Received: 27 March 2023 | Accepted: 25 September 2023

DOI: 10.1002/gps.6015

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Comorbid cerebral amyloid angiopathy in dementia and prodromal stages—Prevalence and effects on cognition

Robert Haussmann[1] | Patricia Homeyer[1] | Cathrin Sauer[1] | Arne Grey[2] | Pawel Krukowski[2] | Moritz D. Brandt[3,4] | Markus Donix[1,4] | Jennifer Linn[2]

[1]Department of Psychiatry, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[2]Department of Neuroradiology, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[3]Department of Neurology, University Hospital Carl Gustac Carus, Technische Universität Dresden, Dresden, Germany

[4]German Center for Neurodegenerative Diseases (DZNE), Dresden, Germany

Correspondence
Robert Haussmann.
Email: robert.haussmann@ukdd.de

Abstract

Objectives: To determine the contribution of cerebral amyloid angiopathy to cognitive impairment in MCI and dementia.

Methods: Patients with subjective memory impairment (SMI), amnestic and non-amnestic mild cognitive impairment ((n)aMCI), Alzheimer's disease (AD), mixed and vascular dementia (MD/VD) from our memory clinic were included in this retrospective analysis. Patients underwent neuropsychological testing and cranial magnetic resonance imaging (MRI). Magnetic resonance imaging data sets were analyzed regarding the presence of CAA-related MRI biomarkers to determine CAA prevalence. ANOVAs were used to investigate the contribution of CAA to cognitive impairment within diagnostic groups and to determine whether differences in cognitive test performance between the diagnostic groups are mediated by total CAA burden.

Results: 475 patients (222 male, 253 female) with SMI (n = 47), naMCI (n = 41), aMCI (n = 189), early AD (n = 9), AD (n = 114), MD (n = 71) and VD (n = 4) were included. Mean age was 73.2 (9.9) years. CAA prevalence was 14.9% in SMI, 14.6% in naMCI, 24.3% in aMCI, 22.2% in early onset AD, 18.4% in late onset AD, 46.5% in MD and 25% in VD. Patients with possible and probable CAA were older than patients without CAA. In particular, diagnosis of aMCI, early onset AD, MD and VD showed high CAA prevalence. In AD but not in aMCI, CAA diagnosis significantly influenced test performance in the CERAD word list recall (F (1,78) = 4505; p = 0.037; partial eta-square = 0.055). Differences in cognitive test performance between the diagnostic groups of naMCI, aMCI, AD and MD were mediated by total CAA burden within AAT simply nouns subtest (F (2,39) = 4059; p = 0.025; partial eta-square = 0.172) and in CERAD verbal fluency test (F (3,129) = 3533; p = 0.017; partial eta-square = 0.076).

Abbreviations: aMCI, amnestic mild cognitive impairment; AAT, Aachen Aphasia test; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MCI, mild cognitive impairment; MD, mixed dementia; NAI, Nuremberg age inventory; naMCI, non amnestic mild cognitive impairment; SMI, subjective memory impairment; TMT, trail making test; VD, vascular dementia; WMH, white matter hyperintensities; WMS, Wechsler Memory Scale.

Conclusion: This retrospective analysis demonstrates high prevalence rates of CAA in cognitive diagnoses. Our data suggest that comorbid CAA independently impacts cognitive test performance in the course of AD with presumably stage-dependent effects. Especially in patients with AD comorbid CAA additionally impairs memory function. Total CAA small vessel disease burden further modulates psychometric differences in cognitive test performance between diagnostic groups regarding word finding and word fluency capabilities.

KEYWORDS
Alzheimer's disease, cerebral amyoid agiopathy, cognition, mild cognitive impairment, mixed dementia

Key points

- In AD, MD and VD coincident CAA is a frequent phenomenon
- Comorbid CAA independently impacts cognitive test performance in the course of Alzheimer's disease (AD)
- In patients with AD comorbid CAA additionally impairs memory function
- Total CAA small vessel disease burden further modulates psychometric differences between MCI, AD and MD

1 | INTRODUCTION

CAA, a highly prevalent cerebrovascular disease in older age, is characterized by β-amyloid deposit in the wall of cerebral vessels.[1,2] In the elderly population CAA is a common cause of intracerebral bleeding and cognitive dysfunction.[3] In accordance with AD, incidence of CAA increases with age.[2] In patients with dementia up to 60% suffer from comorbid CAA and in AD histopathological evidence of CAA is found in more than 80% of patients.[4,5] Previous studies have shown variable CAA prevalence rates due to methodical reasons. Therefore, one aim of the study was to investigate the prevalence of CAA-related magnetic resonance imaging (MRI) biomarkers across different diagnostic groups in a memory clinic sample.

Despite a distinct pathophysiology CAA and AD show strong associations and complex interactions. With a histopathological prevalence of almost 80% in AD, CAA is a common comorbidity which is also related to AD pathology and severity of clinical dementia syndrome.[6,7] CAA-related small vessel disease burden was shown to be an independent predictor for dementia conversion.[8] Independently from non-CAA-related cerebral small vessel disease, CAA in AD seems to contribute to an accelerated global cognitive decline and deficits in perceptual speed, episodic and semantic memory.[6] After controlling for parenchymal amyloid and general vascular pathology on a histopathological level moderate-to-severe CAA seems to be associated with lower perceptual speed and episodic memory, but not with deficits in semantic memory, working memory nor visuospatial skills.[7] Other investigations show independent effects of CAA on memory, executive functioning and perceptual speed, whereas about half of these cognitive CAA effects seem to be mediated by white matter disruption.[9] However, study data investigating the influence of CAA on the clinical phenotype and the rate of cognitive decline in AD are inconsistent[10] so that the contribution of CAA to cognitive decline in AD is incompletely understood.

