Received: 12 January 2021 | Revised: 5 April 2021 | Accepted: 12 April 2021

DOI: 10.1002/alz.12366

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Prevalence of cerebral amyloid angiopathy: A systematic review and meta-analysis

Lieke Jäkel[1] | **Anna M. De Kort**[1] | **Catharina J.M. Klijn**[1] | **Floris H.B.M. Schreuder**[1] | **Marcel M. Verbeek**[1,2]

[1] Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud Alzheimer Centre, Radboud University Medical Cente, Nijmegen, The Netherlands

[2] Department of Laboratory Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence
Marcel M. Verbeek, Department of Neurology, 830 TML, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
Email: marcel.verbeek@radboudumc.nl

Lieke Jäkel, Anna M. De Kort, Floris H.B.M. Schreuder, and Marcel M. Verbeek contributed equally to this work.

Funding information
ZonMW, Grant/Award Numbers: 733050822, 015008048; National Institutes of Health, Grant/Award Number: 5R01NS104147-02; Selfridges Group Foundation, Grant/Award Number: NR170024; Dutch Heart Foundation, Grant/Award Numbers: 2012T077, 2019T060; The Netherlands Organization for Health Research and Development, Grant/Award Number: 015008048

Abstract

Reported prevalence estimates of sporadic cerebral amyloid angiopathy (CAA) vary widely. CAA is associated with cognitive dysfunction and intracerebral hemorrhage, and linked to immunotherapy-related side-effects in Alzheimer's disease (AD). Given ongoing efforts to develop AD immunotherapy, accurate estimates of CAA prevalence are important. CAA can be diagnosed neuropathologically or during life using MRI markers including strictly lobar microbleeds. In this meta-analysis of 170 studies including over 73,000 subjects, we show that in patients with AD, CAA prevalence based on pathology (48%) is twice that based on presence of strictly lobar cerebral microbleeds (22%); in the general population this difference is three-fold (23% vs 7%). Both methods yield similar estimated prevalences of CAA in cognitively normal elderly (5% to 7%), in patients with intracerebral hemorrhage (19% to 24%), and in patients with lobar intracerebral hemorrhage (50% to 57%). However, we observed large heterogeneity among neuropathology and MRI protocols, which calls for standardized assessment and reporting of CAA.

KEYWORDS
Alzheimer's disease, amyloid, Boston criteria, cerebral amyloid angiopathy, immunotherapy, intracerebral hemorrhage, meta-analysis, microbleeds, MRI, neuropathology, prevalence, systematic review

1 | PART 1: NARRATIVE

1.1 | CAA: clinical aspects and diagnosis

Cerebral amyloid angiopathy (CAA) is the accumulation of amyloidogenic proteins, most often amyloid β (Aβ), in cerebral blood vessel walls,[1] leading to a weakened vasculature and thereby creating a major risk for intracerebral hemorrhages (ICH).[2,3] Several types of hereditary disorders exist that result in CAA, caused by missense mutations within the Aβ precursor protein gene.[3] However, CAA most frequently occurs sporadically and is observed in cognitively normal elderly, but also frequently in patients with Alzheimer's disease (AD).[4] In patients with AD, CAA is tightly linked to the development of "amyloid-related imaging abnormalities (ARIA)," a frequently occurring side-effect of anti-Aβ immunotherapy defined by neuroimaging[3] (eg, ≈40% of AD patients treated with aducanumab develop ARIA[5]). Patients with CAA may present with a broad clinical spectrum, including cognitive decline, lobar ICH, and transient focal neurological episodes (recurrent, stereotyped, transient episodes of smoothly spreading paraesthesias, numbness or weakness, lasting typically seconds to minutes, usually resolving over a similar period).[3,6,7] A rare complication of the disease is CAA-related inflammation, characterized by headache, seizures, behavioral change, focal neurological signs, impaired consciousness in combination with asymmetrical hyperintense T2-weighted magnetic resonance imaging (MRI) lesions, which is treatable with immunotherapy.[7]

A definite diagnosis of CAA can only be obtained by *post mortem* neuropathological assessment of brain tissue. Aβ in blood vessels can be visualized by staining with Thioflavin or Congo-Red, or by

immunohistochemistry with antibodies directed against Aβ.[8] For the diagnosis of CAA during life, the (modified) Boston criteria have been developed, which make use of MRI to enable the diagnosis of "probable" or "possible" CAA.[9,10] These Boston criteria are based on two CAA-related imaging markers: strictly lobar cerebral microbleeds (small brain bleeds restricted to cortical and subcortical regions of the brain),[11–13] and cortical superficial siderosis (deposition of blood breakdown products in the cortical sulci over the convexity of the cerebral hemispheres).[14] More recently, positron emission tomography amyloid tracers have been successfully developed, but their diagnostic utility has remained limited so far because tracers are not specific for amyloid deposition in the blood vessels and differentiation from parenchymal amyloid depositions in AD is difficult.[7]

1.2 | Accurate estimates of CAA prevalence are lacking

Since sporadic CAA is associated with an increased risk for cognitive dysfunction and ICH, it is important to have an accurate estimation of the prevalence of CAA, especially in the light of ARIA occurring as severe immunotherapy-related side-effects due to the presence of CAA in AD.[3] Moreover, reported estimates have revealed remarkable variation in the prevalence of CAA, which likely reflects different populations under investigation and application of different diagnostic tools (neuropathology vs MRI). For example, the reported prevalence of neuropathologically diagnosed CAA varies dramatically from 20% to 100% in AD patients,[15–17] to 0% to 79% in non-demented elderly,[18,19] and 16% to 70% in the general elderly population.[20,21] Using the approach of a systematic review and meta-analysis, we have analyzed the literature for reports on the prevalence of CAA either based on neuropathological or neuroimaging investigations, in order to obtain a better insight into the possible impact of CAA on brain health in various populations.

