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RESEARCH ARTICLE

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

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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 (Aβ) 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 Aβ nor SVD (A−V−), 21% had SVD only (A−V+), 23% Aβ 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 Aβ was predictive of cognitive decline, dementia, and mortality. SVD modestly predicts dementia in A−, but did not increase deleterious effects in A+.

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

Highlights

- Amyloid beta (Aβ; 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−.
- Aβ should be assessed even when magnetic resonance imaging indicates vascular cognitive impairment.

1 | BACKGROUND

Cerebral small vessel disease (SVD) and amyloid beta (Aβ) co-exist in up to 47% of dementia cases.[1,2] Aβ 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 Aβ 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 Aβ 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 Aβ-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 Aβ 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 substudy 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 Aβ 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) project[35] 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 Aβ and optional Aβ 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 | Aβ

2.2.1 | CSF

CSF was obtained by lumbar puncture in ADC and EMIF-Twins-60+.[40,41] In ADC Aβ1-42 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 Aβ1-42 according to < 813 pg/mL (drift-corrected;[44] Innotest) or < 1000 pg/mL (Elecsys). In EMIF-Twins-60+ levels of Aβ1-42 and Aβ1-40 in CSF were measured using ADx Neurosciences/Euroimmun[45,46] and were considered positive according to a ratio of Aβ1-42/1-40 < 0.066.[47]

2.2.2 | PET

Aβ PET scans were acquired on Philips Gemini TF PET-CT, Philips Ingenuity TF PET-CT, and Philips Ingenuity PET-MRI. In ADC[5] the Aβ tracers [^{18}F]Florbetapir, [^{18}F] Florbetaben, [^{18}F]Flutemetamol, or [^{11}C] Pittsburgh compound B (PiB) were used and in EMIF-Twins-60+[33] and EMIF-AD 90+[34] [^{18}F]Flutemetamol. Trained and experienced nuclear medicine physicians visually rated the scans as negative or positive for Aβ plaques in line with the company product guidelines of each tracer and for [^{11}C] PiB according to previously published methods.[48] The readers looked for an AD-like pattern of Aβ plaque positivity and also correlated the read with available MRIs. The used visual classification has demonstrated to be capable of detecting early Aβ 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 ≈ 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 | Aβ status

Aβ positivity (A+) was based on dichotomized level in CSF (available in $n = 1005$, 36% A+) or presence of Aβ 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 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

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed literature on the predictive value of amyloid beta (Aβ; 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 Aβ (A−V+). Aβ (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.

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) criteria[56] 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^{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 NTR[38] 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 Aβ (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* Aβ and SVD features on cognitive decline or risk of dementia or mortality, we simultaneously entered standardized Aβ 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 Aβ in CSF is indicative of *less* brain Aβ.[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*) ε4 ($P < 0.001$), level of CSF Aβ ($P < 0.001$), and phosphorylated tau (p-tau; $P < 0.001$) differed among the AV groups, with A+ groups showing a higher *APOE* ε4 prevalence, lower CSF Aβ levels (indicative of higher cerebral Aβ 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* ε4 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 Aβ, 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 ε4 positive, *n*, %	488 of 1060	46.0%
Aβ 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%
Aβ (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; Aβ, 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).