Although pathophysiology of CAA and AD are fundamentally distinct both diagnostic entities share the central pathophysiological role of deregulated β-amyloid production and clearance[11] which leads to accelerated neurodegeneration and a more severe cognitive impairment in AD patients with comorbid CAA.[12–14] But beside the effects on cognition mediated by vasculopathic lesions and accelerated AD pathology it is hypothesized that comorbid CAA in AD harbors autonomous effects on cognition which might be related to the predominating CAA subtype.[1,3,11,13,15,16] Especially, CAA-specific allocortical microinfarcts in the capillary subtype of CAA were shown to be associated with cognitive decline.[16] Thus, CAA-mediated cognitive deficits in AD seem to be partly independent from AD pathology[14,17–19] suggesting a rather multifactorial etiology of cognitive decline in AD with comorbid CAA. Early memory deficits mediated by CAA may be linked to early hippocampal pathology in the capillary CAA subtype[1,16] whereas the expansion of CAA pathology to subcortical structures and consecutive vascular pathology may subsequently result in perceptual slowing and executive dysfunction in the later course of the disease.[1]

We therefore hypothesize that comorbid CAA in dementia and prodromal stages modulates cognitive impairment in a stage-dependent manner and independently of non-CAA-related cerebral angiopathy. Therefore this study investigates differences in neuropsychological test performance in subjects with SMI,[20] naMCI and aMCI,[21,22] AD,[23] MD and VD[24] with or without MRI biomarkers of CAA and aims to determine the impact of comorbid CAA on cognitive

performance within these diagnostic categories and cognitive subscales controlling for age and non-CAA-related cerebral small vessel disease We further hypothesize that, due to the complex interplay of CAA and AD on cognitive impairment, psychometric group differences between MCI, AD and MD are mediated by CAA-associated small vessel disease burden. Therefore, we investigate whether CAA-related small vessel disease burden measured by Total-MRI score[25] modulates differences in cognitive test performance between diagnostic groups.

2 | MATERIALS & METHODS

2.1 | Participants

In this retrospective data analysis we analyzed patients from our memory clinic who underwent first diagnostic approach for suspected cognitive decline including neuropsychological testing and cranial MRI including a standard protocol.[26] We included all patients who underwent neurocognitive evaluation between February 2016 and December 2020 with the diagnosis of SMI,[20] naMCI, aMCI,[21,22] AD,[23] MD and VD.[24]

2.2 | MRI re-evaluation, CAA diagnosis & scoring

Magnetic resonance imaging data sets were analyzed by an experienced neuroradiologist regarding the presence and extent of the following MRI biomarkers of CAA: lobar intracerebral macrohemorrhages (ICH), cortical/subcortical cerebral microbleeds (CMB), cortical superficial siderosis (cSS), cortical microinfarcts, severe (>20) perivascular spaces in the centrum semiovale, and white matter hyperintensities (WMH) of presumed vascular origin. In addition, prevalence of deep ICH and deep CMB was also noted. Lobar ICH, deep ICH and cerebral microinfarcts were categorized as absent (0) or present (1 or more). CMBs were categorized according to their numbers (0, 1, 2–4, 5–10.10–50, >50), cSS was categorized as absent, focal or disseminated. To assess the severity of WMH Fazekas score was used.[27] Diagnosis of possible and probable CAA was made according to the modified Boston criteria.[28–30] With regard to the presence of deep CMB, a maximum of two deep CMB was allowed if the respective patients had at least twice the number of lobar CMB and/or a history of lobar ICH or cSS. To capture total brain burden of small vessel disease in CAA Total-MRI-score was applied.[25]

2.3 | Neuropsychological testing

In the psychometric tests, we investigated intelligence (Horn's LPS reasoning test (the German Leistungs-Prüf-System; LPS),[31] Multiple Choice Word Test-B (MWT-B)),[32] memory (Consortium to Establish a Registry for AD (CERAD) word list recall, Wechsler Memory Scale (WMS), Nuremberg Age-Inventory (NAI)), verbal fluency (CERAD verbal fluency test), speech (Aachen aphasia test; AAT) and executive function/attention (trail making test, TMT). For the interpretation of test results we used age-corrected z-scores in most of the subtests. In the subtests of the WMS and in the repeating numbers subtest of the NAI we used percentile ranks. Within the color word and the labyrinth subtest of the NAI C-scores were obtained.

2.4 | Statistical analysis

Demographic and clinical characteristics of the participants are reported as means and SDs for continuous variables and percentages for categorical variables. Depending on data level analysis, we conducted *t*-tests, chi-square tests or univariate analysis of variance (ANOVA) for the identification of covariates. In multiple comparisons, *p* values were adjusted according to Bonferroni. To investigate the stage-dependent and independent contribution of CAA to cognitive impairment within cognitive subscales and diagnostic groups we used an ANOVA model (ANOVA) categorizing diagnosis of CAA (none vs. possible and probable) as an independent variable and the cognitive measure in each cognitive subtest and diagnostic entity as a dependent variable. Age and Fazekas score were used as covariates. To examine whether differences in cognitive test performance between the diagnostic groups are mediated by CAA-associated small vessel disease burden we used an ANOVA model (ANOVA) using cognitive measure as an independent variable, diagnostic entity as a factor and Total-MRI score, Fazekas score and age as covariates. Statistical computations were conducted using IBM SPSS statistics for Windows, version 25.

3 | RESULTS

475 patients (222 male, 253 female) were included in this retrospective analysis. 47 patients were diagnosed with SMI, 41 with naMCI, 189 with aMCI, 9 with early onset AD, 114 with late onset AD, 71 with mixed dementia and 4 with VD. Mean age was 73.2 ± 9.9 years at time of presentation and diagnostic procedures in our memory clinic (Tables 1 and 2).

116 patients fulfilled the modified Boston diagnostic criteria for CAA (43 patients with possible and 73 patients with probable CAA) (Table 1). Patients with possible or probable CAA tended to be older than patients without CAA (Table 1). CAA prevalence in the different diagnostic groups was 14.9% in SMI, 14.6% in naMCI, 24.3% in aMCI, 22.2% in early onset AD, 18.4% in late onset AD, 46.5% in MD and 25% in VD. Especially patients with aMCI, early onset AD, MD and VD exhibited high CAA prevalences (Table 3).

After controlling for age and Fazekas-score CAA diagnosis influenced cognitive test performance in short term and working memory within the aMCI group. There was a significant effect of CAA diagnosis on the WMS digit span forward (F (1.93) = 9.334; $p = 0.003$; partial eta-square = 0.091) and backward (F (1.93) = 6.303;

TABLE 1 Descriptive statistics including age, sex, diagnosis and CAA prevalence.

		CAA						
	All	No	Possible	Probable	*p*	poss + prob	*p*	
Age means (SD)	*n* = 475	*n* = 359	*n* = 43	*n* = 73		*n* = 116		ANOVA/*t* test
	73.2 (9.9)	71.8 (10.5)	76.7 (5.6)	77.5 (6.6)	<0.001	77.2 (6.2)	<0.001	
Sex (m)	*n* = 475	*n* = 359	*n* = 43	*n* = 73		*n* = 116		Chi-square test
	222 (46.7%)	159 (44.3%)	25 (58.1%)	38 (52.1%)	0.140	63 (54.3%)	0.060	
Diagnosis	*n* = 475	*n* = 359	*n* = 43	*n* = 73		*n* = 116		Chi-square test
SMI	47 (9.9%)	40 (11.1%)	5 (11.6%)	2 (2.7%)		7 (6.0%)		
aMCI	189 (39.8%)	143 (39.8%)	23 (53.5%)	23 (31.5%)		46 (39.7%)		
naMCI	41 (8.6%)	35 (9.7%)	2 (4.7%)	4 (5.5%)		6 (5.2%)		
Early onset AD	9 (1.9%)	7 (1.9%)	0 (0%)	2 (2.7%)		2 (1.7%)		
Late onset AD	114 (24.0%)	93 (25.9%)	5 (11.6%)	16 (21.9%)		21 (18.1%)		
MD	71 (14.9%)	38 (10.6%)	8 (18.6%)	25 (34.2%)		33 (28.4%)		
VD	4 (0.8%)	3 (0.8%)	0 (0%)	1 (1.4%)	<0.001	1 (0.9%)	<0.001	

TABLE 2 Age distribution within diagnostic groups in means (SD).

