


RESEARCH ARTICLE

Contributions of amyloid beta and cerebral small vessel disease in clinical decline

Justine E. F. Moonen^{1,2}  | Renée Haan^{1,2} | Isabelle Bos³ | Charlotte Teunissen^{2,4} | Elsmarieke van de Giessen^{2,5} | Jori Tomassen^{1,2} | Anouk den Braber^{1,2} | Sophie M. van der Landen^{1,2} | Eco J. C. de Geus⁶ | Nienke Legdeur^{1,2} | Argonde C. van Harten^{1,2} | Calvin Trieu^{1,2} | Casper de Boer^{1,2} | Lior Kroeze^{1,2} | Frederik Barkhof^{5,7} | Pieter Jelle Visser^{1,2,8,9} | Wiesje M. van der Flier^{1,2}

¹Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, the Netherlands

²Amsterdam Neuroscience, Neurodegeneration, Amsterdam, the Netherlands

³Nivel, Research Institute for Better Care, Utrecht, the Netherlands

⁴Neurochemistry Laboratory, Department of Clinical Chemistry, Amsterdam Neuroscience, Neurodegeneration, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

⁵Department of Radiology & Nuclear Medicine, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, the Netherlands

⁶Department of Biological Psychology, VU University, Amsterdam, the Netherlands

⁷Institute of Healthcare Engineering and the Institute of Neurology, University College London, London, UK

⁸Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, the Netherlands

⁹Department of Neurobiology, Care Sciences and Society, Division of Neurogeriatrics, Karolinska Institutet, Solna, Sweden

Correspondence

Justine E. F. Moonen, Alzheimercenter Amsterdam, Amsterdam UMC, location VUMC, De Boelelaan 1118, 1081 HZ Amsterdam, the Netherlands.
Email: J.E.moonen@amsterdamumc.nl

Funding information

Netherlands Consortium of Dementia Cohorts, Grant/Award Number: 73305095005; ZonMw, Grant/Award Number: 10510032120003; Dutch National Dementia Strategy; EU/EFPIA Innovative Medicines Initiative, Grant/Award Number: 115372; Dutch Heart Foundation, Grant/Award Numbers: 2018-28, 10510032120003; Dutch National Dementia Strategy

Abstract

INTRODUCTION: We assessed whether co-morbid small vessel disease (SVD) has clinical predictive value in preclinical or prodromal Alzheimer's disease.

METHODS: In 1090 non-demented participants (65.4 ± 10.7 years) SVD was assessed with magnetic resonance imaging and amyloid beta ($A\beta$) with lumbar puncture and/or positron emission tomography scan (mean follow-up for cognitive function 3.1 ± 2.4 years).

RESULTS: Thirty-nine percent had neither $A\beta$ nor SVD (A-V-), 21% had SVD only (A-V+), 23% $A\beta$ only (A+V-), and 17% had both (A+V+). Pooled cohort linear mixed model analyses demonstrated that compared to A-V- (reference), A+V- had a faster rate of cognitive decline. Co-morbid SVD (A+V+) did not further increase rate of decline. Cox regression showed that dementia risk was modestly increased in A-V+ (hazard ratio [95% confidence interval: 1.8 [1.0–3.2)]) and most strongly in A+ groups. Also, mortality risk was increased in A+ groups.

DISCUSSION: In non-demented persons $A\beta$ was predictive of cognitive decline, dementia, and mortality. SVD modestly predicts dementia in A-, but did not increase deleterious effects in A+.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2023 The Authors. *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

KEYWORDS

amyloid beta, cognitive decline, dementia, mortality, small vessel disease

Highlights

- Amyloid beta (A β ; A) was predictive for cognitive decline, dementia, and mortality.
- Small vessel disease (SVD) had no additional deleterious effects in A+.
- SVD modestly predicted dementia in A-.
- A β should be assessed even when magnetic resonance imaging indicates vascular cognitive impairment.

1 | BACKGROUND

Cerebral small vessel disease (SVD) and amyloid beta (A β) co-exist in up to 47% of dementia cases.^{1,2} A β positivity in non-demented persons has been shown to increase the risk of cognitive decline, progression to Alzheimer's disease (AD) dementia,³⁻⁵ and mortality.⁶ Also, magnetic resonance imaging (MRI) features of cerebral SVD, including microbleeds, lacunes, and white matter hyperintensities (WMH) on MRI,⁷ have individually or jointly been associated with cognitive decline,⁸⁻¹⁰ increased risk of AD,¹¹⁻¹³ all-cause dementia,¹⁴⁻¹⁶ and mortality.¹⁷ Neuropathological studies have suggested that in persons with A β burden, co-morbid SVD increases the likelihood of overt AD dementia.^{18,19} However, it remains unknown to what extent co-morbid SVD is predictive of cognitive deterioration or mortality in preclinical or prodromal AD, as most studies have investigated the predictive value of either SVD or A β separately.

The limited available biomarker studies that address the predictive value of both pathologies combined showed inconsistent findings.²⁰⁻²⁹ Some studies suggest that co-morbid SVD further increases risk of cognitive decline,^{20,30} dementia, or mortality^{21,22} in A β -positive individuals, while other studies do not show co-morbid adverse effects of SVD.²³ Studies are limited by small sample sizes, inclusion of patients at advanced disease stages (without data on preclinical dementia),²⁵⁻²⁷ only considering WMH (but not microbleeds or lacunes),^{23,25,26,28,29} and/or not taking the number of microbleeds or lacunes into consideration, but only their presence or absence.^{20,21}

In this study, we included a large non-demented population over a wide age range from two population-based and a memory clinic cohort. We aimed to evaluate the independent and combined contribution of A β and features of SVD (WMH, lacunes, and microbleeds) to cognitive decline, risk of dementia, and mortality.

2 | METHODS**2.1 | Population**

We selected 1090 participants from three ongoing cohorts: (1) the Amsterdam Dementia Cohort (ADC),^{31,32} (2) the Amsterdam sub-

study of the European Medical Information Framework (EMIF) for AD PreclinAD cohort "EMIF-Twins-60+" Study,³³ and (3) the EMIF-AD 90+ Study.³⁴ Selection criteria were no diagnosis of dementia at baseline, available MRI (to quantify SVD features) and positron emission tomography (PET) or cerebrospinal fluid (CSF; to define A β status) within 1 year of the baseline visit and at least one available follow-up for cognitive function. None of the cohorts used selection criteria for presence (or severity) of SVD. Baseline visits (mean follow-up time in years) were between November 2000 to March 2020 (3.2 ± 2.6) in ADC, December 2014 to October 2016 (3.5 ± 1.4) in EMIF-Twins-60+, and June 2016 to August 2018 (2.1 ± 1.4) in EMIF-AD 90+. Cohort characteristics were as follows:

1. $n = 926$ memory clinic patients (456 SCD and 470 MCI) of the ongoing ADC^{31,32} and Subjective Cognitive Impairment Cohort (SCIENCE) project³⁵ at the Alzheimer Center Amsterdam were included. Patients undergo a standardized diagnostic work-up, including neuropsychological evaluation, MRI, and optional CSF to assess level of A β and optional A β plaques PET scan. Diagnoses were made by consensus in a multidisciplinary meeting.³¹ A diagnosis of mild cognitive impairment (MCI) was based on the National Institute on Aging-Alzheimer's Association criteria.^{36,37} Patients were labeled as SCD when clinical assessment was normal and criteria for MCI, dementia, or other neurological disorders were not met.
2. $n = 99$ cognitively unimpaired monozygotic twins aged ≥ 60 years recruited from the Netherlands Twin Register (NTR)³⁸ as part of the EMIF-Twins-60+ study (<http://www.emif.eu/>).³³ Subgroups of NTR twins underwent MRI, CSF, and/or PET and neuropsychological assessment. One person of each twin pair was randomly selected (by selecting the first born of each pair) to avoid impact of dependency within each twin pair (due to being genetically identical) to our findings.
3. $n = 65$ community-dwelling cognitively unimpaired elderly ≥ 90 years of the EMIF-AD 90+ study.³⁴ The EMIF-AD 90+ study is a case-control study including cognitively unimpaired and impaired individuals. Participants were recruited via advertisement, outreach to general practitioners, and the 100-plus Study.³⁹ EMIF-AD 90+ participants underwent MRI, PET, and neuropsychological

assessment. Inclusion and exclusion criteria have been previously described in more detail.^{31–34}

All participants provided written informed consent. The Vrije Universiteit Medical Center (VUmc) ethical review board approved ADC and the EMIF studies.