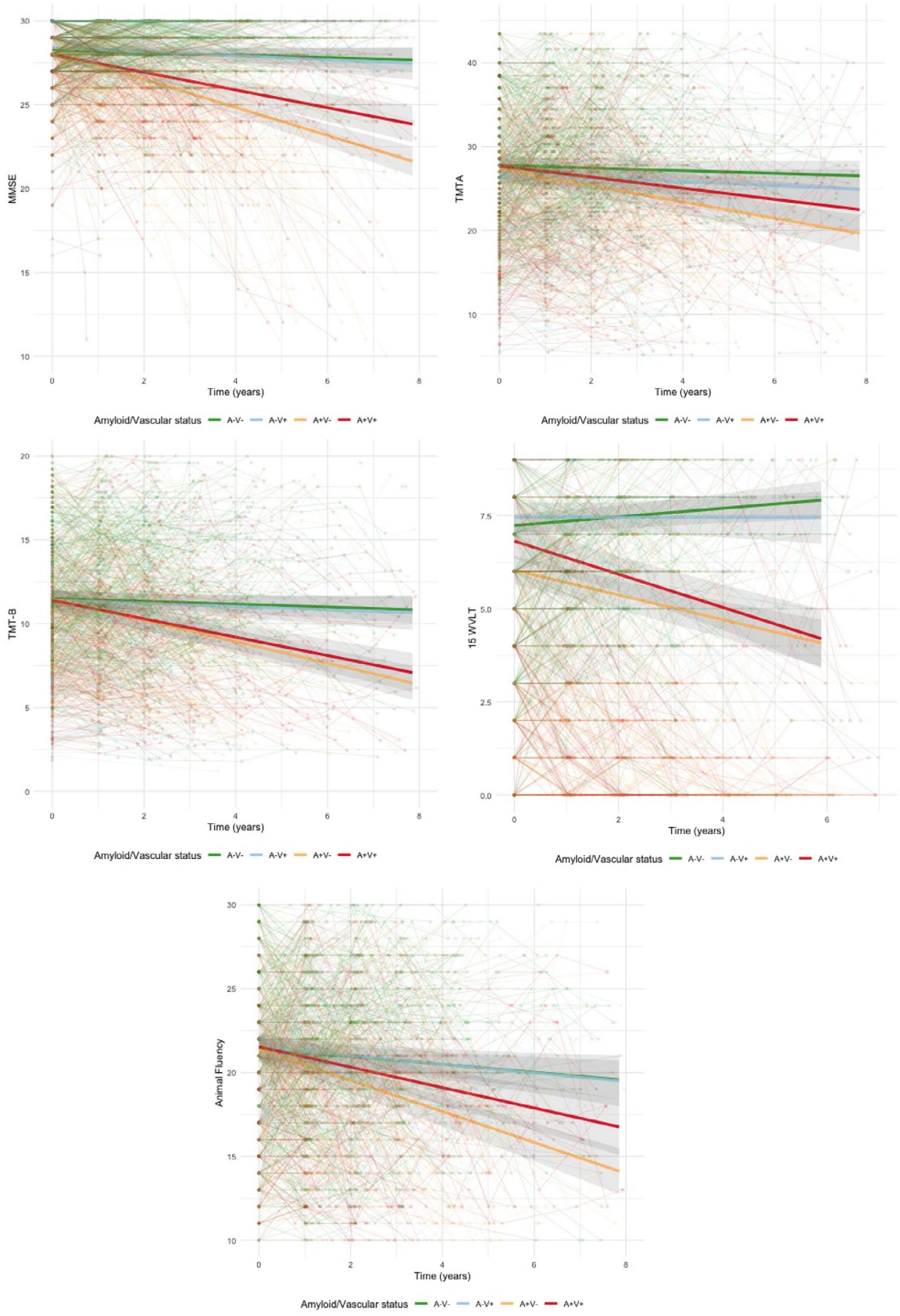


FIGURE 1 Trajectories of neuropsychological test scores over time per AV group. 15WVLT, 15 word verbal learning test (the Rey Auditory Verbal Learning Test); A, amyloid beta status; MMSE, Mini-Mental State Examination; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; V, vascular status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

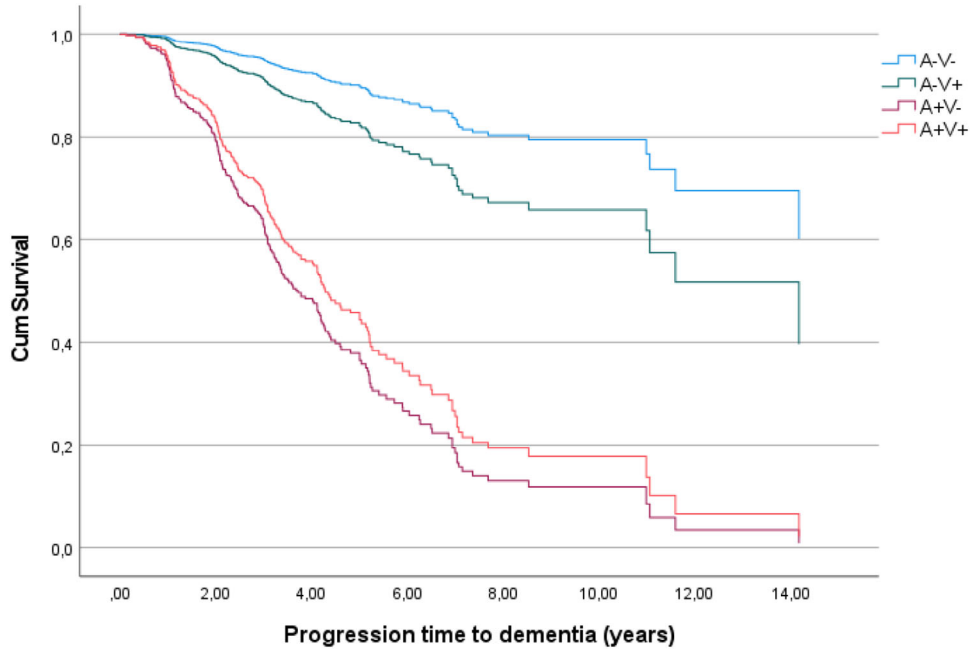
3.2 | Risk of dementia and mortality

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).