		CAA			
Diagnosis	Total (*n* = 475)	No (*n* = 359)	Possible (*n* = 43)	Probable (*n* = 73)	Possible + probable (*n* = 116)
SMI (*n* = 47)	69.4 (10.0)	68.5 (10.1)	76.6 (5.8)	68.0 (11.3)	74.1 (7.8)
	n = 47	*n* = 40	*n* = 5	*n* = 2	*n* = 7
aMCI (*n* = 189)	70.4 (10.4)	68.8 (11.0)	75.3 (4.6)	75.9 (7.2)	75.6 (6.0)
	n = 189	*n* = 143	*n* = 23	*n* = 23	*n* = 46
naMCI (n = 41)	68.5 (11.4)	66.8 (11.4)	81.0 (1.4)	77.5 (2.4)	78.7 (2.7)
	n = 41	*n* = 35	*n* = 2	*n* = 4	*n* = 6
Early onset AD (*n* = 9)	59.2 (6.0)	57.6 (5.8)	-	65.0 (0.0)	65.0 (0.0)
	n = 9	*n* = 7	*n* = 0	*n* = 2	*n* = 2
Late onset AD (*n* = 114)	77.6 (5.2)	77.6 (5.2)	75.4 (7.1)	78.6 (4.5)	77.8 (5.2)
	n = 114	*n* = 93	*n* = 5	*n* = 16	*n* = 21
MD (*n* = 71)	80.1 (5.3)	80.1 (4.9)	80.4 (6.4)	80.0 (5.8)	80.1 (5.8)
	n = 71	*n* = 38	*n* = 8	*n* = 25	*n* = 33
VD (*n* = 4)	72.0 (8.4)	69.7 (8.6)	-	79.0 (-)	79.0 (-)
	n = 4	*n* = 3	-	*n* = 1	*n* = 1

p = 0.014; partial eta-square = 0.063) subtests with better test results in the CAA group. In addition, we found a trend in the NAI color word test (*F* (1.159) = 3.394; *p* = 0.067; partial eta-square = 0.021) within aMCI group. In AD with comorbid CAA we detected poorer memory functioning with significant effects of CAA on test performance in CERAD word list recall (*F* (1.78) = 4.505; *p* = 0.037; partial eta-square = 0.055). In the naMCI group there was a trend within memory function in CERAD word list recall (*F* (1.34) = 3.188; *p* = 0.083; partial eta-square 0.086). In MD we found a trend regarding CAA-mediated effects on speech within CERAD Boston naming test (*F* 1.44) = 3.389; *p* = 0.072; partial eta-square = 0.072) (Table 4).

Differences in cognitive test performance between the different diagnostic groups of aMCI, naMCI, AD and MD were mediated by total CAA-related small vessel disease burden regarding speech and word fluency. Total-MRI score mediated psychometric group differences in the AAT simply nouns subtest (*F* (2.39) = 4.059; *p* = 0.025; partial eta-square = 0.172) and the CERAD verbal fluency s-words subtest (*F* (3.129) = 3.544; *p* = 0.017; partial eta-square = 0.076) (Table 5).

Magnetic resonance imaging findings are summarized in Table 6.

TABLE 3 CAA prevalence within diagnostic groups.

	CAA					
Diagnosis	No (n = 359)	Possible (n = 43)	Probable (n = 73)	Possible + probable (n = 116)		
SMI (n = 47)	40 (85.1%)	5 (10.6%)	2 (4.3%)	7 (14.9%)		
aMCI (n = 189)	143 (75.7%)	23 (12.2%)	23 (12.2%)	46 (24.3%)		
naMCI (n = 41)	35 (85.4%)	2 (4.9%)	4 (9.8%)	6 (14.6%)	Chi-square test	p (Bonferroni-corr.)
Early onset AD (n = 9)	7 (77.8%)	0 (0.0%)	2 (22.2%)	2 (22.2%)	No versus possible + probable	0.001
Late onset AD (n = 114)	93 (81.6%)	5 (4.4%)	16 (14.0%)	21 (18.4%)	No versus possible	0.459
MD (n = 71)	38 (53.5%)	8 (11.3%)	25 (35.2%)	33 (46.5%)	No versus probable	<0.001
VD (n = 4)	3 (75.0%)	0 (0.0%)	1 (25.0%)	1 (25.0%)		

4 | CONCLUSION

Our data show high prevalences of possible and probable CAA especially in patients with aMCI, early onset AD, MD and VD. Controlling for age and non-CAA-related cerebral small vessel disease the conducted analyses suggest that comorbid CAA in AD and its prodromal stages significantly impacts cognitive test performance in the course of AD in a stage-dependent manner. In patients with aMCI short term and working memory were conterintuitively influenced by comorbid CAA in terms of better test performances in patients with CAA compared to the no CAA group. Beyond, there was a trend regarding the influence of CAA on executive functioning and perceptual speed in aMCI patients. In patients with AD comorbid CAA mediated poorer memory functioning. Further trends were demonstrated regarding the impact of comorbid CAA on memory function in naMCI patients and speech in patients with MD. Total burden of CAA-related small vessel disease contributed to psychometric differences between diagnostic groups with regard to speech and verbal fluency.

Our results indicate that accompanying CAA in AD and its prodromal stages is a frequent phenomenon, which requires consideration within general medical treatment of elderly patients with dementia and cognitive decline. Furthermore, management of CAA in patients with cognitive impairment, for example, in terms of optimal blood pressure control, might also be of functional relevance since cognitive performance is additionally influenced by CAA.