2.2 | A β

2.2.1 | CSF

CSF was obtained by lumbar puncture in ADC and EMIF-Twins-60+.^{40,41} In ADC A β 1-42 level was measured using sandwich enzyme-linked immunosorbent assays (Innotest),⁴² or with the Roche Elecsys assay (from June 2018).⁴³ CSF concentrations were considered positive for A β 1-42 according to < 813 pg/mL (drift-corrected;⁴⁴ Innotest) or < 1000 pg/mL (Elecsys). In EMIF-Twins-60+ levels of A β 1-42 and A β 1-40 in CSF were measured using ADx Neurosciences/Euroimmun^{45,46} and were considered positive according to a ratio of A β 1-42/1-40 < 0.066.⁴⁷

2.2.2 | PET

A β PET scans were acquired on Philips Gemini TF PET-CT, Philips Ingenuity TF PET-CT, and Philips Ingenuity PET-MRI. In ADC⁵ the A β tracers [¹⁸F]Florbetapir, [¹⁸F] Florbetaben, [¹⁸F]Flutemetamol, or [¹¹C] Pittsburgh compound B (PiB) were used and in EMIF-Twins-60+³³ and EMIF-AD 90+³⁴ [¹⁸F]Flutemetamol. Trained and experienced nuclear medicine physicians visually rated the scans as negative or positive for A β plaques in line with the company product guidelines of each tracer and for [¹¹C] PiB according to previously published methods.⁴⁸ The readers looked for an AD-like pattern of A β plaque positivity and also correlated the read with available MRIs. The used visual classification has demonstrated to be capable of detecting early A β pathology and has previously shown excellent agreement against the quantitative Centiloid (CL)-based classification (using a cut-off of > 17 CL) with a sensitivity and specificity of \approx 98% in ADC.^{49,50} The intra- and inter-rater reliability in ADC has previously reported to be good ($\kappa = 0.7$ up to 0.9).^{48,49}

2.2.3 | A β status

A β positivity (A+) was based on dichotomized level in CSF (available in $n = 1005$, 36% A+) or presence of A β plaques on PET (available in $n = 450$, 32% A+). Forty percent had either positive CSF and/or PET and were classified as A+.

2.3 | Small vessel disease

2.3.1 | MRI acquisition and processing

Brain MRI scans were obtained on a 3.0 T Philips Achieva in EMIF-Twins-60+³³ and EMIF-AD 90+⁵¹ and on different 1.5 and 3.0T MRI

RESEARCH IN CONTEXT

- 1. Systematic review:** The authors reviewed literature on the predictive value of amyloid beta (A β ; A) and small vessel disease (SVD) for cognitive decline, incident dementia, and mortality in non-demented individuals. The few available biomarker studies that address the predictive value of both pathologies simultaneously were limited by small sample sizes and/or the inclusion of patients with advanced cognitive impairment.
- 2. Interpretation:** Pooled analyses of a large memory clinic and two smaller population-based cohorts in a total of 1090 non-demented participants show that SVD modestly predicted dementia in those without A β (A-V+). A β (A+V-) predicted cognitive decline, dementia, and mortality, while co-morbid SVD (A+V+) did not further increase rate of cognitive decline, nor the risk of dementia or mortality.
- 3. Future directions:** Amyloid may be the key predictive factor in clinical decline, which is informative for clinical trial recruitment of high-risk patients and for the prognosis of a patient with co-morbid pathologies. Our results underline the need to assess amyloid in clinical practice, even when magnetic resonance imaging findings indicate a diagnosis of vascular cognitive impairment.

scanners in the ADC.^{52,53} The scan protocol included structural 3D-T1, T2, fluid-attenuated inversion recovery (FLAIR), and susceptibility weighted imaging (SWI). Acquisition parameters and pre-processing have been previously described.^{33,51–53} Definitions of MRI features of SVD were based on the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE-1) criteria.⁷ MRI scans were assessed visually by a neuroradiologist or trained rater, who were blind to clinical data. WMH were rated on the FLAIR images using the 4-point Fazekas scale.⁵⁴ Microbleeds were defined as round foci up to 10 mm in the brain parenchyma with hypointense signal on SWI. Lacunes were defined as subcortical lesions of 3 to 15 mm with CSF-like signal on FLAIR and T1- and T2-weighted images. Microbleeds and lacunes were counted.

2.3.2 | SVD status

The SVD score was derived by awarding 1 point for presence of each of the following MRI features: a WMH Fazekas score ≥ 2 , or microbleeds ≥ 1 and/or lacunes ≥ 1 (ranging 0–3). Participants were categorized as SVD positive (V+) according to SVD score ≥ 1 or as SVD negative (V-; SVD score = 0).

The use of an SVD sum score has been previously validated in a large sample of older persons, for which more complex latent

variable modeling showed that individual MRI features formed a unitary SVD construct, which demonstrated consistent associations with general cognitive ability compared to the SVD sum score.⁵⁵ Various studies have examined different combinations of individual SVD markers and Standards for Reporting Vascular Changes on Neuroimaging-2 (STRIVE) criteria⁵⁶ define a summary SVD score as any grouping of accepted SVD markers into a single index score.

To evaluate the effect of a higher load of SVD, we increased the classification threshold for SVD positivity according to a score of ≥ 4 points on "the modified SVD score," that is, $V^{\text{high}+}$. The modified SVD score [range 0–9] was defined as the sum of the WMH Fazekas scale score [range 0–3], the lacune score [range 0–3] (0 = 0, 1 = 1, 2 = 2 or 3, and 3 > 4) and microbleed score [range 0–3] (0 = 0, 1 = 1, 2 = 2 or 3, and 3 > 4).

2.4 | Neuropsychological assessment

All participants received an extensive standardized neuropsychological assessment.³³ The Mini-Mental State Examination (MMSE) was used to assess global cognition.⁵⁷ To determine memory we used delayed recall of Rey Auditory Verbal Learning Task (RAVLT), also known as the 15 Word Verbal Learning Test (15 WVLT).⁵⁸ To examine language animal fluency (1 minute) was used.⁵⁹ The Trail Making Test Parts A and B (TMT-A and B) were performed to assess attention and executive function.⁶⁰ For the 1090 participants, a total number of 3858 neuropsychological investigations were available ($n = 3439$ of ADC/SCIENCe, range 2–17, median 3; $n = 263$ EMIF-Twins-60+, range 2–3, median 2; $n = 156$ EMIF-AD 90+, range 2–3, median 2).

2.5 | Dementia

At follow-up, dementia was diagnosed in memory clinic patients of ADC according to common clinical and research criteria.³¹ In EMIF-Twins-60+ the study physician consulted a neurologist when neuropsychological tests and (functional) questionnaires at follow-up visits suggested conversion to dementia, and if necessary, a diagnostic work-up in the hospital was performed. In EMIF-AD 90+ progression to dementia was defined by a global Clinical Dementia Rating (CDR) score ≥ 1 .³⁴

2.6 | Mortality

Data on mortality were obtained from the Municipal Personal Records Database in ADC, from the NTR³⁸ in EMIF-Twins-60+, and from the Central Bureau of Statistics in EMIF-AD 90+ (dates of information: April 2022, July 2022, and Sept 2021, respectively).