1.3 | A meta-analysis to provide reliable estimates of CAA prevalence

We performed a systematic review and meta-analysis to provide reliable estimates of the prevalence of CAA pathology (Table 1) and sporadic CAA based on the (modified) Boston criteria (Table 2). We included 170 studies reporting on 73,000 subjects in five populations: patients with AD, the general population (a cross-sectional selection of individuals representing the general elderly society as closely as possible, also including individuals with known cerebrovascular or neurodegenerative disease), cognitively normal elderly (elderly individuals free of dementia or cognitive impairment after clinical examination, or without neurodegenerative changes upon neuropathological examination, making the presence of cognitive problems unlikely), patients with ICH (irrespective of its location), and patients with lobar ICH. For pathology studies, we extracted the severity of CAA, focusing on moderate-to-severe CAA, but also reporting separately all CAA (mild-to-severe) and severe CAA. In addition, we separately assessed the prevalence of the two most important MRI markers of CAA: strictly lobar cerebral microbleeds and cortical superficial siderosis, which are both considered "CAA-related imaging markers" (Table 2). Using meta-analyses to pool data, we found that in AD patients and in the general population, imaging data underestimated the prevalence of CAA pathology: in patients with AD, the prevalence of moderate-to-severe CAA pathology was ≈48%, which was double the estimate based on the presence of strictly lobar cerebral microbleeds (22%). In the general population, the prevalence of moderate-to-severe CAA pathology was 23%, whereas the prevalence of strictly lobar cerebral microbleeds was 7%. In contrast, the prevalence of moderate-to-severe CAA based on pathology and on imaging was similar in other populations: ≈5% in cognitively normal elderly, around 20% to 25% in patients with ICH, and around 50% to 60% in patients with lobar ICH.

RESEARCH IN CONTEXT

1. **Systematic review**: Cerebral amyloid angiopathy (CAA) is an important cause of cognitive impairment and may also lead to intracerebral hemorrhages. Besides, CAA is tightly linked to the development of "amyloid-related imaging abnormalities" (ARIA), a rare and sporadic complication of CAA, that also frequently occurs as a side-effect of anti-amyloid β immunotherapy in Alzheimer's disease (AD) patients. Knowledge of the prevalence of CAA is important to understand the risk of each individual to develop clinical symptoms due to CAA and to understand the potential risks of developing CAA-related ARIA in immunotherapy. In this systematic review and meta-analysis we provide accurate estimates of the prevalence of CAA in AD, in the general population, in cognitively normal elderly, and in patients with (lobar) intracerebral hemorrhage.
2. **Interpretation**: Based on neuropathological examination, the prevalence of moderate-to-severe CAA in AD is 48% and in the general population 23%. Prevalence of CAA based on MRI criteria was remarkably lower: 22% in AD and 7% in the general population. Both methods yielded similar CAA prevalence in cognitively normal elderly (5% to 7%), in patients with intracerebral hemorrhage (19% to 24%), and in patients with lobar intracerebral hemorrhage (50% to 57%). There was large heterogeneity in methodology and criteria for CAA both in neuropathology and neuroimaging studies.
3. **Future directions**: These observations call for development of accurate biomarkers to detect CAA during life, including biomarkers in cerebrospinal fluid or blood. In addition, future studies should assess MRI biomarkers for CAA specifically in AD patients. In addition we propose harmonized and standardized protocols to facilitate uniform reporting of CAA, both in neuropathology and neuroimaging studies.

TABLE 1 Pooled prevalence estimates of CAA pathology

	Degree CAA pathology	Studies, *n*	*n* individuals	Mean age (years)	% female	Prevalence, % (95% CI)	I^2, % (95% CI)	Q(p)
Alzheimer's disease	Mild-to-severe	54	6409	79.8	53.8	79.2 (72.5-85.3)	97.1 (96.7-97.5)	<0.0001
	Moderate-to-severe	**23**	**2715**	**80.6**	**58.9**	**47.5 (38.8-56.2)**	**94.1 (92.3-95.5)**	**<0.0001**
	Severe	23	2276	79.9	54.1	23.3 (18.2-28.7)	85.5 (79.4-89.7)	<0.0001
General population	Mild-to-severe	22	11651	83.3	54.7	41.5 (33.1-50.2)	98.7 (98.4-98.9)	<0.0001
	Moderate-to-severe	**10**	**7157**	**84.9**	**55.3**	**23.0 (17.3-29.1)**	**95.8 (93.9-97.1)**	**<0.0001**
	Severe	11	7354	84.3	54.6	6.3 (3.4-10.0)	95.7 (93.8-97.0)	<0.0001
Cognitively normal elderly	Mild-to-severe	38	3003	80.5	47.2	28.9 (22.8-35.3)	92.1 (90.1-93.7)	<0.0001
	Moderate-to-severe	**16**	**1095**	**81.8**	**51.8**	**6.4 (3.2-10.5)**	**77.9 (64.5-86.2)**	**<0.0001**
	Severe	21	1797	80.8	46.8	2.7 (0.2-6.7)	91.7 (88.6-93.9)	<0.0001
Intracerebral hemorrhage	Mild-to-severe	13	2153	58.8	36.6	28.5 (19.2-38.7)	94.7 (92.5-96.3)	<0.0001
	Moderate-to-severe	**4**	**1249**	**56.8**	**31.8**	**24.1 (3.8-54.1)**	**98.4 (97.4-99.0)**	**<0.0001**
	Severe	4	1289	56.2	29.3	13.6 (0.1-40.0)	98.3 (97.3-99.0)	<0.0001
Lobar intracerebral hemorrhage	Mild-to-severe	6	202	72.7	56.6	52.8 (31.9-73.3)	88.5 (77.6-94.1)	<0.0001
	Moderate-to-severe	**5**	**207**	**73.2**	**59.3**	**56.7 (41.7-71.0)**	**77.8 (46.6-90.8)**	**0.0012**
	Severe	1	29	73.2	51.7	65.5 (47.1-81.9)	NA	NA

Pooled prevalence estimates of mild-to-severe CAA, moderate-to-severe CAA (in bold, considered most important outcome parameter), and severe CAA, in Alzheimer's disease patients, the general population, cognitively normal elderly, patients with intracerebral hemorrhage, and patients with lobar intracerebral hemorrhage. Some studies did not provide data on mean age or distribution of sex; the summarizing demographic data is based on the available data.
I^2 = measure of heterogeneity, Q(p) = *P*-value of Cochran's Q statistics.
Abbreviations: CAA, cerebral amyloid angiopathy; CI, confidence interval; NA, not applicable.

1.4 | High prevalence of CAA in AD patients: clinical implications

Regarding AD patients, 23 studies reported the prevalence of moderate-to-severe CAA pathology (2715 individuals, mean age 80.6 years), whereas 12 studies reported the prevalence of strictly lobar microbleeds (2398 individuals, mean age 72.8 years).

Moderate-to-severe CAA pathology was observed in almost 50% of AD patients. This observation is very important with the recognition that ARIA may develop as a frequent (up to ~40% of the patients[5]) consequence of Aβ immunotherapy and that immunotherapy treatment may augment existing CAA pathology.[3,22–25] Two types of ARIA have been described: parenchymal vasogenic edema and sulcal effusion (ARIA-E), and hemosiderin deposits including microbleeds and superficial siderosis (ARIA-H).[5] The mechanisms underlying ARIA are not fully understood, but studies have suggested that antibody-mediated breakdown of amyloid plaques results in solubilization of Aβ, which is dragged along interstitial fluid flow and eventually deposited in cerebral vessel walls, leading to a focal inflammatory reaction.[3,25] Therefore, caution is warranted when including AD patients with (prominent) CAA into Aβ immunotherapy trials.