CAA prevalence is highly age dependent[2] which was also demonstrated in our data set (Table 1). In an autopsy study by Boyle et al. prevalence of moderate-to-severe CAA was 36% in patients with a mean age of 89.7 years[33] According to population-based studies CAA prevalence is consistently higher in patients with dementia compared to non-demented individuals (55%–59% vs. 28%–38%).[4] Especially in AD up to 80% of patients show histopathologic evidence of CAA.[5] Current metaanalytic data analyzing the prevalence of CAA in AD demonstrate a histopathologically-based prevalence of 48%,[34] but estimates of CAA prevalence vary widely. In this respect, Jäkel et al. referred to an enormous heterogeneity among neuropathology and MRI protocols in CAA recognition.[34] Since CAA is linked to side-effects in upcoming immunotherapies in AD this aspect calls for standardized assessment and reporting of CAA.[34] Taking the lower diagnostic sensitivity of cerebral imaging compared to histopathological approach into account, CAA prevalence estimates in our cohort seem to be widely in line with current data. But regarding CAA prevalence estimates of 2%–3% between the ages of 65 and 74 years[2] the relatively high CAA prevalence in our subjective memory impairment (SMI) group (mean age 69.4 (10.0) years; prevalence possible + probable CAA: 14.9%) is suggestive of a high rate of underlying neurodenerative SMI etiology in our memory clinic cohort.[35,36] The relatively high CAA prevalence in individuals with aMCI (mean age 70.4 (10.4) of 24.3% and early onset AD (mean age 59.2 (6.0) years) of 22.2% (0% possible, 22.2% probable CAA) may be driven by the close relations between capillary cerebral amyloid angiopathy, the APOE epsilon 4 allele and early onset of AD.[37–39] Since vascular pathology with white matter disruption is known to account for about half of CAA-specific effects on cognition the high prevalence rates of CAA in MD and VD in our cohort are not surprising and seem to be attributable to overlapping pathomecanism.[9]

Regarding the objectified influence of comorbid CAA on cognitive test results in patients with aMCI our findings with better short and working memory test performance in aMCI patients with CAA compared to aMCI patients without CAA are rather counterintuitive with respect to current knowledge on CAA distribution in the brain.[1] Like AD, CAA involves different brain areas following a hierarchical sequence starting with a capillary pathology in leptomeningeal or parenchymal vessels or neocortical areas spreading to allocortical and, thus, hippocampal areas in a second step before involving basal ganglia, thalamus and brainstem.[1] Against this background, early disadvantageous effects of comorbid CAA on short term memory would have been expected. This surprising finding might be partly attributable to the heterogenous etiology of aMCI which might also be due to medication side effects, depression or other somatic factors instead of beginning neurodegenerative disease.[40] It might be possible that the aMCI cases within the no-CAA group were more frequently of neurodegenerative origin resulting in more prominent short and working memory deficits due to AD pathology overreaching and probably masking CAA-related cognitive effects.

TABLE 4 Analysis of cognitive performance within different diagnostic groups and cognitive measures divided into no CAA versus possible and probable CAA.

	aMCI						naMCI						AD						MD					
	n	No CAA mean (SD)	Poss + prob CAA mean (SD)		*p*	Partial eta-square	*n*	No CAA mean (SD)	Poss + prob CAA mean (SD)		*p*	Partial eta-square	*n*	No CAA mean (SD)	Poss + prob CAA mean (SD)		*p*	Partial eta-square	*n*	No CAA mean (SD)	Poss + prob CAA mean (SD)		*p*	Partial eta-square
CERAD word list learning (z-scores)	133/46	−1.0 (1.3)	−1.0 (1.1)	*F* (1.175) = 0.020	0887	0.000	33/5	−0.3 (0.8)	0.4 (1.7)	*F* (1.34) = 1805	0.188	0050	67/15	−2.3 (1.0)	−2.7 (1.3)	*F* (1.78) = 1712	0.195	0021	28/25	−2.5 (1.2)	−2.3 (1.5)	*F* (1.49) = 0.463	0500	0.009
CERAD word list recall (z-scores)	133/46	−1.3 (1.0)	−1.3 (0.9)	*F* (1.175) = 0.157	0692	0.001	**33/5**	**−0,4 (0.8)**	**0,4 (1,8)**	***F* (1.34) = 3188**	**0,083**	**0086**	**67/15**	**−2,3 (1.3)**	**−3,0 (0.7)**	***F* (1.78) = 4505**	**0,037**	**0055**	28/25	−2.4 (0.9)	−2.5 (1.1)	*F* (1.49) = 0.083	0775	0.002
CERAD word list recognition (z-scores)	133/46	−1.1 (1.3)	−0.8 (1.2)	*F* (1.175) = 1058	0.305	0006	33/5	−0.2 (1.0)	0.4 (0.9)	F (1,34) = 1142	0.293	0033	67/15	−2.0 (1.3)	−2.0 (1.4)	*F* (1.78) = 0.779	0380	0.010	29/25	−1.6 (1.3)	−1.7 (1.3)	*F* (1.50) = 0.060	0807	0.001
CERAD Boston naming (z-scores)	58/27	−0.8 (1.2)	−0.1 (1.2)	*F* (1.81) = 0.001	0975	0.000	11/4	0.1 (1.2)	−0.3 (1.4)	-	-	-	51/12	−0.9 (1.4)	−1.2 (1.1)	*F* (1.59) = 0.345	0559	0.006	**26/22**	**−1,4 (1.2)**	**−0,8 (1.2)**	***F* (1.44) = 3389**	**0.072**	**0072**
CERAD figures (z-scores)	56/27	−0.0 (1.1)	−0.1 (1.1)	*F* (1.79) = 0.109	0742	0.001	10/4	−0.9 (1.2)	−1.0 (1.0)	-	-	-	50/12	−0.5 (1.3)	−0.9 (1.7)	*F* (1.58) = 0.341	0562	0.006	26/22	−0.9 (1.5)	−1.0 (1.4)	*F* (1.44) = 0.010	0921	0.000
CERAD figures recall (z-scores)	56/27	−0.9 (1.2)	−0.6 (1.0)	*F* (1.79) = 0.684	0411	0.009	10/4	−0.2 (1.3)	−0.4 (1.0)	-	-	-	50/12	−1.9 (1.1)	−2.4 (0.9)	*F* (1.58) = 2329	0.132	0039	25/22	−2.2 (2.0)	−2.1 (0.8)	*F* (1.43) = 0.251	0619	0.006
WMS visual immediate (percentile ranks)	81/19	39.7 (31.9)	45.8 (31.0)	*F* (1.96) = 2694	0.104	0027	24/1	50.6 (31.2)	31.0 (–)	-	-	-	17/3	18.6 (19.2)	1.7 (2.1)	-	-	-	1/3	10.0 (–)	7.7 (6.7)	-	-	-
WMS visual delayded (percentile ranks)	81/19	35.0 (30.0)	32.7 (32.4)	*F* (1.96) = 0.981	0325	0.010	24/1	48.5 (30.6)	46.0 (–)	-	-	-	17/3	7.1 (11.9)	0.7 (1.2)	-	-	-	1/3	0.0 (–)	0.7 (1.2)	-	-	-
WMS digit span forward (percentile ranks)	**79/18**	**32,6 (27.6)**	**60,0 (28.4)**	***F* (1.93) = 9334**	**0,003**	**0091**	23/1	42.7 (32.2)	53.0 (–)	-	-	-	17/3	42.3 (32.6)	45.0 (26.9)	-	-	-	1/3	76.0 (–)	55.3 (41.5)	-	-	-
WMS digit span backward (percentile ranks)	**79/18**	**30,1 (22.5)**	**46,4 (32.7)**	***F* (1.93) = 6303**	**0,014**	**0063**	23/1	32.2 (27.6)	13.0 (–)	-	-	-	17/3	29.6 (23.4)	26.0 (23.4)	-	-	-	1/3	27.0 (–)	44.3 (15.0)	-	-	-
AAT simple nouns (z-scores)	29/7	0.3 (0.6)	−0.03 (1.0)	*F* (1.32) = 0.110	0742	0.003	5/1	−0.2 (0.8)	0.3 (–)	-	-	-	5/0	0.1 (0.9)	-	-	-	-	0/1	-	0.3 (–)	-	-	-
AAT compound nouns (z-scores)	29/7	0.0 (0.8)	−0.3 (1.2)	*F* (1.32) = 0.324	0573	0.010	5/1	−0.7 (1.7)	0.8 (–)	-	-	-	5/0	0.0 (0.8)	-	-	-	-	0/1	-	−0.7 (–)	-	-	-
CERAD verbal fluency animals (z-scores)	133/46	−0.4 (1.7)	−0.6 (0.9)	*F* (1.175) = 2191	0.141	0012	33/5	−0.9 (1.0)	−0.3 (1.9)	*F* (1.34) = 0.728	0400	0.021	65/14	−1.2 (1.1)	−1.7 (0.6)	*F* (1.75) = 2585	0.112	0033	28/25	−1.4 (0.9)	−1.2 (1.1)	*F* (1.49) = 0.260	0612	0.005
CERAD verbal fluency s-words (z-scores)	74/18	−0.7 (1.1)	−0.8 (0.7)	*F* (1.88) = 1152	0.286	0013	20/2	−0.1 (3.3)	7.9 (10.1)	-	-	-	18/3	−1.0 (1.0)	−2.0 (1.6)	-	-	-	1/3	0.2 (–)	−0.7 (1.2)	-	-	-