2.7 | Demographics

Baseline data on age, sex, and years of education were collected during the diagnostic workup in the ADC^{31,32} or through structured questionnaires in the EMIF studies.^{33,34}

2.8 | Statistical analyses

We constructed a four-level variable based on binary assessment of $A\beta$ (A) and SVD (V): A–V– (reference category), A–V+, A+V–, and A+V+. Baseline characteristics were compared among these four AV biomarker groups and among the four study samples (ADC-SCD, ADC-MCI, EMIF-Twins-60+, EMIF-AD 90+). Chi-square was used for categorical variables, analysis of variance for continuous variables, and the Kruskal–Wallis test for continuous variables with a skewed distribution. Raw test scores for TMT-A and TMT-B were inverted by $(1/x*1000)$ to ensure a normal distribution and for higher score to indicate better performance.

Linear mixed models were used to investigate the relationship between AV groups (independent variable) and cognitive test scores (dependent variables; separate models for each cognitive test). AV groups (with A–V– as reference), time, and the interaction between AV group and time were entered as determinants. Intercept and time were included as random factors and age, sex, education, and the four study samples were included as covariates.

Cox proportional hazard analyses were performed to evaluate the association between AV groups (A–V– as reference) and dementia and mortality (outcomes in separate models). Age, sex, education, and study sample were included as covariates. All analyses were also performed stratified by study sample.

2.8.1 | Sensitivity analyses

To evaluate the effect of severity of SVD, we reran our analyses with A–V^{high}– (reference), A–V^{high}+, A+V^{high}–, or A+V^{high}+ as independent variable. Furthermore, to evaluate the effect of *burden of $A\beta$* and SVD features on cognitive decline or risk of dementia or mortality, we simultaneously entered standardized $A\beta$ level in CSF (not available in EMIF-AD 90+) and the modified SVD score (ranging 0–9) as *continuous* independent variables into our models (i.e., as replacement for the ordinal AV group predictor in our main analyses). Of note, a *higher* concentration of $A\beta$ in CSF is indicative of *less* brain $A\beta$.⁶¹ Analyses were stratified per study sample and per CSF assay and forest plots were computed. Some study samples could not be represented in the forest plot, as a result of too few dementia or mortality cases, that is, two or fewer, which does not allow the computation of hazard ratios with Cox regression. Effect estimates of each analysis were pooled using random-effect meta-analyses. Between-study heterogeneity was assessed via the I^2 and the Cochrane Q.

To evaluate whether clinical decline over time per AV group was modified by sex we included the 3-way interaction term AV group x time x sex into our mixed models for the outcome cognitive decline, or the term AV group x sex into our Cox regression models for progression to dementia or mortality.

The effect of the competing risk of death in the association between AV group and incident dementia was evaluated with the Fine–Gray competing risk hazard model.⁶²

Analyses were performed with SPSS version 26. R studio 4.0.3 was used for Fine and Gray analyses (cmprsk) and random effects meta-analyses (metafor) as well as for figures showing association between AV groups and cognitive decline (ggplot2, lme4). *P* value < 0.05 was considered significant.

3 | RESULTS

The 1090 participants were on average 65.4 ± 10.7 years old (range 36–102 years), 43% were women, and mean MMSE was 28 ± 2 . Thirty nine percent ($n = 430$) were classified as A–V–, 21% ($n = 227$) as A–V+, 23% ($n = 252$) as A+V–, and 17% ($n = 181$) as A+V+ (Table 1). Demographic and clinical characteristics are shown per AV biomarker group in Table S1.A in supporting information and per study sample in Table S1.B. Table S1.A shows that the prevalence of apolipoprotein E (APOE) $\epsilon 4$ ($P < 0.001$), level of CSF A β ($P < 0.001$), and phosphorylated tau (p-tau; $P < 0.001$) differed among the AV groups, with A+ groups showing a higher APOE $\epsilon 4$ prevalence, lower CSF A β levels (indicative of higher cerebral A β burden), and higher p-tau level. Post hoc analyses were performed to compare A+V– to A+V+. The z scored CSF amyloid level was -0.94 (standard deviation [SD] 0.46) in A+V– versus -1.04 (SD 0.45) in A+V+ (between-group mean difference -0.11 [standard error (SE) 0.06], $P = 0.08$). Prevalence of APOE $\epsilon 4$ positivity in A+V– (71%) also did not significantly differ from A+V+ (66%), $P = 0.28$. The CSF level of p-tau, however, was significantly higher in A+V– 0.68 (SE 1.16) versus 0.45 (SE 1.1) in A+V+ (between-group mean difference -0.23 [SE 0.10], $P = 0.018$). Table S1.B shows that the distribution of AV groups differed between cohorts ($P < 0.001$); V+ groups were most prevalent in EMIF-AD 90+ and A+ groups were most prevalent in ADC MCI patients.

3.1 | Cognitive decline

Figure 1 shows the neuropsychological test scores and trajectories over time. Compared to the reference group (A–V–), A–V+ did not differ in baseline cognitive function nor decline over time (Table 2). A+ groups (A+V+ and A+V–) showed lower baseline scores on RAVLT, but not on the other cognitive tests. A+V– showed steeper decline over time on MMSE, TMT-A, TMT-B, RAVLT, and animal fluency. Having co-morbid SVD pathologies (A+V+) did not further increase rate of cognitive decline A β , as effect sizes were in the same order of magnitude compared to A+V–.

TABLE 1 Characteristics ($n = 1090$).

Age, y, mean, SD	65.4	10.7
Sex, female, n, %	464	42.6%
Education, mean, SD	11.9	3.2
APOE $\epsilon 4$ positive, n, %	488 of 1060	46.0%
A β positive, n, %	433 of 1090	39.7%
CSF positive	366 of 1005	36.4%
PET positive	145 of 450	32.2%
Vascular positive, n, %	408	37.4%
Fazekas ≥ 2	228	20.9%
Lacunes ≥ 1	113	10.4%
Microbleeds ≥ 1	237	21.7%
A β (A) and vascular (V) groups, n, %		
A–V–	430	39.4%
A–V+	227	20.8%
A+V–	252	23.1%
A+V+	181	16.6%
Baseline cognitive function		
Follow-up time cognition, years, mean, SD	3.1	2.4
MMSE score, mean, SD	27.6	2.1
Time on TMTA, seconds, median, IQR	39.0	30.0–51.0
Time on TMTB, seconds, median, IQR	96.0	71.5–132.0
RAVLT score, delayed recall, mean, SD	6.1	5.0
Animal fluency score, mean, SD	20.0	10.0
Progression to dementia, n, %	247	22.7%
Progression time to dementia, years, mean, SD	3.0	2.2
Mortality, n, %	252	23.1%
Progression time to death, mean, SD	7.9	3.8

Abbreviations: A, amyloid beta status; A β , amyloid beta; APOE, apolipoprotein E; CSF, cerebrospinal fluid; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test, i.e., the 15 Word Verbal Learning Test; SCD, subjective cognitive decline; SD, standard deviation; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; V, vascular status (small vessel disease status).

Stratified analyses per study show a similar pattern of results for cognitive decline over time in ADC SCD, ADC MCI, and EMIF twins, with the largest effect estimates in the A+ groups. EMIF-AD 90+ shows less consistent results with no clear pattern of effect sizes per AV group. All stratified analyses show less significant findings compared to pooled analyses, due to suboptimal power (Table S2 in supporting information).