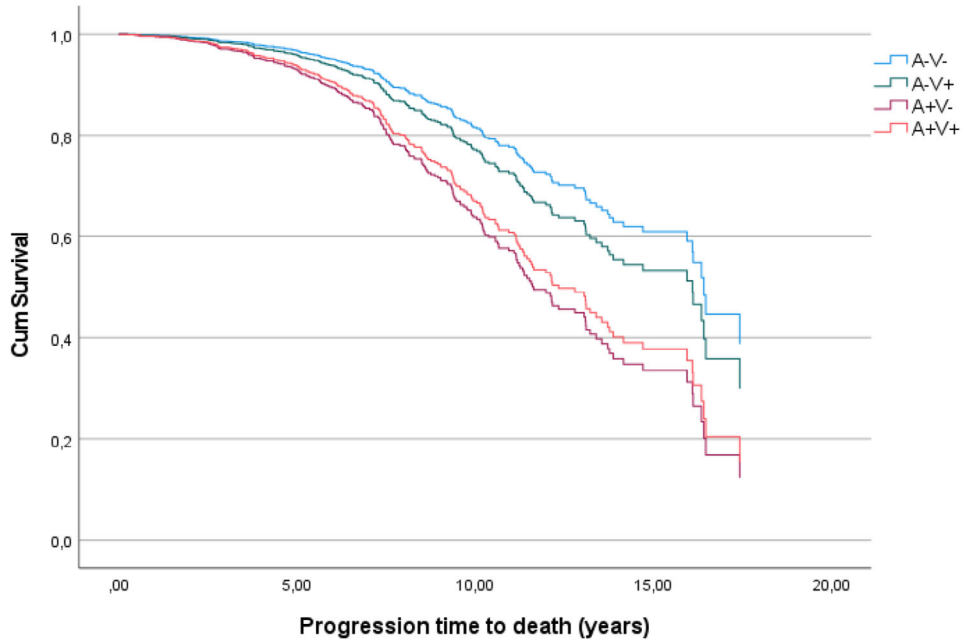


FIGURE 2 AV group and progression to dementia or mortality. A, amyloid beta status; V, vascular status (small vessel disease status).

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 Aβ 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 Aβ. 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 Aβ do reach significance. A higher concentration of CSF Aβ (indicative of *less* Aβ brain pathology[61]) predicted less decline in MMSE (random effects meta-analyses estimate for Aβ [95% CI] 0.22 [0.09 to 0.35]), whereas SVD did not (see Figure S1 in supporting information). Similarly, higher level of Aβ, but not SVD load, predicted less decline in TMT-A, TMT-B, and the RAVLT. Only animal fluency was next to Aβ level also predicted by the modified SVD score (estimate [95% CI] 0.10 [0.01 to 0.20]). A higher CSF level of Aβ 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 x time x 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 x 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 Aβ 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 Aβ (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 Aβ 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 Aβ (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 Aβ-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 Aβ 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 Aβ, 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 Aβ, in accordance with the ATN (amyloid/tau/neurodegeneration) framework.

Previous longitudinal studies that did not account for presence of Aβ have suggested that features of SVD are associated with cognitive decline in various domains[64] 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 (Aβ 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 Aβ 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 Aβ 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 Aβ 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 Aβ monomers into toxic soluble Aβ oligomers and insoluble Aβ plaques.[71,72] Vice versa, deposition of Aβ into the walls of small cerebral vessels, that is, cerebral amyloid angiopathy (CAA), may induce adverse vascular changes.[72] The modified Boston criteria[73] 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 Aβ 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 Aβ status. Future studies should adhere to the recently updated STRIVE-2[56] 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 location 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. Aβ 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 Aβ in clinical practice, even when MRI findings indicate a diagnosis of vascular cognitive impairment.

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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.

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SUPPORTING INFORMATION

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

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