TABLE 4 (Continued)

	aMCI					naMCI					AD					MD				
	n	No CAA mean (SD)	Poss + prob CAA mean (SD)		*p*	Partial eta-square	*n*	No CAA mean (SD)	Poss + prob CAA mean (SD)		*p*	Partial eta-square	*n*	No CAA mean (SD)	Poss + prob CAA mean (SD)		*p*	Partial eta-square
TMT A (*z*-scores)	137/45	1.1 (9.1)	−0.3 (1.1)	F (1.178) = 0.001	0976	0.000	34/5	−0.5 (1.2)	−0.7 (0.8)	F (1.35) = 0.475	0495	0.013	64/14	−0.9 (1.0)	−1.4 (1.3)	F (1.74) = 1283	0.261	0017	27/24	−1.5 (1.1)	−1.7 (1.0)	F (1.47) = 0.111	0740	0.002
TMT B (*z*-scores)	133/42	0.5 (8.3)	−0.5 (1.1)	F (1.171) = 0.001	0976	0.000	34/5	−0.8 (1.0)	−1.6 (0.9)	F (1.35) = 2860	0.100	0076	54/9	−1.3 (0.9)	−1.1 (1.1)	F (1.59) = 0.283	0597	0.005	17/12	−1.4 (0.6)	1.3 (0.9)	F (1.25) = 1974	0.172	0073
NAI labyrinth (C-scores)	126/43	4.7 (2.1)	5.0 (2.0)	F (1.165) = 0.024	0877	0.000	31/5	4.1 (1.9)	4.5 (2.7)	F (1.32) = 0.232	0633	0.007	61/12	4.1 (1.9)	4.4 (2.6)	F (1.69) = 0.543	0464	0.008	25/23	3.6 (2.2)	3.4 (1.8)	F (1.44) = 0.013	0909	0.000
NAI color word test (C-scores)	**122/41**	**4.9 (2.0)**	**5.8 (1.8)**	**F (1.159) = 3394**	**0.067**	**0021**	31/4	4.5 (1.9)	4.4 (1.7)	-	-	-	64/14	4.1 (2.0)	4.2 (2.1)	F (1.74) = 0.089	0766	0.001	24/22	4.3 (1.8)	4.1 (1.6)	F (1.42) = 0.007	0935	0.000
NAI repeating numbers (percentile ranks)	42/21	54.4 (28.6)	50.0 (34.7)	F (1.59) = 0.225	0637	0.004	6/2	59.2 (26.6)	27.0 (10.0)	-	-	-	37/10	44.7 (32.8)	47.6 (33.4)	F (1.43) = 0.006	0940	0.000	23/20	32.3 (30.7)	38.0 (27.2)	F (1.39) = 1316	0.258	0033

Note: ANOVA; independent variable: CAA diagnosis (no vs. probable + possible); dependent variable: cognitive measure. Bold letters within the table mark significant results ($p < 0.05$) or trends ($p < 0.1$).

Furthermore, the relatively high percentage of possible CAA cases in the aMCI group (12.2% possible vs. 12.2% probable CAA) and corresponding diagnostic sensitivity and specificity issues should be taken into consideration when discussing this implausible finding. Beyond, it should be discussed that controlling for general cerebral microangiopathy might also weaken CAA-associated effects on cognition mediated by white matter pathology. But according to our data set CAA alone does not seem to have detrimental effects on memory in aMCI patients.