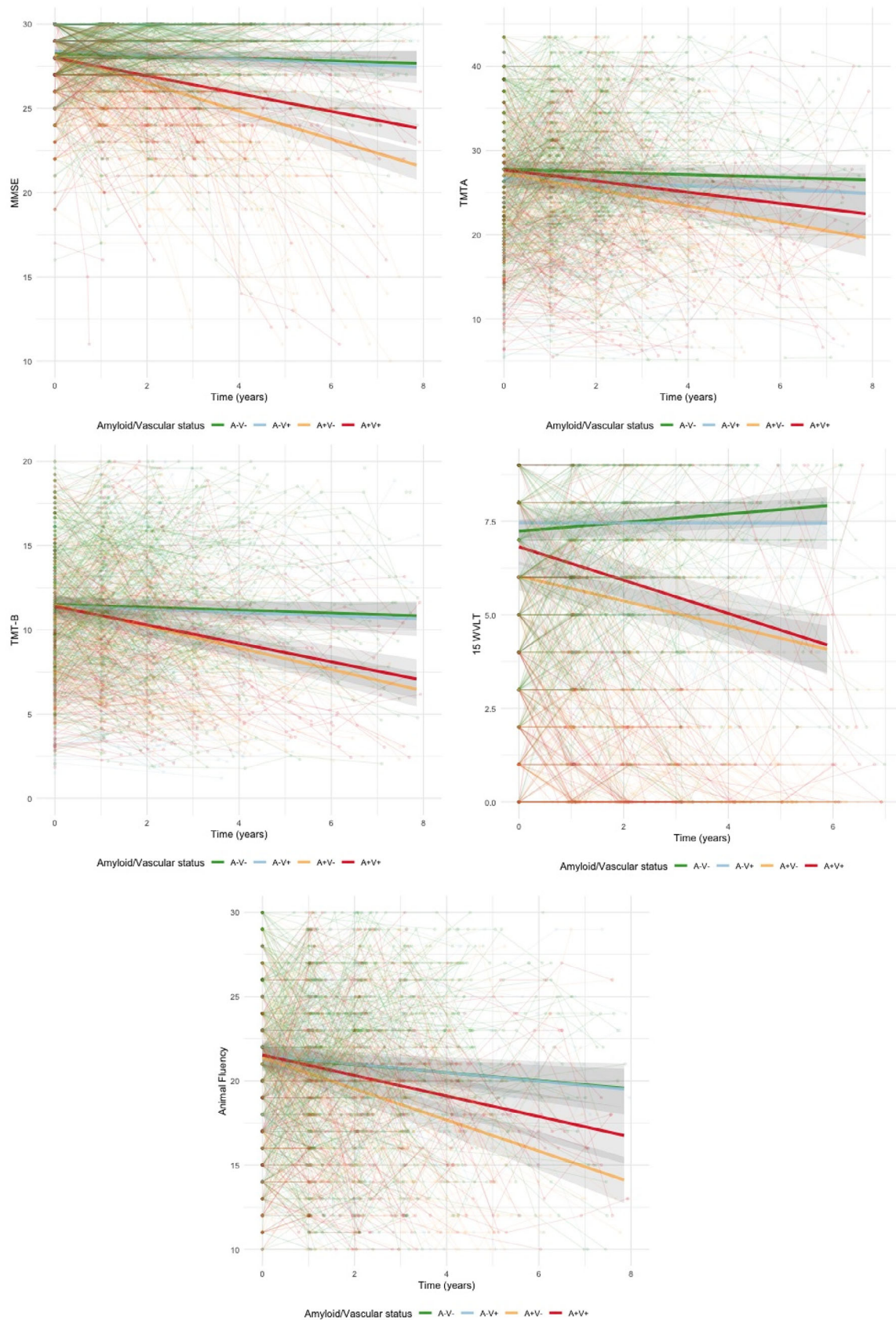


FIGURE 1 Trajectories of neuropsychological test scores over time per AV group. 15WVLT, 15 word verbal learning test (the Rey Auditory Verbal Learning Test); A, amyloid beta status; MMSE, Mini-Mental State Examination; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; V, vascular status (small vessel disease status).

TABLE 2 AV group and cognitive function.

	Baseline			Longitudinal			
	Mean	SE	P	Estimate	Lower CI	Upper CI	P
MMSE							
A-V-	28.2	0.1	Ref				Ref
A-V+	28.4	0.1	0.27	-0.1	-0.2	0.1	0.56
A+V-	28.2	0.1	0.52	-0.8	-0.9	-0.6	<0.001
A+V+	28.0	0.1	0.09	-0.5	-0.7	-0.3	<0.001
TMTA							
A-V-	27.6	0.4	Ref				Ref
A-V+	26.7	0.5	0.12	-0.3	-1.1	0.4	0.41
A+V-	27.2	0.5	0.51	-1.0	-1.7	-0.3	0.007
A+V+	27.6	0.6	0.99	-0.7	-1.5	0.1	0.07
TMTB							
A-V-	11.5	0.2	Ref				Ref
A-V+	11.3	0.2	0.43	0.0	-0.4	0.3	0.84
A+V-	11.4	0.2	0.79	-0.7	-1.0	-0.3	<0.001
A+V+	11.3	0.3	0.55	-0.6	-1.0	-0.2	0.005
RAVLT (15WVLT)							
A-V-	7.2	0.1	Ref				Ref
A-V+	7.4	0.2	0.26	-0.2	-0.5	0.1	0.28
A+V-	5.9	0.2	<0.001	-0.4	-0.7	-0.1	0.006
A+V+	6.7	0.2	0.02	-0.6	-1.0	-0.3	<0.001
Animal Fluency							
A-V-	21.4	0.2	Ref				Ref
A-V+	21.4	0.3	0.78	-0.02	-0.5	0.4	0.92
A+V-	21.1	0.3	0.32	-0.6	-1.0	-0.2	0.007
A+V+	21.3	0.3	0.62	-0.3	-0.8	0.2	0.20

Abbreviations: 15WVLT, 15 word verbal learning test; A, amyloid beta status; CI, confidence interval; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; Ref, reference group; SE, standard error; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; V, vascular status (small vessel disease status).

3.2 | Risk of dementia and mortality

Kaplan–Meier curves illustrate progression to dementia and mortality (Figure 2). After a mean follow-up time of 3.0 ± 2.2 years, 28 (7%) participants in A-V+, 125 (50%) in A+V-, and 68 (38%) in A+V+ developed incident dementia compared to 28 (7%) in A-V-. Cox regression showed that compared to A-V-, the groups with any form of pathology had an increased risk of dementia, with the strongest risks for A+ groups (HR^{Cox} [95% confidence interval (CI)] A-V+ 1.8 [95% CI 1.0–3.2], A+V- 9.3 [95% CI 6.0–14.3], and A+V+ 7.5 [95% CI 4.6–12.1]; Table 3).

During a mean follow-up time of 7.9 ± 3.8 years, 252 deaths occurred: 53 (12%) in A-V-, 53 (23%) in A-V+, 86 (34%) in A+V-, and 60 (33%) in A+V+. Compared to A-V-, participants in the A+ groups showed increased risk of mortality (HR [95% CI] A+V- 2.2 [1.5–3.2] and A+V+ 2.0 [1.3–3.0]), while A-V+ did not (1.3 [0.8–1.9]; Table 4).

Cox models for progression to dementia (Table S3 in supporting information) or mortality (Table S4 in supporting information) are reported for ADC, but not for EMIF-Twins-60+ or EMIF-AD 90+, as the number of cases per AV group would not allow meaningful statistics.

3.3 | Sensitivity analyses

To evaluate the impact of the severity of SVD to our results, we re-ran analyses with V^{high} defined as a score of ≥ 4 points on the modified SVD score. Apart from A-V^{high}+ having lower baseline scores for TMT-B, compared to A-V^{high}- (reference), there were no associations with cognitive decline (Table S5 in supporting information). There was no associations in A- between V^{high} and dementia (only in A+ groups). Severity of SVD, however, was related with increased mortality risk also in A- (HR [95% CI]: A-V^{high}+; 2.0 [1.2–3.3]; A+V^{high}-; 2.2 [1.7–3.0]; Table S6 in supporting information).