Although not validated in AD patients, the (modified) Boston criteria that were developed for patients with ICH are applied by some to estimate the prevalence of CAA in AD patients during life, under the assumption that the presence of strictly lobar microbleeds in AD reflects CAA.[26–28] The presence of strictly lobar cerebral microbleeds in AD patients has also been associated with lower levels of Aβ40 in cerebrospinal fluid,[29] as decreased Aβ40 levels are associated with CAA.[30] The presence of strictly lobar cerebral microbleeds in 22% of AD patients has clinical relevance, as AD patients with multiple cerebral microbleeds had more severe cognitive impairment.[31] It has been shown that CAA contributes to AD dementia independently of senile plaques and neurofibrillary tangles (the neuropathological hallmarks of AD),[32,33] and that CAA is associated with faster rates of cognitive decline.[33] Therefore, CAA pathology may be an important therapeutic target in AD, in addition to senile plaques or tau pathology, and its timely recognition using appropriate diagnostic tools is of utmost importance.

1.5 | Moderate-to-severe CAA in the general population: clinical relevance

A total of 10 studies reported the prevalence of moderate-to-severe CAA pathology (7157 individuals, mean age 84.9 years) in the general population, whereas 14 studies reported the prevalence of strictly lobar microbleeds (21,197 individuals, mean age 67.6 years).

The observation that almost a quarter of the general population has moderate-to-severe CAA is striking and bears clinical relevance. CAA presents with a wide clinical spectrum, and clinical signs and symptoms of CAA may be overlooked or disregarded as being the result of age-related complaints or other diseases. Our finding that

TABLE 2 Pooled prevalence estimates of MRI markers of CAA

	Imaging marker	Studies, n	*n* individuals	Mean age (years)	% female	Prevalence, % (95% CI)	I^2, % (95% CI)	Q(p)
Alzheimer's disease	Probable CAA	1	14	66.2	28.6	14.3 (0.00-32.6)	NA	NA
	Possible CAA	1	14	66.2	28.6	14.3 (0.00-32.6)	NA	NA
	Strictly lobar cerebral microbleeds	12	2398	72.8	53.9	21.8 (16.3-27.8)	90.7 (85.6-93.9)	<0.0001
	Mixed cerebral microbleeds	10	1889	73.9	56.1	5.3 (1.8-10.2)	93.1 (89.3-95.5)	<0.0001
	Cortical superficial siderosis	7	1045	69.6	52.0	5.3 (3.6-7.2)	24.3 (0.0-66.7)	0.2435
General population	Probable CAA	0	NA	NA	NA	NA	NA	NA
	Possible CAA	0	NA	NA	NA	NA	NA	NA
	Strictly lobar cerebral microbleeds	14	21197	67.6	53.5	7.1 (4.9-9.8)	97.8 (97.2-98.3)	<0.0001
	Mixed cerebral microbleeds	10	10033	66.0	52.4	3.1 (2.2-4.2)	87.3 (78.6-92.4)	<0.0001
	Cortical superficial siderosis	2	2472	69.6	48.9	0.8 (0.5-1.2)	0.0	0.4956
Cognitively normal elderly	Probable CAA	2	41	74.4	70.6	5.1 (0.0-31.2)	79.1 (9.5-95.2)	0.0287
	Possible CAA	2	41	74.4	70.6	6.7 (0.5-17.7)	0.0	0.4388
	Strictly lobar cerebral microbleeds	18	11598	62.0	48.7	6.6 (3.8-10.1)	97.0 (96.1-97.6)	<0.0001
	Mixed cerebral microbleeds	9	5334	62.1	47.0	1.5 (0.4-2.9)	71.7 (44.1-85.6)	0.0004
	Cortical superficial siderosis	2	469	66.9	45.2	0.5 (0.0-1.5)	0.0	0.4740
Intracerebral hemorrhage	Probable CAA	7	1652	67.4	37.4	20.2 (9.5-33.7)	97.2 (95.9-98.2)	<0.0001
	Possible CAA	4	1256	70.5	39.6	14.8 (7.8-23.5)	93.1 (85.6-96.7)	<0.0001
	Strictly lobar cerebral microbleeds	10	1466	63.4	39.1	19.2 (14.6-24.1)	75.4 (54.3-86.8)	<0.0001
	Mixed cerebral microbleeds	9	1269	64.6	38.8	27.2 (17.3-38.2)	92.9 (88.6-95.5)	<0.0001
	Cortical superficial siderosis	4	1010	68.6	42.3	15.6 (8.9-23.7)	90.2 (78.0-95.7)	<0.0001
Lobar intracerebral hemorrhage	Probable CAA	5	374	72.5	47.6	49.6 (29.1-70.3)	93.4 (87.6-96.5)	<0.0001
	Possible CAA	4	209	74.2	48.8	45.2 (15.8-76.5)	95.4 (91.2-97.6)	<0.0001
	Strictly lobar cerebral microbleeds	0	NA	NA	NA	NA	NA	<0.0001
	Mixed cerebral microbleeds	0	NA	NA	NA	NA	NA	<0.0001
	Cortical superficial siderosis	3	454	73.4	51.5	32.5 (24.7-40.9)	63.3 (0.0-89.5)	0.0654

Pooled prevalence estimates of MRI imaging markers, including possible or probable CAA according to the Boston criteria, strictly lobar cerebral microbleeds, mixed cerebral microbleeds, and cortical superficial siderosis. Some studies did not provide data on mean age or distribution of sex; the summarizing demographic data are based on the available data. I^2 = measure of heterogeneity, Q(p) = *P*-value of Cochran's Q statistics.
Abbreviations: CAA, cerebral amyloid angiopathy; CI, confidence interval; MRI, magnetic resonance imaging; NA, not applicable.