Investigating the effects of comorbid CAA on cognitive impairment in patients with AD the strong association of CAA with parenchymal amyloid pathology, severity and accelerated progression of clinical dementia syndrome has to be considered.[7,33,41] Since CAA significantly interacts with AD pathology in terms of Braak stages[41] a parallelism in the evolution of AD and CAA was expected so that poorer memory functioning in AD patients with CAA is in line with our expectations and current data in this field. Capillary CAA pathology starts early in AD and develops simultaneously with progressing parenchymal amyloid pathology[1] which results in a CAA-mediated contribution to neurodegeneration with a global cortical thickness reduction in patients with CAA regionally overlapping with an AD cortical atrophy signature.[14] Beyond, new data show diminished functional brain connectivity in patients with CAA with an impairment of visual, executive control and bilateral frontoparietal networks.[18] As a consequence of these far-reaching functional effects, CAA per se is known to be associated with progressive cognitive deficits in multiple domains.[19] Even in non-demented individuals CAA was shown to mediate a cognitive decline in episodic memory, executive function, semantic fluency and attention[19] whereas about half the effect of CAA on cognition is mediated by vascular pathology and white matter disruption.[9] Taken together, effects of comorbid CAA on cognitive performance in AD can be interpreted as an interplay of advanced parenchymal, CAA-related- and non-CAA-related vascular pathology in multiple areas of the brain. Thus, our measured effects of comorbid CAA on memory in patients with AD might be best understood as a cumulative effect of CAA-related and AD-associated hippocampal pathology.[1] The fact that CAA-specific effects on cognition were not demonstrated in other cognitive domains and that no significant effects on memory functioning were measured in the MD group might be due to methodical aspects in terms of controlling for Fazekas score which seems to underpin the functional relevance of white matter disruption in CAA-mediated cognitive effects in AD.

Our data further demonstrate that CAA-related small vessel disease burden contributes to psychometric group differences between naMCI, aMCI, AD and MD within the cognitive domains of word finding and verbal fluency. But in contrast to our categorical and cross-sectional approach when measuring effects of CAA on cognitive performance within diagnostic groups Total-MRI score did not contribute to psychometric group differences with regard to memory functioning. Dimensional CAA detection using the Total-MRI score is a valid approach.[25] But our study results imply that it

TABLE 5 Analysis of interaction between diagnosis and Total-MRI score.

		aMCI		naMCI		AD		MD		Interaction diagnostic group x total MRI score
	n	Means	SD	Means	SD	Means	SD	Means	SD	
CERAD word list learning (z-scores)	352	−1.03	1.23	−0.20	0.97	−2.41	1.05	−2.41	1.32	*F* (3,342) = 0.144; *p* = 0.933; partial eta-square = 0.001
CERAD word list recall (z-scores)	352	−1.27	0.97	−0.33	1.03	−2.44	1.23	−2.43	1.00	*F* (3,342) = 0.386; *p* = 0.763; partial eta-square = 0.003
CERAD word list recognition (z-scores)	353	−1.04	1.28	−0.10	1.04	−1.97	1.41	−1.65	1.29	*F* (3,343) = 0.732; *p* = 0.533; partial eta-square = 0.006
CERAD Boston naming (z-scores)	211	−0.09	1.22	0.01	1.18	−0.97	1.32	−1.14	1.26	*F* (3,201) = 0.801; *p* = 0.495; partial eta-square = 0.012
CERAD figures (z-scores)	207	−0.05	1.11	−0.89	1.14	−0.57	1.40	−0.94	1.41	*F* (3,197) = 0.584; *p* = 0.626; partial eta-square = 0.009
CERAD figures recall (z-scores)	206	−0.79	1.12	−0.26	1.15	−1.96	1.05	−2.16	1.57	*F* (3,196) = 0.891; *p* = 0.447; partial eta-square = 0.013
WMS visual immediate (percentile ranks)	149	40.84	31.69	49.86	30.76	16.06	18.68	8.25	5.56	*F* (3,139) = 0.408; *p* = 0.748; partial eta-square = 0.009
WMS visual delayded (percentile ranks)	149	34.55	30.28	48.42	29.92	6.10	11.21	0.50	1.00	*F* (3,139) = 0.499; *p* = 0.684; partial eta-square = 0.011
WMS digit span forward (percentile ranks)	145	37.72	29.61	43.08	31.52	42.70	31.15	60.50	35.46	F (3,135) = 0.784; *p* = 0.505; partial eta-square = 0.017
WMS digit span backward (percentile ranks)	145	33.15	25.35	31.36	27.29	29.05	22.83	40.00	15.01	F (3.135) = 0.910; *p* = 0.438; partial eta-square = 0.020
AAT simply nouns (z-scores)	47	0.27	0.67	−0.08	0.73	0.06	0.88			**F (2.39) = 4059; p = 0,025; partial eta-square = 0.172**
AAT compound nouns (z-scores)	47	−0.02	0.91	−0.47	1.68	0.00	0.76			*F* (2,39) = 1895; *p* = 0.164; partial eta-square = 0.089
CERAD verbal fluency animals (z-scores)	349	−0.45	1.53	−0.79	1.16	−1.26	1.00	−1.33	0.99	*F* (3.339) = 1193; *p* = 0.312; partial eta-square = 0.010
CERAD verbal fluency s-words (z-scores)	139	−0.76	1.01	0.67	4.47	−1.11	1.14	−0.50	1.11	**F (3.129) = 3533; p = 0,017; partial eta-square = 0.076**
TMT A (z-scores)	350	0.73	7.97	−0.53	1.14	−1.02	1.09	−1.59	1.05	*F* (3,340) = 0.604; *p* = 0.613; partial eta-square = 0.005
TMT B (z-scores)	306	0.28	7.28	−0.87	1.00	−1.31	0.96	−1.39	0.72	*F* (3.296) = 0.329; *p* = 0.804; partial eta-square = 0.003
NAI labyrinth (C-scores)	326	4.77	2.06	4.15	1.97	4.12	2.04	3.52	2.03	*F* (3.316) = 0.515; *p* = 0.672; partal eta-square = 0.005
NAI color word test (C-scores)	322	5.16	1.99	4.49	1.85	4.10	1.98	4.23	1.66	**F (3.312) = 2150; p = 0.094; partial eta-square = 0.020**
NAI repeating numbers (percentile ranks)	161	53.91	30.52	51.13	27.25	45.32	32.58	34.92	28.92	*F* (3.151) = 0.652; *p* = 0.583; partial eta-square = 0.013

Note: ANOVA; independent variable: cognitive measure; factor: diagnostic group; covariates: Total-MRI score, Fazekas-score, age. Bold letters within the table mark significant results ($p < 0.05$) or trends ($p < 0.1$).

is important to use different approaches when investigating the complex interactions between AD and CAA on cognitive decline. Methodical aspects have to be closely regarded when interpreting effects of CAA on cognition in AD.

Considering our study results with different approaches comorbid CAA in MCI and dementia modulates cognitive performance in memory functioning, word finding and word fluency in a presumably stage-dependant manner. Within the AD group prominent CAA-related effects on memory were objectified whereas effects on speech and word fluency were demonstrated across the diagnostic groups of naMCI, aMCI, AD and MD.

Our study has relevant limitations. Beside the retrospective and cross-sectional design, not obtaining biomarkers like CSF, amyloid PET or APOE e4 genotyping, especially in the heterogenous constructs of

TABLE 6 Summary of MRI findings.