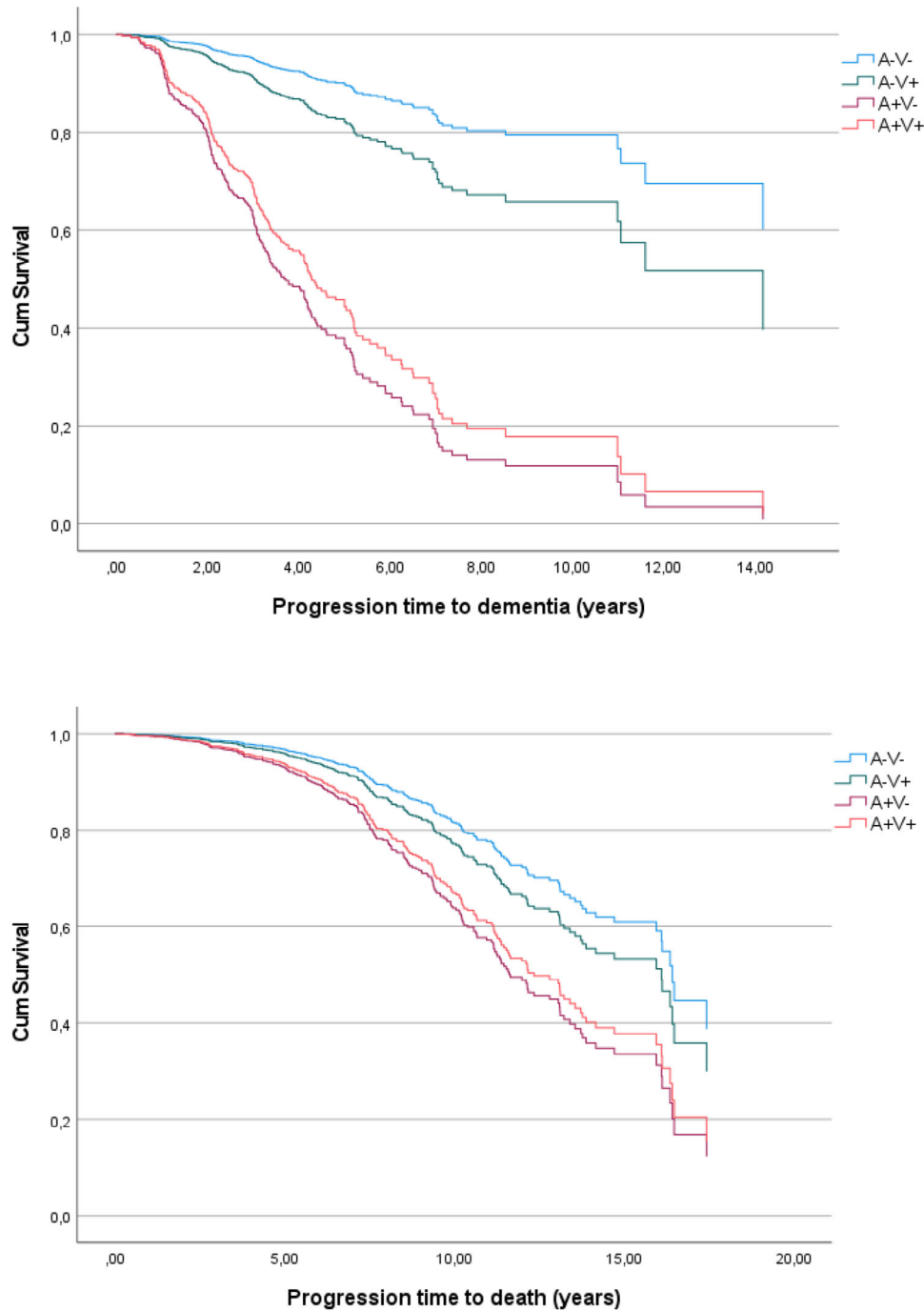


FIGURE 2 AV group and progression to dementia or mortality. A, amyloid beta status; V, vascular status (small vessel disease status).

TABLE 3 AV group and progression to dementia (n = 1090).

	n	n (%)	HR	Lower CI	Upper CI	P
A-V-	430	28 (6.5%)	Ref			
A-V+	227	26 (11.5%)	1.8	1.0	3.2	0.04
A+V-	252	125 (50.4%)	9.3	6.0	14.3	<0.001
A+V+	181	68 (37.6%)	7.5	4.6	12.1	<0.001

Abbreviations: A, amyloid beta status; CI, confidence interval; HR, hazard ratio; Ref, reference group; V, vascular status (small vessel disease status).

TABLE 4 AV group and mortality (n = 1090).

	n	n (%)	HR	Lower CI	Upper CI	P
A-V-	430	53 (12.3%)	Ref			
A-V+	227	53 (23.3%)	1.3	0.8	1.9	0.25
A+V-	252	86 (34.1%)	2.2	1.5	3.2	<0.001
A+V+	181	60 (33.1%)	2.0	1.3	3.0	0.001

Abbreviations: A, amyloid beta status; CI, confidence interval; HR, hazard ratio; Ref, reference group; V, vascular status (small vessel disease status).

Our stratified results by study sample and by CSF assay with $A\beta$ in CSF and the modified SVD score (range 0–9) as continuous predictors are in line with our pooled results, showing consistently the same directionality of effect estimates for $A\beta$. The effect estimates vary somewhat in size across study samples and across CSF assays. Some stratified results do not reach significance, because of lack of power due to smaller sample sizes per stratum (e.g., ADC with MCI with the Elecsys assay only includes 38 participants), but pooled random effects meta-analyses estimates for $A\beta$ do reach significance. A higher concentration of CSF $A\beta$ (indicative of less $A\beta$ brain pathology⁶¹) predicted less decline in MMSE (random effects meta-analyses estimate for $A\beta$ [95% CI] 0.22 [0.09 to 0.35]), whereas SVD did not (see Figure S1 in supporting information). Similarly, higher level of $A\beta$, but not SVD load, predicted less decline in TMT-A, TMT-B, and the RAVLT. Only animal fluency was next to $A\beta$ level also predicted by the modified SVD score (estimate [95% CI] 0.10 [0.01 to 0.20]). A higher CSF level of $A\beta$ significantly reduced risk of dementia (random effects meta-analyses HR 0.53 [0.36 to 0.71]) and of mortality (random effects meta-analyses HR 0.71 [0.55 to 0.88]), which risks were not predicted by SVD load (Figures S2 and S3 in supporting information, respectively).

To evaluate modification by sex we added the three-way interaction term AV group \times time \times sex in our mixed models, which was not significant for any of the cognitive tests. Also, progression to dementia or mortality was not modified by sex as the interaction term AV group \times sex did not reach significance in the Cox regression models.

To evaluate the impact of the competing risk of death for incident dementia we used the Fine and Gray regression model, which showed that Cox regression may have overestimated the HRs (HR^{Fine&Gray} [95% CI] A–V+ 1.4 [0.8–2.4], A+V– 5.5 [3.5–8.7], and A+V+ 4.1 [2.5–6.8], compared to A–V–).

4 | DISCUSSION

We showed $A\beta$ positivity (A+) and SVD (V+) are equally common in non-demented research participants. Compared to persons with normal biomarkers (A–V–), A+ was strongly predictive for decline in memory, language, attention, executive function, and global cognition, as well as for risk of dementia and mortality. By contrast, V+ only modestly predicted dementia in A– and had no additional deleterious effects in A+ on cognitive decline or predicting dementia or mortality.