CAA is highly prevalent in the general population indicates that CAA should be considered in the differential diagnosis for patients presenting with cognitive decline, as CAA is strongly associated with cognitive impairment,[34] even after correction for the co-occurrence of AD pathology and other pathologies.[32,35] Moreover, CAA-related cognitive impairment can precede the occurrence of ICH.[36] Furthermore, transient focal neurological episodes are a recognized clinical presentation of CAA, which occurred in 14% of patients diagnosed with *probable* CAA in a multicenter cohort of 172 patients.[37] In daily practice however, transient focal neurological episodes may be underdiagnosed

and mistaken for other clinical problems including transient ischemic attacks, focal epileptic seizures, migraine aura, or functional neurological symptoms.[7,38] Avoiding misdiagnosis is crucial, as the administration of anti-platelet medication and anticoagulants for transient ischemic attacks may increase the risk of CAA-related ICH.[39]

The presence of strictly lobar cerebral microbleeds in 7% of the general population is also clinically relevant, as it has been demonstrated that strictly lobar cerebral microbleeds are associated even in the general population with impaired cognitive functioning,[40,41] and with an increased risk of ICH.[42,43] Therefore, in individuals with strictly lobar cerebral microbleeds, careful management of vascular risk factors, such as hypertension, may be of importance.

1.6 | CAA in cognitively normal elderly

Regarding cognitively normal elderly, 16 studies reported the prevalence of moderate-to-severe CAA pathology (1095 individuals, mean age 81.8 years), whereas 18 studies reported the prevalence of strictly lobar microbleeds (11,598 individuals, mean age 62.0 years).

We found that the prevalence of moderate-to-severe CAA pathology in cognitively normal elderly (6%) was four times lower than in the general population (23%), while the mean age of the population was similar. This may be explained by the fact that patients with stroke and/or dementia were excluded from the cohorts of cognitively normal elderly, but not from the general population.

Although often asymptomatic, the presence of strictly lobar cerebral microbleeds in almost 7% may have clinical relevance. The presence of cortical microbleeds in cognitively normal elderly has been associated with a significant and widespread reduction in resting state cerebral blood flow, which suggests the presence of chronic cerebral hypoperfusion in these individuals.[44] This could put them at risk for neuronal injury or cerebrovascular events: for example, in a population enriched for cardiovascular disease, individuals with one or more lobar cerebral microbleeds had a >7-fold risk of stroke-related death compared to individuals without cerebral microbleeds.[45]

1.7 | CAA in patients with (lobar) ICH

The prevalence of moderate-to-severe CAA pathology was reported in four studies of ICH patients (1249 individuals, mean age 56.8 years) and five studies of lobar ICH patients (207 individuals, mean age 73.2 years). Probable CAA according to the (modified) Boston criteria was reported in seven studies of ICH patients (1652 individuals, mean age 67.4 years) and in five studies of lobar ICH patients (374 individuals, mean age 72.5 years).

Moderate-to-severe CAA pathology was observed in 24% of patients with ICH, and in 57% of patients with lobar ICH. Interestingly, diagnosis of CAA based on the (modified) Boston criteria yielded similar proportions of probable CAA cases (20% in patients with ICH and 50% in patients with lobar ICH). These findings support the accuracy of the (modified) Boston criteria to detect CAA in patients with ICH.[46] In contrast, a radiological-pathological correlation study in individuals without ICH, but with other clinical presentations of CAA such as transient focal neurological episodes and cognitive impairment, found a low sensitivity (42.4%) for detecting "probable CAA" (two or more strictly lobar cerebral microbleeds as per Boston criteria).[46,47]

Our finding that only half of the cases with lobar ICH could be explained by the presence of moderate-to-severe CAA indicates that other etiologies, including arteriosclerotic arteriopathy, may contribute to the development of lobar hemorrhages as well. Indeed, in a recent meta-analysis hypertension was an important risk factor for lobar ICH.[48] Similarly, we found a relatively high prevalence of mixed cerebral microbleeds in patients with ICH irrespective of location, which may reflect the presence of etiologies other than or in addition to CAA.[49,50]

Our observation that the prevalence of cortical superficial siderosis was much higher in patients with ICH or lobar ICH compared to the general population, cognitively normal individuals, and patients with AD, indicates that cortical superficial siderosis is not a marker for CAA in general, but may be confined to specific clinical phenotypes[37] and related with the development of lobar ICH.[51]

1.8 | Discrepancy between imaging and pathology data

Importantly, in AD patients and in the general population, the prevalence estimates of CAA markers detected in imaging studies underestimates the prevalence of CAA reported by pathology studies by a factor two (AD) to three (general population), suggesting that MRI markers of CAA may reflect only "the tip of the iceberg" in these populations. Our finding that in both AD patients and population-based studies the prevalence estimates for severe CAA pathology (23% and 6%, respectively) are similar to those based on strictly lobar microbleeds (22% and 7%, respectively), suggests that the latter only identifies severe CAA. It has previously been shown that cognitive decline due to CAA may precede lobar ICH,[52,53] which further supports the hypothesis that hemorrhagic lesions detected by MRI represent late-stage CAA. In pre-symptomatic carriers of hereditary cerebral hemorrhage with amyloidosis-Dutch type (a genetic form of CAA), vascular reactivity is altered well before the occurrence of hemorrhagic events.[54] Furthermore, amyloid deposition is detected by amyloid-positron emission tomography in pre-symptomatic mutation carriers,[55] providing further evidence that amyloid deposition precedes the occurrence of hemorrhages.

An explanation for the difference between prevalence estimates based on pathology and MRI findings is that MRI is performed on living individuals with often modest stages of CAA pathology, whereas autopsy data de facto reflects end-stage pathology. This corresponds with a difference of 10 to 20 years in the mean/median ages of participants in the neuropathology and imaging studies.

Biomarkers that can accurately detect early-stage CAA would enable treatment before the occurrence of hemorrhagic complications. Blood- and cerebrospinal fluid-based biomarkers for the detection of

early-stage CAA are currently being developed.[30,56–58] A caveat in biomarker studies is that patients are often selected on the basis of hemorrhagic imaging biomarkers.[46] However, non-hemorrhagic MRI markers of CAA emerge, including white matter hyperintensities, microinfarcts, and enlarged perivascular spaces in the centrum semiovale, which may prove themselves as early biomarkers of CAA and may aid in the detection of CAA before the onset of hemorrhagic events.[59–61]

The high prevalence of moderate-to-severe CAA in AD patients raises the question why these patients develop ICH relatively infrequently. It has been suggested that differences in enzyme levels involved in the degradation of the extracellular matrix might play a role[62] and mechanistic studies may provide answers to this unsolved question.

1.9 | Heterogeneity in pathology studies

A lot of variability existed among studies. We assessed the effects of clinical and methodological parameters on estimates of prevalence of CAA using meta-regression models. Some of the observed heterogeneity could be explained by differences in patient characteristics: in pathology studies, higher age was associated with decreased prevalence of moderate-to-severe CAA pathology in AD patients. A possible explanation may be earlier death in AD patients with severe CAA. However, a lot of heterogeneity was left unaccounted for. Possible explanations may include different inclusion and exclusion criteria of the study populations. Furthermore, during data extraction we encountered more than thirty different staging systems for CAA pathology: some systems staged CAA based on the percentages or numbers of vessels affected per cortical area or per microscopic field, whereas others focused on the degree of staining in individual vessels or rather on "an estimate of overall severity." In addition, the extent to which the brain was sampled and searched for CAA differed widely.