MRI findings	Number (for ICH, CMB, microinfarcts, lacunar infarcts), grade (for CSS, CSO, WMH)	Total (n = 475)	CAA			
			No (n = 359)	Possible (n = 43)	Probable (n = 73)	Possible + probable (n = 116)
Lobar ICH	No	471 (99.2%)	359 (100.0%)	43 (100.0%)	69 (94.5%)	112 (96.6%)
	1 or more	4 (0.8%)	0 (0.0%)	0 (0.0%)	4 (5.5%)	4 (3.4%)
Deep ICH	No	470 (98.9%)	355 (98.9%)	43 (100%.0%)	72 (98.6%)	115 (99.1%)
	1 or more	5 (1.0%)	4 (1.2%)	0 (0.0%)	1 (1.4%)	1 (0.9%)
Cortical/subcortical CMB	No	358 (75.4%)	356 (99.2%)	2 (4.7%)	0 (0.0%)	2 (1.7%)
	1	44 (9.3%)	0 (0.0%)	41 (95.3%)	3 (4.1%)	44 (37.9%)
	2–4	43 (9.0%)	1 (0.3%)	0 (0.0%)	42 (57.5%)	42 (36.2%)
	3: 5–10	21 (4.4%)	2 (0.6%)	0 (0.0%)	19 (26.0%)	19 (16.4%)
	4: 10–50	9 (1.9%)	0 (0.0%)	0 (0.0%)	9 (12.3%)	9 (7.8%)
	5: >50	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deep CMB	No	415 (87.4%)	320 (89.1%)	39 (90.7%)	56 (76.7%)	95 (81.9%)
	1	42 (8.8%)	28 (7.8%)	4 (9.3%)	10 (13.7%)	14 (12.1%)
	2–4	15 (3.2%)	8 (2.2%)	0 (0.0%)	7 (9.6%)	7 (6.0%)
	3: 5–10	3 (0.6%)	3 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4: 10–50	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	5: >50	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CSS	No	461 (97.1%)	359 (100.0%)	41 (95.3%)	61 (83.6%)	102 (87.9%)
	Focal	14 (2.9%)	0 (0.0%)	2 (4.7%)	12 (16.4%)	14 (12.1%)
	Disseminated	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CSO	Mild (<20)	150 (31.6%)	127 (35.4%)	11 (25.6%)	12 (16.4%)	23 (19.8%)
	Moderate to severe	325 (68.4%)	232 (64.6%)	32 (74.4%)	61 (83.6%)	93 (80.2%)
Cortical microinfarcts	No	471 (99.2%)	356 (99.2%)	43 (100.0%)	72 (98.6%)	115 (99.1%)
	1	3 (0.6%)	2 (0.6%)	0 (0.0%)	1 (1.4%)	1 (0.9%)
	>1	1 (0.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
WMH	Fazekas 0–1	254 (53.5%)	216 (60.2%)	18 (41.9%)	20 (27.4%)	38 (32.8%)
	Fazekas 2–3	221 (46.5%)	143 (39.8%)	25 (58.1%)	53 (72.6%)	78 (67.2%)
Total MRI scale	0	100 (21.1%)	93 (25.9%)	7 (16.3%)	0 (0.0%)	7 (6.0%)
	1	173 (36.4%)	158 (44.0%)	13 (30.2%)	2 (2.7%)	15 (12.9%)
	2	148 (31.2%)	106 (29.5%)	23 (53.5%)	19 (26.0%)	42 (36.2%)
	3	28 (5.9%)	0 (0.0%)	0 (0.0%)	28 (38.4%)	28 (24.1%)
	4	22 (4.6%)	2 (0.6%)	0 (0.0%)	20 (27.4%)	20 (17.2%)
	5	4 (0.8%)	0 (0.0%)	0 (0.0%)	4 (5.5%)	4 (3.4%)

SMI[42] and MCI,[22] represent relevant constraints impeding the interpretability and generalizability of our study data. But beside the real world character of our data set, the relatively large number of patients as well as the extensive neuropsychological and neuroradiologic assessment strengthen the validity of our study results.

ACKNOWLEDGMENTS

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The authors report no relevant financial disclosures.