In contrast to our findings, a population-based study by Vemuri et al. in cognitively unimpaired elderly showed a similar magnitude of effect for $A\beta$ (A+V–) and SVD (A–V+; lacunes and WMH) on rate of cognitive decline over 3 years compared to A–V–, and additive combined effects, that is, larger effect size for A+V+ compared to A+V–.²⁰ A memory clinic study in non-demented persons also suggested deleterious effects of co-morbid pathologies as it found significant interaction between $A\beta$ and WMH (but not with microbleeds or lacunes) on global cognitive dysfunction, yet this study did not have a longitudinal design.²⁴ Another memory clinic study by Bos et al. found comparable effect sizes for isolated WMH (A–WMH+) and $A\beta$ (A+WMH–), yet

did not observe that the combination was associated with faster global cognitive decline over 2 years in non-demented patients.²³

Our pooled estimates were largely driven by tertiary memory clinic patients, who were overall younger, had a lower load of SVD, and may be at a more advanced AD stage than participants of other studies. Moreover, our population-based samples were carefully selected to be cognitively normal at baseline, which may explain discrepancies with other population-based studies that do show adverse (co-morbid) effects of SVD. Particularly, the oldest old EMIF-AD 90+ participants with normal cognitive function at baseline may have been resilient for their acquired vascular and/or amyloid cerebral damage.

A–V+ showed a modestly increased risk of developing dementia, followed by A+V+, and was highest in A+V–. The latter counterintuitive finding could be explained by a higher load of p-tau in A+V– compared to A+V+, indicating that A+V– is at a more advanced AD pathological stage than A+V+.

One could speculate that our V+ cut-off was too liberal, and that only more severe SVD was predictive of clinical progression. Nonetheless, sensitivity analyses using a higher V threshold demonstrated an increased dementia risk only in A+ groups while significance was lost in A–V^{high}+. This could be explained by lack of power as after increasing the threshold for vascular positivity only $n = 67$ persons were included in A–V^{high}+ versus $n = 227$ in A–V+ in the main analyses (effect sizes remained in similar order of magnitude). Similarly, although mortality risk was increased in both A+ groups in the main analyses, results of sensitivity analyses in A+V^{high}+ (in only $n = 54$) no longer reached significance. Of note, despite the limited power, sensitivity analyses did reveal a significantly increased mortality risk in A–V^{high}+, indicating that $A\beta$ -negative individuals with the highest load of SVD are also at increased risk of mortality. A high SVD burden is known to increase mortality risk.⁶³ Furthermore, this finding is in line with the main analyses, where A–V+ was at modestly increased risk of dementia. This also shows that particularly in the absence of amyloid, SVD is by no means benign.

Additional sensitivity analyses on the impact of a higher $A\beta$ burden (according to level in CSF) and higher load of SVD (a compound score ranging from 0–9, accounting for severity of WMH and number of lacunes and microbleeds) confirmed results of the main analyses, namely that $A\beta$, but not SVD, is the key predictor in cognitive decline and risk of dementia and mortality. P-tau or loss of brain volume could be of additional predictive value next to $A\beta$, in accordance with the ATN (amyloid/tau/neurodegeneration) framework.

Previous longitudinal studies that did not account for presence of $A\beta$ have suggested that features of SVD are associated with cognitive decline in various domains⁶⁴ and increased risk of developing dementia.^{11–13,65,66} SVD prevalence greatly increases with aging, and is present in the majority of dementia cases, but is rarely a cause of dementia on its own.^{67–69} In the majority of older persons who develop dementia, the brain shows multiple pathologies next to features of SVD, including AD pathologies ($A\beta$ and tau), inflammation, and/or other markers of neurodegeneration.² The multi-factorial nature of dementia underlines the need for future studies to investigate the

interplay between vascular and other pathologies in their etiological contributions to dementia.

Our results indicate that parenchymal manifestation of SVD, that is, lacunes, microbleeds, and/or WMH, do not interact with $A\beta$ in accelerating cognitive decline, as we did not find that the combined effect of A+V+ was larger than the sum of each pathology independently. These results should be interpreted with caution, as conventional MRI does not capture functional or microstructural vascular alterations, which may interact with $A\beta$ in promoting brain damage and dysfunction. Dysfunction of vascular cells, such as endothelial cells, that are part of the neurovascular unit and that play a role in regulating cerebral blood flow (CBF) and the blood–brain barrier (BBB), may induce $A\beta$ deposition by reducing clearance.^{70,71} Dysregulation of CBF may lead to hypoperfusion and congestion of interstitial fluid in the brain parenchyma, thereby facilitating the aggregation of nontoxic $A\beta$ monomers into toxic soluble $A\beta$ oligomers and insoluble $A\beta$ plaques.^{71,72} Vice versa, deposition of $A\beta$ into the walls of small cerebral vessels, that is, cerebral amyloid angiopathy (CAA), may induce adverse vascular changes.⁷² The modified Boston criteria⁷³ for “probable CAA” (the most commonly used diagnostic category) additionally incorporate hemosiderin subpial deposits in the cortical sulci, that is, cortical superficial siderosis, next to multiple lobar (micro) hemorrhages. Although we have incorporated microbleeds in our V definition, undetected CAA in the form of cortical superficial siderosis may have contributed to clinical decline in the V- groups.

Major strengths of our study are the inclusion of a large sample of > 1000 participants and the long-term follow-up with repeated cognitive testing covering multiple domains. Our multi-cohort design strengthens generalizability of our findings, as we included participants with either normal cognitive function, SCD, or MCI, over a wide age range with varying load of SVD and $A\beta$ pathologies. External validity of our findings should be further enhanced by the consideration of the impact of race, sex, gender, and socioeconomic status. Of note, our findings cannot be extrapolated to persons with established (AD) dementia.

Our study has several limitations. We may have had limited power to detect (co-morbid) adverse effects of SVD in the community-based EMIF studies that contributed with smaller samples and fewer follow-up visits. Novel AD biomarkers in blood will facilitate future community-based studies in this field, as they provide a non-invasive and accessible method to determine $A\beta$ status. Future studies should adhere to the recently updated STRIVE-2⁵⁶ and consider: (1) other features of SVD, next to WMH, microbleeds, and lacunes, including perivascular spaces, recent small subcortical infarcts, cortical superficial siderosis, or cortical cerebral microinfarcts; (2) the use of sophisticated MRI sequences such as diffusion weighted imaging (DWI) to characterize tissue microstructure (to detect emerging SVD features, such as “incidental DWI-positive lesions”), arterial spin labelling to measure cerebral perfusion, and/or dynamic contrast-enhanced MRI for BBB imaging; and (3) the use of computational image analyses instead of visual rating or segmentation.⁷⁴ A large-multi cohort study in > 3000 memory clinic patients underlines the need to use computational image analyses to define strategic location of WMH tracts, as it shows that the impact of WMH on cognitive function is loca-

tion dependent.⁷⁵ The use of novel MRI sequences and/or automated image analyses will increase sensitivity to detect sub-visible vascular tissue damage and will likely demonstrate that our effect estimates for vascular positivity are an underestimation of the true effect size.

In conclusion, our findings indicate that in preclinical or prodromal AD co-morbid SVD does not further increase risk of prospective cognitive deterioration or mortality. $A\beta$ may be the key predictive factor in clinical decline, which is informative for clinical trial recruitment of high-risk patients and for the prognosis of a patient with co-morbid pathologies. Our results underline the need to assess $A\beta$ in clinical practice, even when MRI findings indicate a diagnosis of vascular cognitive impairment.