1.10 | Heterogeneity in imaging studies

In MRI studies, higher age increased the prevalence of strictly lobar cerebral microbleeds when data from all populations were pooled, and in populations of cognitively normal elderly specifically, which is not surprising since it is generally assumed that the prevalence of cerebral microbleeds increases with age.[63] Substantial heterogeneity in the MRI studies could be explained by the influence of MRI parameters, including magnetic field strength and slice thickness, in line with previous reports.[64,65] However, in contrast to expectations,[66,67] phase information (SWI vs T2*) was not a modifier. This may possibly be explained by a lack of power since only relatively few studies that made use of SWI sequences were included in our analysis. Other factors that were not systematically assessed but may have introduced heterogeneity include the definition of "strictly lobar cerebral microbleeds," which varied among studies: whereas some authors defined these as cerebral microbleeds located *only* in the cortico-subcortical areas (in case of cerebellar microbleeds, the individual was then classified as having mixed cerebral microbleeds), others did not take cerebellar microbleeds into account at all, and one study classified cerebellar cortical microbleeds as "strictly lobar cerebral microbleeds." Also, the size by which cerebral microbleeds were defined differed, often with a maximum of either 5 or 10 mm, whereas sometimes no information was provided. Other MRI parameters that may have affected cerebral microbleed prevalence include slice gap and the use of multiple imaging planes.

1.11 | High degree of heterogeneity calls for standardized assessment and reporting of CAA and CAA imaging markers

We found that, despite the existence of several protocols,[68–71] consensus on how to grade and report the severity of CAA at neuropathological examination is currently lacking. Harmonization of CAA grading is therefore an important next step in CAA research, to be able to compare and interpret the findings of studies. Similarly, for neuroimaging studies, we would like to emphasize the importance of adhering to the recommendations of the Microbleed Study Group[64] to always specify the imaging parameters, preferably keeping them constant in longitudinal studies, and taking them into account when interpreting study results.

1.12 | Strengths and limitations of this meta-analysis

Strengths of this review include the large number of studies and number of individuals included, and the comprehensive search that was performed without date and language restrictions. We included all studies that reported the prevalence of CAA or CAA imaging biomarkers, not only those that were primarily aimed at investigating the prevalence of CAA or CAA imaging biomarkers. We assessed the prevalence by use of both neuropathology and MRI imaging and in five domains. The large number of studies also allowed assessment of modifiers of CAA prevalence. Our review also has limitations. First, studies had a high degree of heterogeneity, which could only be partly explained by the variety in age and MRI parameters. Second, although we meticulously tried to exclude potential overlap of participants in the various studies, we cannot fully rule out that some participants appeared in more than one study. Third, studies may have included individuals of different ethnicities, which may have affected the prevalence, but information on ethnicity was too limited to analyze. Of note, many studies lacked descriptions of (some of) the methodological parameters and were therefore not included in the meta-regression analyses.

1.13 | Conclusions

With this systematic review and meta-analysis, we provide reliable estimates of the prevalence of CAA pathology and MRI imaging

markers of CAA in AD patients, the general population, cognitively normal elderly, and patients with (lobar) ICH. We show that almost a quarter of the general population has moderate-to-severe CAA pathology. Also, in AD patients (48%) and patients with lobar ICH (57%), CAA is highly prevalent. Since CAA is associated with the development of ARIA in anti-Aβ immunotherapy and with a growing spectrum of clinical symptoms, awareness of the high prevalence of CAA is important. Therefore, if immunotherapy becomes available for AD patients as part of regular care, screening for the presence of CAA is vital. As neuroimaging markers seriously underestimate the prevalence of CAA in the target populations of such immunotherapies, that is, AD patients and people-at-risk for AD from the general population, the identification and characterization of robust biomarkers that could identify CAA during life may enable early AD treatment, while limiting the risk of ARIA development. Finally, our results emphasize the need for standardized reporting of CAA pathology and CAA-related MRI markers.

Based on the findings of our systematic review and meta-analysis we propose the following steps forward enabling more accurate detection of CAA and a higher appreciation of its association with the occurrence of adverse events associated with immunotherapy:

1. We propose that harmonized and standardized protocols be developed facilitating uniform reporting of CAA, both in neuropathology and neuroimaging studies.
2. We suggest that the search for biomarkers that accurately detect CAA during life be intensified. Candidates may include fluid biomarkers (CSF, blood), or advanced MR or nuclear imaging biomarkers of CAA.
3. We propose that MRI criteria for CAA be developed for AD patients, by comparing the occurrence of CAA using both MRI investigations during life and *post mortem* neuropathological examination in the same patient population.
4. We suggest that in future anti-Aβ immunotherapies, the presence of CAA be systematically analyzed (using the newly developed accurate biomarkers and protocols as proposed above) in relation to the potential occurrence of ARIA as a consequence of this type of treatment.

2 | PART 2: CONSOLIDATED METHODS AND RESULTS

2.1 | Methods

2.1.1 | Search strategy and selection criteria

We searched EMBASE and PubMed using a comprehensive search strategy on June 26th, 2019, using search terms including "cerebral amyloid angiopathy," "cerebral hemorrhage," "neuroimaging," "neuropathology," "amyloid-beta," and "strictly lobar cerebral microbleeds" (Appendix A). Neither date nor language restrictions were applied. The protocol for this review was registered in PROSPERO (registration number 93159).

2.1.2 | Inclusion and exclusion criteria

Research papers were eligible for inclusion if they described one of the following study populations: (1) patients with AD, (2) the general population, (3) cognitively normal elderly, (4) patients with ICH irrespective of the location, (5) patients with lobar intracerebral hemorrhage. We included papers that reported summary estimates on the prevalence of (1) CAA pathology, (2) clinical CAA according to the (modified) Boston criteria, (3) strictly lobar cerebral microbleeds, or (4) cortical superficial siderosis.

Other inclusion criteria were: (1) study population comprised at least 10 subjects, (2) mean/median age of the population was ≥55 years, (3) clearly defined diagnostic criteria to detect CAA which included the use of either neuropathology or MRI (T2* or SWI).