DATA AVAILABILITY STATEMENT

Original data are not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

ORCID

Robert Haussmann https://orcid.org/0000-0002-2936-5180

REFERENCES

1. Thal DR, Griffin WS, de Vos RA, Ghebremedhin E. Cerebral amyloid angiopathy and its relationship to Alzheimer's disease. *Acta Neuropathol*. 2008;115(6):599-609. https://doi.org/10.1007/s00401-008-0366-2
2. Greenberg SM, Vonsattel JP. Diagnosis of cerebral amyloid angiopathy. Sensitivity and specificity of cortical biopsy. *Stroke*. 1997;28(7):1418-1422. https://doi.org/10.1161/01.str.28.7.1418
3. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. *Ann Neurol*. 2011;70(6):871-880. https://doi.org/10.1002/ana.22516
4. Keage HA, Carare RO, Friedland RP, et al. Population studies of sporadic cerebral amyloid angiopathy and dementia: a systematic review. *BMC Neurol*. 2009;9(1):3. https://doi.org/10.1186/1471-2377-9-3
5. Jellinger KA. Alzheimer disease and cerebrovascular pathology: an update. *J Neural Transm*. 2002;109(5-6):813-836. https://doi.org/10.1007/s007020200068
6. Boyle PA, Yu L, Nag S, et al. Cerebral amyloid angiopathy and cognitive outcomes in community-based older persons. *Neurology*. 2015;85(22):1930-1936. https://doi.org/10.1212/wnl.0000000000002175
7. Arvanitakis Z, Leurgans SE, Wang Z, Wilson RS, Bennett DA, Schneider JA. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. *Ann Neurol*. 2011;69(2):320-327. https://doi.org/10.1002/ana.22112
8. Xiong L, Boulouis G, Charidimou A, et al. Dementia incidence and predictors in cerebral amyloid angiopathy patients without intracerebral hemorrhage. *J Cerebr Blood Flow Metabol*. 2018;38(2):241-249. https://doi.org/10.1177/0271678x17700435
9. Durrani R, Wang M, Cox E, et al. Mediators of cognitive impairment in cerebral amyloid angiopathy. *Int J Stroke*. 2023;18(1):78-84. https://doi.org/10.1177/17474930221099352
10. Costa AS, Pinho J, Kucikiene D, Reich A, Schulz JB, Reetz K. Cerebral amyloid angiopathy in amyloid-positive patients from a memory clinic cohort. *J Alzheimers Dis*. 2021;79(4):1661-1672. https://doi.org/10.3233/jad-201218
11. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease—one peptide, two pathways. *Nat Rev Neurol*. 2020;16(1):30-42. https://doi.org/10.1038/s41582-019-0281-2
12. Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet*. 1999;354(9182):919-920. https://doi.org/10.1016/s0140-6736(99)02355-7
13. 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(10):813-817. https://doi.org/10.1001/jama.277.10.813
14. Subotic A, McCreary CR, Saad F, et al. Cortical thickness and its association with clinical cognitive and neuroimaging markers in cerebral amyloid angiopathy. *J Alzheimers Dis*. 2021;81(4):1663-1671. https://doi.org/10.3233/jad-210138
15. Pfeifer LA, White LR, Ross GW, Petrovitch H, Launer LJ. Cerebral amyloid angiopathy and cognitive function: the HAAS autopsy study. *Neurology*. 2002;58(11):1629-1634. https://doi.org/10.1212/wnl.58.11.1629
16. Hecht M, Kramer LM, von Arnim CAF, Otto M, Thal DR. Capillary cerebral amyloid angiopathy in Alzheimer's disease: association with allocortical/hippocampal microinfarcts and cognitive decline. *Acta Neuropathol*. 2018;135(5):681-694. https://doi.org/10.1007/s00401-018-1834-y
17. Greenberg SM, Gurol ME, Rosand J, Smith EE. Amyloid angiopathy-related vascular cognitive impairment. *Stroke*. 2004;35(Suppl l):2616-2619. https://doi.org/10.1161/01.str.0000143224.36527.44
18. Drenth N, van der Grond J, Rombouts S, et al. Cerebral amyloid angiopathy is associated with decreased functional brain connectivity. *Neuroimage Clin*. 2021;29:102546. https://doi.org/10.1016/j.nicl.2020.102546
19. Xiong L, Davidsdottir S, Reijmer YD, et al. Cognitive profile and its association with neuroimaging markers of non-demented cerebral amyloid angiopathy patients in a stroke unit. *J Alzheimers Dis*. 2016;52(1):171-178. https://doi.org/10.3233/jad-150890
20. Abdulrab K, Heun R. Subjective Memory Impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. *Eur Psychiatr*. 2008;23(5):321-330. https://doi.org/10.1016/j.eurpsy.2008.02.004
21. 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(3):270-279. https://doi.org/10.1016/j.jalz.2011.03.008
22. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194. https://doi.org/10.1111/j.1365-2796.2004.01388.x
23. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology*. 1984;34(7):939-944. https://doi.org/10.1212/wnl.34.7.939
24. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord*. 2014;28(3):206-218. https://doi.org/10.1097/wad.0000000000000034
25. Charidimou A, Martinez-Ramirez S, Reijmer YD, et al. Total magnetic resonance imaging burden of small vessel disease in cerebral amyloid angiopathy: an imaging-pathologic study of concept validation. *JAMA Neurol*. 2016;73(8):994-1001. https://doi.org/10.1001/jamaneurol.2016.0832
26. Haller S, Vernooij MW, Kuijer JPA, Larsson EM, Jager HR, Barkhof F. Cerebral microbleeds: imaging and clinical significance. *Radiology*. 2018;287(1):11-28. https://doi.org/10.1148/radiol.2018170803
27. 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(2):351-356. https://doi.org/10.2214/ajr.149.2.351
28. Greenberg SM, Charidimou A. Diagnosis of cerebral amyloid angiopathy: evolution of the Boston criteria. *Stroke*. 2018;49(2):491-497. https://doi.org/10.1161/strokeaha.117.016990
29. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. *Neurology*. 2001;56(4):537-539. https://doi.org/10.1212/wnl.56.4.537
30. Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology*. 2010;74(17):1346-1350. https://doi.org/10.1212/wnl.0b013e3181dad605
31. Neubauer AC, Grabner RH, Freudenthaler HH, Beckmann JF, Guthke J. Intelligence and individual differences in becoming neurally efficient. *Acta Psychol*. 2004;116(1):55-74. https://doi.org/10.1016/j.actpsy.2003.11.005

32. Kessler J, Fast K, Mielke R. [Premorbid intelligence diagnosis with the MWT-B(multiple Choice word test-B) in patients with Alzheimer disease]. *Nervenarzt*. 1995;66:696-702.
33. Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. Person-specific contribution of neuropathologies to cognitive loss in old age. *Ann Neurol*. 2018;83(1):74-83. https://doi.org/10.1002/ana.25123
34. Jakel L, De Kort AM, Klijn CJM, Schreuder F, Verbeek MM. Prevalence of cerebral amyloid angiopathy: a systematic review and meta-analysis. *Alzheimers Dement*. 2022;18(1):10-28. https://doi.org/10.1002/alz.12366
35. Ryu SY, Lim EY, Na S, et al. Hippocampal and entorhinal structures in subjective memory impairment: a combined MRI volumetric and DTI study. *Int Psychogeriatr*. 2017;29(5):785-792. https://doi.org/10.1017/s1041610216002349
36. Rabin LA, Smart CM, Amariglio RE. Subjective cognitive decline in preclinical Alzheimer's disease. *Annu Rev Clin Psychol*. 2017;13(1):369-396. https://doi.org/10.1146/annurev-clinpsy-032816-045136
37. Caselli RJ, Dueck AC, Osborne D, et al. Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. *N Engl J Med*. 2009;361(3):255-263. https://doi.org/10.1056/nejmoa0809437
38. Rannikmae K, Samarasekera N, Martinez-Gonzalez NA, Al-Shahi Salman R, Sudlow CL. Genetics of cerebral amyloid angiopathy: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2013;84(8):901-908. https://doi.org/10.1136/jnnp-2012-303898
39. Charidimou A, Boulouis G, Gurol ME, et al. Emerging concepts in sporadic cerebral amyloid angiopathy. *Brain*. 2017;140(7):1829-1850. https://doi.org/10.1093/brain/awx047
40. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: mild cognitive impairment: report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology. *Neurology*. 2018;90(3):126-135. https://doi.org/10.1212/wnl.0000000000004826
41. Malek-Ahmadi M, Perez SE, Chen K, Mufson EJ. Braak stage, cerebral amyloid angiopathy, and cognitive decline in early Alzheimer's disease. *J Alzheimers Dis*. 2020;74(1):189-197. https://doi.org/10.3233/jad-191151
42. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. *Lancet Neurol*. 2020;19(3):271-278. https://doi.org/10.1016/s1474-4422(19)30368-0

How to cite this article: Haussmann R, Homeyer P, Sauer C, et al. Comorbid cerebral amyloid angiopathy in dementia and prodromal stages—Prevalence and effects on cognition. *Int J Geriatr Psychiatry*. 2023;e6015. https://doi.org/10.1002/gps.6015