ACKNOWLEDGMENTS

The authors thank all Amsterdam Dementia Cohort, EMIF-Twins and EMIF-90+ participants and investigators for their contributions. The authors acknowledge all researchers of the Netherlands Consortium of Dementia Cohorts (NCDC), funded in the context of Deltaplan Dementie from ZonMW Memorabel (projectnr 73305095005) and Alzheimer Nederland. The authors acknowledge the Timely, Accurate, and Personalized Diagnosis of Dementia (TAP-dementia) project that receives funding from ZonMw (#10510032120003) in the context of Onderzoeksprogramma Dementie, which is part of the Dutch National Dementia Strategy. Amsterdam UMC locations VUmc and AMC, ErasmusMC, UMCU, University Maastricht, UMCG, VU University, Elisabeth-TweeSteden Ziekenhuis Tilburg, and Vilans participate in TAP-dementia (www.tap-dementia.nl). TAP-dementia receives co-financing from Avid Radiopharmaceuticals, Roche Diagnostics, and Amprion. Gieskes-Strijbis fonds also contributes to TAP-dementia. Research of Alzheimer Center Amsterdam is part of the neurodegeneration research program of Amsterdam Neuroscience. Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting VUmc fonds. EMIF-90+ and EMIF-Twins-60+ were supported by the EU/EFPIA Innovative Medicines Initiative Joint Undertaking EMIF grant agreement no. 115372. The SCIENCE cohort (of the Amsterdam Dementia Cohort) receives funding from stichting Dioraphte. The chair of Wiesje van der Flier is supported by the Pasman stichting. WF is recipient of HBC-X, which has received funding from the [Dutch Heart Foundation](http://www.dutchheartfoundation.nl) under grant agreement 2018-28. Wiesje van der Flier is also recipient of TAP-dementia, a ZonMw funded project (#10510032120003) in the context of the Dutch National Dementia Strategy. Frederik Barkhof (FB) is supported by the NIHR biomedical research center at UCLH. FB reports consultancy fees from Apitope, Bayer-Schering Pharma, Biogen Idec, GeNeuro, IXICO, Janssen Research, Merck-Serono, Novartis, Roche, Sanofi Genzyme, and Teva; speakers' fees from Biogen Idec and IXICO; and grants or pending grants from AMYPAD (IMI), Dutch MS Society, ECTRIMS-MAGNIMS, EuroPOND (Horizon 2020), University College London Hospitals National Institute for Health Research Biomedical Research Centre, PICTURE (IMDI-NWO), and the UK Multiple Sclerosis Society. Pieter Jelle Visser has received funding for the Netherlands Consortium of Dementia Cohorts (NCDC) in the context of Deltaplan Dementie from ZonMW Memorabel (projectnr 73305095005) and

Alzheimer Nederland. Justine Moonen is appointed at NCDC. Please find funding sources of all co-authors in the attached ICMJE disclosure forms.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided written informed consent. The VU University Medical Center (VUmc) ethical review board approved ADC and the EMIF studies.

ORCID

Justine E. F. Moonen  <https://orcid.org/0000-0001-8260-8762>

REFERENCES

- Liu W, Wong A, Law ACK, Mok VCT. Cerebrovascular disease, amyloid plaques, and dementia. *Stroke*. 2015;46:1402-1407.
- Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007;69:2197-2204.
- Roberts RO, Aakre JA, Kremers WK, et al. Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting. *JAMA Neurol*. 2018;75:970-979.
- Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol*. 2013;12:357-367.
- Ebenau JL, Timmers T, Wesselman LMP, et al. ATN classification and clinical progression in subjective cognitive decline. *The SCIENCe Project*. 2020;95:e46-e58.
- Boumenir A, Cognat E, Sabia S, et al. CSF level of β -amyloid peptide predicts mortality in Alzheimer's disease. *Alzheimer's Res Ther*. 2019;11:29.
- Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822-838.
- Prins ND, van Dijk EJ, den Heijer T, et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain*. 2005;128:2034-2041.
- Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003;348:1215-1222.
- Chiang GC, Cruz Hernandez JC, Kantarci K, Jack CR Jr, Weiner MW. Cerebral microbleeds, CSF p-Tau, and cognitive decline: significance of anatomic distribution. *AJNR Am J Neuroradiol*. 2015;36:1635-1641.
- Rosano C, Aizenstein HJ, Wu M, et al. Focal atrophy and cerebrovascular disease increase dementia risk among cognitively normal older adults. *J Neuroimaging*. 2007;17:148-155.
- Kuller LH. [Risk factors for dementia in the Cardiovascular Health Study cognition study]. *Rev Neurol*. 2003;37:122-126.
- Ye S, Dong S, Tan J, et al. White-matter hyperintensities and lacunar infarcts are associated with an increased risk of Alzheimer's disease in the elderly in China. *J Clin Neurol*. 2019;15:46-53.
- Miwa K, Tanaka M, Okazaki S, et al. Multiple or mixed cerebral microbleeds and dementia in patients with vascular risk factors. *Neurology*. 2014;83:646.
- Kim S, Choi SH, Lee YM, et al. Periventricular white matter hyperintensities and the risk of dementia: a CREDOS study. *Int Psychogeriatr*. 2015;27:2069-2077.
- Amin Al Olama A, Wason JMS, Tuladhar AM, et al. Simple MRI score aids prediction of dementia in cerebral small vessel disease. *Neurology*. 2020;94:e1294-e1302.
- Yilmaz P, Ikram MK, Niessen WJ, Ikram MA, Vernooij MW. Practical small vessel disease score relates to stroke, dementia, and death. *Stroke*. 2018;49:2857-2865.
- Arvanitakis Z, Capuano AW, Leurgans SE, Bennett DA, Schneider JA. Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study. *Lancet Neurol*. 2016;15:934-943.
- Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA*. 1997;277:813-817.
- Vemuri P, Lesnick TG, Przybelski SA, et al. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. *Brain*. 2015;138:761-771.
- Benedictus MR, Prins ND, Goos JD, Scheltens P, Barkhof F, van der Flier WM. Microbleeds, mortality, and stroke in Alzheimer disease: the MISTRAL Study. *JAMA Neurol*. 2015;72:539-545.
- Henneman WJ, Sluimer JD, Cordonnier C, et al. MRI biomarkers of vascular damage and atrophy predicting mortality in a memory clinic population. *Stroke*. 2009;40:492-498.
- Bos I, Verhey FR, Ramakers I, et al. Cerebrovascular and amyloid pathology in predementia stages: the relationship with neurodegeneration and cognitive decline. *Alzheimers Res Ther*. 2017;9:101.
- Saridin FN, Hilal S, Villaraza SG, et al. Brain amyloid β , cerebral small vessel disease, and cognition. *Memory Clinic Study*. 2020;95:e2845-e2853.
- Lee MJ, Seo SW, Na DL, et al. Synergistic effects of ischemia and β -amyloid burden on cognitive decline in patients with subcortical vascular mild cognitive impairment. *JAMA Psychiatry*. 2014;71:412-422.
- Park JH, Seo SW, Kim C, et al. Effects of cerebrovascular disease and amyloid beta burden on cognition in subjects with subcortical vascular cognitive impairment. *Neurobiol Aging*. 2014;35:254-260.
- Ye BS, Seo SW, Kim JH, et al. Effects of amyloid and vascular markers on cognitive decline in subcortical vascular dementia. *Neurology*. 2015;85:1687-1693.
- Lopez OL, Becker JT, Chang Y, et al. Amyloid deposition and brain structure as long-term predictors of MCI, dementia, and mortality. *Neurology*. 2018;90:e1920-e1928.
- Lopez OL, Klunk WE, Mathis C, et al. Amyloid, neurodegeneration, and small vessel disease as predictors of dementia in the oldest-old. *Neurology*. 2014;83:1804-1811.
- Ottoy J, Ozzoude M, Zukotynski K, et al. Vascular burden and cognition: mediating roles of neurodegeneration and amyloid PET. *Alzheimer Dementia*. 2023;19:1503-1517.
- van der Flier WM, Pijnenburg YA, Prins N, et al. Optimizing patient care and research: the Amsterdam Dementia Cohort. *J Alzheimers Dis*. 2014;41:313-327.
- van der Flier WM, Scheltens P. Amsterdam dementia cohort: performing research to optimize care. *J Alzheimers Dis*. 2018;62:1091-1111.
- Konijnenberg E, Carter SF, ten Kate M, et al. The EMIF-AD PreclinAD study: study design and baseline cohort overview. *Alzheimer Res Ther*. 2018;10:75.
- Legdeur N, Badissi M, Carter SF, et al. Resilience to cognitive impairment in the oldest-old: design of the EMIF-AD 90+ study. *BMC Geriatrics*. 2018;18:289.
- Slot RER, Verfaillie SCJ, Overbeek JM, et al. Subjective Cognitive Impairment Cohort (SCIENCe): study design and first results. *Alzheimers Res Ther*. 2018;10:76.
- Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). *Neurology*. 2001;56:1133-1142.

37. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:270-279.
38. Boomsma DI, de Geus EJ, Vink JM, et al. Netherlands Twin Register: from twins to twin families. *Twin Res Hum Genet*. 2006;9:849-857.
39. Holstege H, Beker N, Dijkstra T, et al. The 100-plus Study of cognitively healthy centenarians: rationale, design and cohort description. *Eur J Epidemiol*. 2018;33:1229-1249.
40. Konijnenberg E, den Braber A, Ten Kate M, et al. Association of amyloid pathology with memory performance and cognitive complaints in cognitively normal older adults: a monozygotic twin study. *Neurobiol Aging*. 2019;77:58-65.
41. Teunissen CE, Tumani H, Engelborghs S, Mollenhauer B. Biobanking of CSF: international standardization to optimize biomarker development. *Clin Biochem*. 2014;47:288-292.
42. Duits FH, Prins ND, Lemstra AW, et al. Diagnostic impact of CSF biomarkers for Alzheimer's disease in a tertiary memory clinic. *Alzheimers Dement*. 2015;11:523-532.
43. Willemse EAJ, van Maurik IS, Tijms BM, et al. Diagnostic performance of Elecsys immunoassays for cerebrospinal fluid Alzheimer's disease biomarkers in a nonacademic, multicenter memory clinic cohort: the ABIDE project. *Alzheimers Dement (Amst)*. 2018;10:563-572.
44. Tijms BM, Willemse EAJ, Zwan MD, et al. Unbiased approach to counteract upward drift in cerebrospinal fluid amyloid- β 1-42 analysis results. *Clin Chem*. 2018;64:576-585.
45. Konijnenberg E, Tomassen J, den Braber A, et al. Onset of preclinical Alzheimer disease in monozygotic twins. *Ann Neurol*. 2021;89:987-1000.
46. De Vos A, Jacobs D, Struyfs H, et al. C-terminal neurogranin is increased in cerebrospinal fluid but unchanged in plasma in Alzheimer's disease. *Alzheimer's & Dementia*. 2015;11:1461-1469.
47. Tomassen J, den Braber A, van der Landen SM, et al. Abnormal cerebrospinal fluid levels of amyloid and tau are associated with cognitive decline over time in cognitively normal older adults: a monozygotic twin study. *Alzheimers Dement*. 2022;8:e12346.
48. Zwan MD, Ossenkoppele R, Tolboom N, et al. Comparison of simplified parametric methods for visual interpretation of 11C-Pittsburgh compound-B PET images. *J Nucl Med*. 2014;55:1305-1307.
49. Collij LE, Salvadó G, Shekari M, et al. Visual assessment of [(18)F]flutemetamol PET images can detect early amyloid pathology and grade its extent. *Eur J Nucl Med Mol Imaging*. 2021;48:2169-2182.
50. Timmers T, Ossenkoppele R, Verfaillie SCJ, et al. Amyloid PET and cognitive decline in cognitively normal individuals: the SCIENCe project. *Neurobiol Aging*. 2019;79:50-58.
51. Legdeur N, Badissi M, Yaqub M, et al. What determines cognitive functioning in the oldest-old? The EMIF-AD 90+ Study. *J Gerontol Series B*. 2020;76:1499-1511.
52. Kester MI, Goos JDC, Teunissen CE, et al. Associations between cerebral small-vessel disease and Alzheimer disease pathology as measured by cerebrospinal fluid biomarkers. *JAMA Neurol*. 2014;71:855-862.
53. Rhodius-Meester HFM, Benedictus MR, Wattjes MP, et al. MRI visual ratings of brain atrophy and white matter hyperintensities across the spectrum of cognitive decline are differently affected by age and diagnosis. *Front Aging Neurosci*. 2017;9:117.
54. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987;149:351-356.
55. Staals J, Booth T, Morris Z, et al. Total MRI load of cerebral small vessel disease and cognitive ability in older people. *Neurobiol Aging*. 2015;36:2806-2811.
56. Duering M, Biessels GJ, Brodtmann A, et al. Neuroimaging standards for research into small vessel disease – advances since 2013. *Lancet Neurol*. 2023;22:602-618.
57. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
58. Rey A. L'examen clinique en psychologie. [The clinical examination in psychology]. Presses Universitaires De France. 1958.
59. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Arch Clin Neuropsychol*. 1999;14:167-177.
60. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8:271-276.
61. Hansson O, Batrla R, Brix B, et al. The Alzheimer's Association international guidelines for handling of cerebrospinal fluid for routine clinical measurements of amyloid β and tau. *Alzheimer Dementia*. 2021;17:1575-1582.
62. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Statist Assoc*. 1999;94:496-509.
63. Del Brutto VJ, Mera R, Recalde BY, Rumbea DA, Costa AF, Del Brutto OH. Total cerebral small vessel disease score and all-cause mortality in older adults of Amerindian ancestry: the Atahualpa Project. *Eur Stroke J*. 2021;6:412-419.
64. Gyanwali B, Lui B, Tan CS, et al. Cerebral microbleeds and white matter hyperintensities are associated with cognitive decline in an Asian Memory Clinic Study. *Curr Alzheimer Res*. 2021;18:399-413.
65. Liu Y, Braidly N, Poljak A, Chan DKY, Sachdev P. Cerebral small vessel disease and the risk of Alzheimer's disease: a systematic review. *Ageing Res Rev*. 2018;47:41-48.
66. Staekenborg SS, Koedam EL, Henneman WJ, et al. Progression of mild cognitive impairment to dementia: contribution of cerebrovascular disease compared with medial temporal lobe atrophy. *Stroke*. 2009;40:1269-1274.
67. Emrani S, Lamar M, Price CC, et al. Alzheimer's/vascular spectrum dementia: classification in addition to diagnosis. *J Alzheimers Dis*. 2020;73:63-71.
68. Wolters FJ, Ikram MA. Epidemiology of vascular dementia. *Arterioscler Thromb Vasc Biol*. 2019;39:1542-1549.
69. James BD, Bennett DA, Boyle PA, Leurgans S, Schneider JA. Dementia from Alzheimer disease and mixed pathologies in the oldest old. *JAMA*. 2012;307:1798-1800.
70. Bannai T, Mano T, Chen X, et al. Chronic cerebral hypoperfusion shifts the equilibrium of amyloid β oligomers to aggregation-prone species with higher molecular weight. *Sci Rep*. 2019;9:2827.
71. ElAli A, Thériault P, Préfontaine P, Rivest S. Mild chronic cerebral hypoperfusion induces neurovascular dysfunction, triggering peripheral beta-amyloid brain entry and aggregation. *Acta Neuropathologica Communications*. 2013;1:75.
72. Cortes-Canteli M, Iadecola C. Alzheimer's disease and vascular aging. *J Am Coll Cardiol*. 2020;75:942-951.
73. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol*. 2022;21:714-725.
74. Lu H, Kashani AH, Arfanakis K, et al. MarkVCID cerebral small vessel consortium: II. Neuroimaging protocols. *Alzheimers Dement*. 2021;17:716-725.
75. Coenen M, Kuijff HJ, Huenges Wajer IMC, et al. Strategic white matter hyperintensity locations for cognitive impairment: a multicenter lesion-symptom mapping study in 3525 memory clinic patients. *Alzheimers Dement*. 2023;19:2420-2432.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Moonen JEF, Haan R, Bos I, et al. Contributions of amyloid beta and cerebral small vessel disease in clinical decline. *Alzheimer's Dement*. 2024;20:1868–1880. <https://doi.org/10.1002/alz.13607>