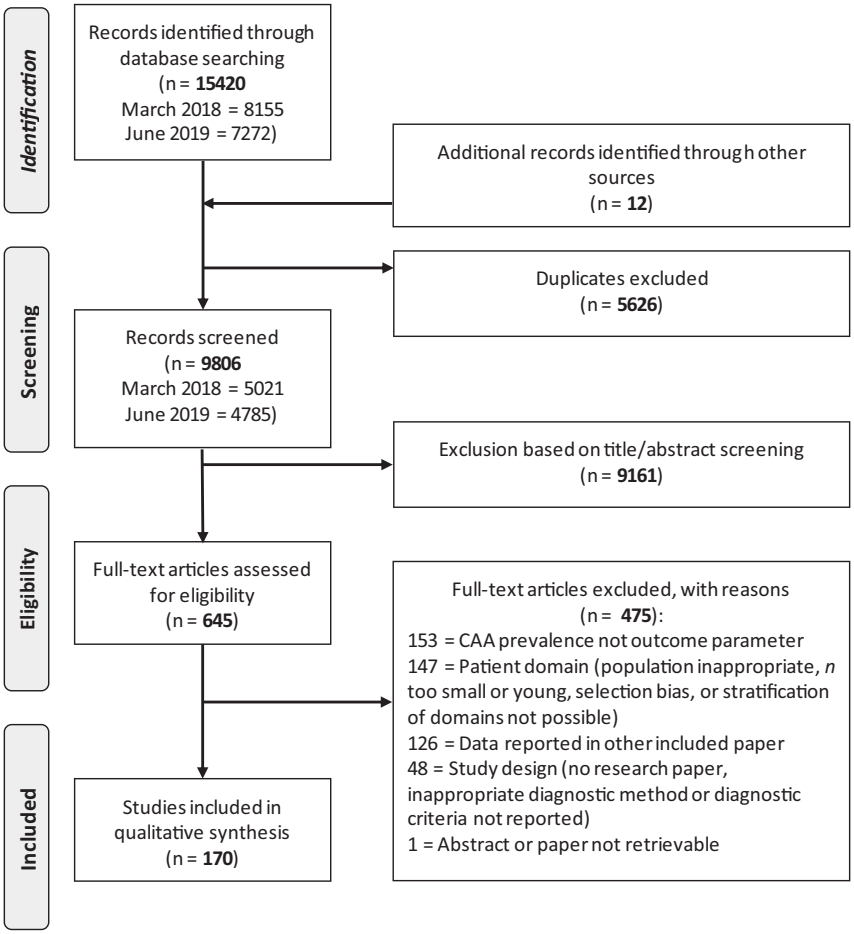
2.1.3 | Data extraction

Two authors independently screened titles and abstracts, assessed full-text articles for eligibility, and extracted relevant data into Covidence systematic review software (Melbourne, Australia).[72] For CAA pathology studies, we considered the prevalence of moderate-to-severe CAA as the primary outcome, since the risk of ICH is higher in individuals with moderate-to-severe CAA compared to individuals with mild CAA,[73] and this stage of CAA pathology has been associated with cognitive impairment during life.[32,35] We also extracted mild-to-severe CAA (including all CAA grades) and severe CAA separately. When the Boston criteria were used for CAA diagnosis, we considered probable CAA as the primary outcome parameter, but also extracted data on the prevalence of possible CAA. For the prevalence of cerebral microbleeds, we considered the prevalence of strictly lobar cerebral microbleeds as the primary outcome, but also extracted the prevalence of mixed cerebral microbleeds, when available. Quality of the studies was independently assessed by two authors using an adapted and combined version (Appendix B) of the quality assessment tool by Hoy and the Newcastle-Ottawa scale.[74,75] The maximum possible score was 18 points, and studies with a score equal to or lower than the median value were considered to be of high quality.

2.1.4 | Data analysis

Statistical analyses were performed using the "meta" and "metafor" packages of R (version 3.4.4). Pooled prevalence estimates of CAA were calculated using Freeman Tukey Double Arcsine transformation and Dersimonian-Laird random-effects models. Heterogeneity was quantified using I^2 statistics, and its significance was determined using Cochran's Q test. We assessed the effects of potential modifiers (Appendix C) of prevalence by meta-regression analysis. The *P*-value of QM statistics was used to indicate the significance of a modifier. Furthermore, overall pooled estimates were recalculated including only high-quality studies. $P < .05$ was considered statistically significant.

FIGURE 1 Flow chart[82] of study selection



2.2 | Results

2.2.1 | Included studies

From a total of 9806 unique records, we included 170 studies that fulfilled the inclusion criteria (Figure 1). There were 100 studies that reported on CAA pathology, 13 on the diagnosis of CAA according to the (modified) Boston criteria, 52 on strictly lobar cerebral microbleeds, and 16 on cortical superficial siderosis (Appendix D).

2.2.2 | Prevalence of CAA and CAA imaging markers

The prevalence of CAA pathology (mild-to-severe, moderate-to-severe, and severe only) is reported in Table 1. The prevalence of clinical CAA according to the Boston criteria, and the prevalence of MRI markers of CAA are reported in Table 2. Most meta-analyses showed substantial heterogeneity.

2.2.3 | Quality of included studies

Quality assessment scores ranged from 0 to 16.5 points (Appendix E). Across neuropathology studies, the median quality assessment score was 4 (interquartile range [IQR]: 3-6) points, 3 (IQR: 2.38-6) across studies reporting the prevalence of CAA according to the (modified) Boston criteria, 1.75 (IQR: 0.75-3) across studies reporting the prevalence of strictly lobar cerebral microbleeds, and 2.75 (IQR: 1-4) across studies reporting the prevalence of cortical superficial siderosis. Meta-analyses of high-quality studies only did not result in significant differences from the main findings (Appendix F).

2.2.4 | Meta-regression analysis

In meta-regression analyses of pathology studies (Appendix G, Table 3), older age was associated with lower prevalence of moderate-to-severe CAA pathology in AD ($P = .004$), but not in other study populations. In meta-regression analyses of MRI studies (Appendix H, Table 4), older age had a statistically significant association with higher prevalence of strictly lobar cerebral microbleeds across all studies (pooling all data, $P < .0001$), and in the subset of studies reporting on cognitively normal elderly ($P < .0001$). MRI parameters contributed significantly to heterogeneity in imaging studies; higher field strength ($P = .01$) and smaller slice thickness ($P < .0001$), but not use of SWI or T2* sequences ($P = .16$), were associated with increased detection of strictly lobar cerebral microbleeds. In population-based studies, but not in any other domains, more recent publications reported higher prevalence of strictly lobar cerebral microbleeds ($P = .023$).

