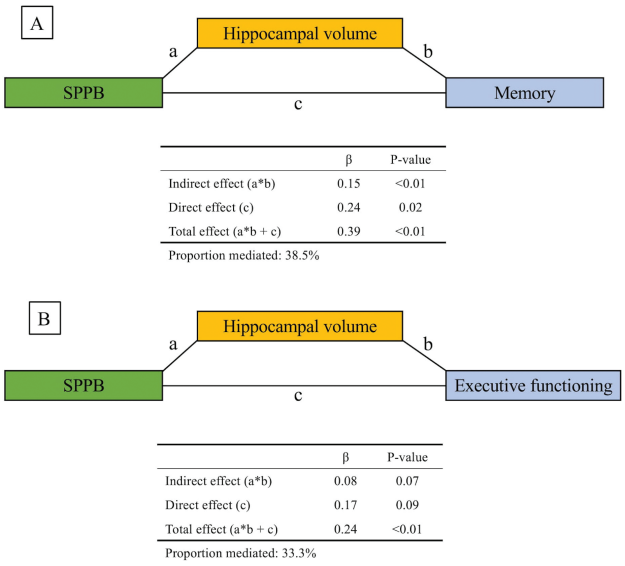

	β	P-value
Indirect effect (a*b)	0.15	<0.01
Direct effect (c)	0.24	0.02
Total effect (a*b + c)	0.39	<0.01

Proportion mediated: 38.5%

	β	P-value
Indirect effect (a*b)	0.08	0.07
Direct effect (c)	0.17	0.09
Total effect (a*b + c)	0.24	<0.01

Proportion mediated: 33.3%

Figure 3. Mediation analyses. β is the standardized regression coefficient from the mediation analysis adjusted for age, sex and years of education performed with Lavaan. Proportion mediated is determined as the indirect effect divided by the total effect. SPPB = Short Physical Performance Battery. Full color version is available within the online issue.

lifestyle changes in individuals with AD pathology (Vidoni et al., 2011).

Inflammatory Markers

We found a lower number of leukocytes in the cognitively impaired compared to the cognitively normal individuals but no association between leukocyte count and cognition. In AD, decreased levels of lymphocytes and basophils have been shown before, which may indicate bone marrow suppression in the presence of neurodegeneration (Chen et al., 2017). More specific white blood cell counts, for example by studying peripheral blood mononuclear cells (PBMCs), are necessary to further elucidate this finding (Arosio et al., 2014). In addition, we did not find an association between CRP level and cognitive functioning, which is in line with a previous study performed in individuals aged 85 years (Schram et al., 2007). An association between CRP and cognitive functioning has, however, been found in younger elderly (Schram et al., 2007). The lack of an association in our study might be explained by selective survival as high levels of CRP are related to increased mortality risk leaving only the individuals who are less susceptible for the negative consequences of high CRP levels in the study sample (Kravitz et al., 2009). Alternatively, this finding might be due to the low sensitivity assay used to measure CRP.

Cardiovascular Risk Factors

The lack of an association between blood pressure and cholesterol with cognition is in line with most previous literature who found that cardiovascular risk factors measured in late-life are not associated with cognitive impairment (Legdeur, Heymans, et al., 2018), unlike cardiovascular risk factors measured in midlife (Knopman et al., 2018).

The positive association of glucose levels with memory and executive functioning may reflect a better nutritional status in those with better cognitive functioning (Abdelhafiz & Sinclair, 2015). There was no association between the cardiovascular risk factors and brain pathology biomarkers. Especially for WMH and blood pressure, this is remarkable as previous studies in younger elderly showed that hypertension is an important risk factor for WMH (Skoog, 1998). A possible explanation is the selective survival of individuals who are less susceptible for the negative effects of cardiovascular risk factors on brain pathologies (de Leeuw et al., 2002). In addition, we did not have information about the duration of the high blood pressure and especially long-standing high blood pressure might be associated with WMH (de Leeuw et al., 2002).

Brain Pathology Biomarkers

Neuropathological studies suggested that the association between brain pathologies and cognitive status weakens in the oldest-old (Savva et al., 2009). However, we found that WMH, hippocampal atrophy, and amyloid aggregation were still independently associated with memory, executive functioning, or processing speed. These biomarkers did not correlate with each other, which is for WMH and amyloid aggregation in line with most previous literature (Roseborough et al., 2017). However, in younger cognitively normal elderly, amyloid aggregation and WMH are associated with hippocampal atrophy (Bourgeat et al., 2010; Fiford et al., 2017). This could indicate that other pathologies than AD pathology or vascular damage underlie hippocampal atrophy in the oldest-old, such as hippocampal sclerosis and argyrophilic grain disease (Barkhof et al., 2007). The finding that brain pathologies are associated with cognitive functioning at higher age, is in line with another study conducted in a population aged 90 years and older (Legdeur et al., 2019).

Strengths and Limitations

The strength of this study is that we tested the association between a broad range of risk factors with three important brain pathology biomarkers in the oldest-old. We applied Bonferroni correction (after which four of the 22 significant associations became non-significant) and reported these in Tables 2 and 3, but given the explorative nature of this study, we described the uncorrected results. A limitation of the study is the small sample size which may have limited statistical power. The cross-sectional design precluded conclusions on the causality of associations observed. Muscle strength was measured by use of handgrip strength, which cannot be seen as proxy for overall muscle strength. Furthermore, CRP

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and leukocyte count are relatively insensitive markers to measure inflammation and also for cognitive activity a more comprehensive measurement than the CAQ would potentially be more sensitive.

Conclusions and Future Directions

Cognitive impairment in the oldest-old does not occur in isolation and this study showed that a broad range of risk and protective factors needs to be considered. This study is unique in its extensive phenotyping of oldest-old individuals. We found that especially higher physical performance and strength seem to be important aspects in preserving cognitive functioning in the oldest-old, which indicates that physical parameters are potential targets for interventions to prevent cognitive deterioration in cognitively normal individuals at high age. Furthermore, this study adds important findings regarding the role of brain pathology biomarkers in the oldest-old as it shows that, although some postmortem studies have suggested otherwise, brain pathology biomarkers are also in the oldest-old associated with cognitive functioning. Longitudinal studies are needed to further elucidate the effect of these factors on cognition in the oldest-old.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of Interest

None declared.

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