TABLE 3 Meta-regression analyses of the effect of six potential modifiers of prevalence of moderate-to-severe CAA pathology

Modifier	Population	Studies, n	R^2, %	I^2, % (95% CI)	QM(p)
Age	Overall	51	10.30	96.49 (97.02-98.73)	0.74
	Alzheimer's disease	21	28.87	92.24 (84.35-96.03)	**0.004**[a]
	Population	10	0.00	95.99 (89.06-98.74)	0.36
	Cognitively normal elderly	14	15.71	70.85 (39.24-89.56)	0.23
	Intracerebral hemorrhage	4	NA	NA	NA
	Lobar intracerebral hemorrhage	2	NA	NA	NA
Sampling	Overall	35	0.00	95.56 (95.19-98.30)	0.81
	Alzheimer's disease	16	0.00	95.90 (89.08-97.75)	0.81
	Population	5	NA	NA	NA
	Cognitively normal elderly	10	0.00	55.89 (3.80-91.89)	0.63
	Intracerebral hemorrhage	3	NA	NA	NA
	Lobar intracerebral hemorrhage	1	NA	NA	NA
Staining	Overall	49	0.00	97.08 (96.42-98.51)	0.93
	Alzheimer's disease	19	42.47	90.19 (82.79-96.27)	0.16
	Population	8	NA	NA	NA
	Cognitively normal elderly	13	0.00	67.27 (31.32-90.90)	0.42
	Intracerebral hemorrhage	4	NA	NA	NA
	Lobar intracerebral hemorrhage	5	NA	NA	NA
Study design	Population	10	2.21	95.72 (91.08-98.95)	0.97
Diagnosis	Alzheimer's disease	23	3.47	93.83 (88.46-97.04)	0.45
	Cognitively normal elderly	16	17.80	74.56 (45.68-89.97)	0.09
Publication year	Overall	58	0.00	97.08 (97.17-98.72)	0.49
	Alzheimer's disease	23	0.00	94.37 (88.00-96.78)	0.29
	Population	10	7.24	95.54 (91.14-98.96)	0.99
	Cognitively normal elderly	16	0.31	77.77 (56.15-91.75)	0.43
	Intracerebral hemorrhage	4	NA	NA	NA
	Lobar intracerebral hemorrhage	5	NA	NA	NA

Univariable meta-regression analyses for potential modifiers of prevalence estimates of moderate-to-severe CAA. R^2 is the proportion of heterogeneity that can be explained by the modifying factor. The *P*-value of the QM statistics shows whether a potential modifier had a statistically significant effect on prevalence (either a [a]negative or [b]positive association). I^2 statistics and their 95% CIs indicate the residual heterogeneity that cannot be explained by the modifier. Modifiers that significantly affected prevalence are indicated in bold. Scatterplots and box-and-whisker plots illustrating the modifier analyses can be found in Appendix G. NA: not applicable (eg, <10 studies available for modifier analysis).
Abbreviations: CAA, cerebral amyloid angiopathy; CI, confidence interval.

3 | PART 3: DETAILED METHODS AND RESULTS

3.1 | Methods

3.1.1 | Search strategy and selection criteria

We searched EMBASE and PubMed using a comprehensive search strategy on March 20th, 2018. The search syntax was built in consultation with a university librarian with systematic review experience. Controlled search terms (MeSH) terms were combined with free text words. On June 26th, 2019, the search was updated and adjusted to search for additional studies on strictly lobar cerebral microbleeds (see Appendix A for the detailed search strategies). The reference lists of eligible studies and relevant reviews were searched for additional potentially relevant studies. Papers were translated when necessary. References were imported into Endnote (version 9X), which was used to remove duplicates.

3.1.2 | Inclusion and exclusion criteria

The inclusion criteria are described in Part 2: Consolidated methods and results. If a study reported on more than one of the study populations and segregation of data was not possible, the study was excluded.

TABLE 4 Meta-regression analyses of the effect of six potential modifiers of prevalence of strictly lobar cerebral microbleeds

Modifier	Population	Studies, n	R^2, %	I^2, % (95% CI)	QM(p)
Age	Overall	48	16.14	96.77 (96.98-98.81)	<**0.0001**[b]
	Alzheimer's disease	10	0.00	91.65 (91.07-99.03)	0.33
	Population	14	0.00	97.87 (94.28-98.94)	0.06
	Cognitively normal elderly	16	28.19	92.69 (84.54-97.98)	<**0.0001**[b]
	Intracerebral hemorrhage	8	NA	NA	NA
Hypertension	Overall	42	0.00	97.31 (96.47-98.66)	0.25
	Alzheimer's disease	8	NA	NA	NA
	Population	14	0.00	97.97 (95.53-99.18)	0.86
	Cognitively normal elderly	13	7.59	88.05 (84.82-98.38)	0.17
	Intracerebral hemorrhage	7	NA	NA	NA
Field strength	Overall	46	11.34	97.27 (97.78-99.13)	**0.01**[b]
	Alzheimer's disease	11	0.00	90.94 (89.90-98.73)	0.92
	Population	14	2.26	97.78 (95.33-99.16)	0.15
	Cognitively normal elderly	17	45.54	94.45 (92.99-98.61)	**0.0006**[b]
	Intracerebral hemorrhage	4	NA	NA	NA
MRI sequence	Overall	45	0.00	97.64 (98.05-99.23)	0.16
	Alzheimer's disease	9	NA	NA	NA
	Population	14	0.00	97.97 (96.13-99.30)	0.91
	Cognitively normal elderly	16	0.00	97.32 (95.65-99.17)	0.62
	Intracerebral hemorrhage	6	NA	NA	NA
Slice thickness	Overall	42	2.35	95.79 (96.79-98.80)	<**0.0001**[a]
	Alzheimer's disease	11	12.52	89.94 (87.28-98.38)	**0.044**[a]
	Population	12	14.49	96.40 (91.97-98.75)	**0.039**[a]
	Cognitively normal elderly	17	38.49	94.53 (91.41-98.31)	**0.0014**[a]
	Intracerebral hemorrhage	2	NA	NA	NA
Publication year	Overall	54	0.00	97.51 (97.64-98.99)	0.07
	Alzheimer's disease	12	1.16	90.65 (90.13-98.63)	0.17
	Population	14	26.78	97.00 (94.26-98.98)	**0.023**[b]
	Cognitively normal elderly	18	0.00	97.15 (95.63-99.06)	0.31
	Intracerebral hemorrhage	10	0.00	77.91 (45.52-94.14)	0.57

Univariable meta-regression analyses for modifiers of prevalence estimates of strictly lobar cerebral microbleeds. R^2 is the proportion of heterogeneity that can be explained by the modifier. The *P*-value of the QM statistics shows whether a modifier has a statistically significant effect on prevalence (either a [a]negative or [b]positive association). I^2 statistics and their 95% CIs indicate the residual heterogeneity that cannot be explained by the modifier. Modifiers that significantly affected prevalence are indicated in bold. Scatterplots and box-and-whisker plots illustrating the modifier analyses can be found in Appendix H. As no studies were included that reported on the prevalence of strictly lobar cerebral microbleeds in patients with lobar intracerebral hemorrhage, no meta-regression analyses were performed on this population. NA: not applicable (eg, <10 studies available for modifier analysis). CI, confidence interval.

Studies were excluded if they were (1) reviews, conference abstracts, commentaries, editorials, or policy reports; (2) primarily focused on other pathologies as a cause of hemorrhagic neuroimaging markers, such as central nervous system malignancy, vascular malformation, excessive warfarin use, antecedent head trauma or ischemic stroke, vasculitis, blood dyscrasia or coagulopathy; or (3) focused on patients with isolated convexity subarachnoid hemorrhage. If multiple papers reported on overlapping parts of the same cohort, the study reporting on the largest population was included.

3.1.3 | Data extraction

Titles and abstracts were screened by two independent authors (MMV and either LJ or AMK). Full-text articles were independently assessed for eligibility by two authors (LJ and AMK). Disagreement on study eligibility was resolved in consultation with a third researcher (MMV). Extraction was performed by two independent authors (LJ and AMK) and discrepancies were resolved in consultation with a third researcher (MMV or CJMK). Extracted information included data

on study characteristics (publication year, diagnostic method, study design, MRI sequence and parameters, amyloid staining protocol), participant characteristics (age, sex, presence of hypertension), and outcome parameters (see Part 2: Consolidated methods and results, for further details). Quality of the studies was independently assessed by two authors (LJ and AMK) using an adapted and combined version of the quality assessment tool by Hoy and the Newcastle-Ottawa scale,[74,75] which included the following items: (1) representativeness of the sample, (2) recruitment (random selection of patients), (3) appropriateness of outcome parameter definition, (4) reliability and validity of the diagnostic tool, (5) uniformity in method of data collection, (6) appropriate reporting of numerators and denominators (Appendix B). The median quality assessment scores with IQR values for studies on neuropathology, (modified) Boston criteria, microbleeds, and cortical superficial siderosis were calculated separately.

3.1.4 | Data analysis

Pooled prevalence estimates of CAA were calculated using Freeman Tukey Double Arcsine transformation to stabilize variance and to appropriately weigh studies reporting a prevalence of 0%.[76,77] Transformed prevalence estimates were combined in meta-analyses using Dersimonian-Laird random-effects models and later back-transformed for the purpose of interpretation. Meta-analyses were repeated using generalized linear mixed models to confirm the appropriate use of the Freeman Tukey Double Arcsine transformation.[78] Heterogeneity was quantified using I^2 statistics, and its significance was determined using Cochran's Q test to assess whether potential heterogeneity was genuine, or whether variation in findings was due to chance alone.[79] I^2 values >50% in combination with a $P < .1$ for Cochran's Q were considered to represent significant heterogeneity.

We assessed the effects of potential modifiers of prevalence by meta-regression analysis. We chose the modifiers a priori based on hypothetical sources of heterogeneity (Appendix C). For neuropathological studies, we assessed in univariable meta-regression models the effect of: (1) age (mean, or if not available median or midpoint of age range), (2) number of cortical lobes examined, (3) method of amyloid staining (immunohistochemistry vs amyloid staining [by Congo Red or Thioflavin], or both), (4) study sample (population- or registry-based studies vs clinical sample-based studies), (5) method of diagnosis (clinical diagnosis vs neuropathological diagnosis of AD, and of cognitively normal elderly), (6) publication year. For neuroimaging studies, we assessed in univariable meta-regression analyses the effect on the reported prevalence of strictly lobar cerebral microbleeds of: (1) age (mean, or if not available median or midpoint of age range), (2) history of hypertension, (3) MRI field strength, (4) MRI slice thickness, (5) MRI sequence (T2* vs SWI), (6) publication year. If data were missing for a specific variable, that study was excluded from analyses. Univariable meta-regression analyses were performed only if ten or more studies were available for analysis. To quantify the results of modifier analyses, R^2 was used to indicate the proportion of heterogeneity that could be explained by a potential modifier, the *P*-value of QM statistics was used to indicate the significance of a modifier ($P < .05$ was considered statistically significant), and I^2 was used to indicate the residual heterogeneity that could not be explained by the modifier.

A series of influence analyses was conducted. Leave-one-out analyses were performed, in which every study was consecutively excluded once to assess its influence on overall pooled estimates. Studentized residual inspections[80] and Baujat plots[81] were used to detect studies that contributed substantially to heterogeneity and overall results. Studies were considered to contribute excessively to the heterogeneity if studentized residuals were larger than two or if they appeared in the top right quadrant of Baujat plots. Overall pooled estimates were then recalculated, excluding these influential studies, and results were compared with the main findings. Furthermore, overall pooled estimates were recalculated including only high-quality studies. In case a set of studies included five studies or fewer, the number of studies was deemed too low for meaningful recalculation of the pooled prevalence estimates of high-quality studies only. To detect potential publication bias and small study effects, funnel plots were visually inspected and funnel plot asymmetry was tested using unweighted regression tests. In case a set of studies included five studies or fewer, funnel plots and regression tests were not conducted. $P < .05$ was considered statistically significant.

3.2 | Results

Out of 9806 identified unique records, 170 studies fulfilled the inclusion criteria (Figure 1). Individual study characteristics are summarized in Appendix D. The quality assessment of these studies is shown in Appendix E. See Part 2: Consolidated methods and results for more details on the quality assessment.

Funnel plots neither showed publication bias, nor small study effects, except for studies reporting on the prevalence of strictly lobar cerebral microbleeds and cortical superficial siderosis in AD patients, as smaller studies tended to report a higher prevalence (Appendix I).

In AD patients, the pooled prevalence of moderate-to-severe CAA was 47.5% (95% confidence interval [CI]: 38.8-56.2, Figure 2A). Prevalence of CAA according to the (modified) Boston criteria was only reported in one study (14.3%). The pooled prevalence of strictly lobar cerebral microbleeds was 21.8% (95% CI: 16.3-27.8, Figure 2B), and of cortical superficial siderosis 5.3% (95% CI: 3.6-7.2, Figure 2C).

In population-based cohorts, the pooled prevalence of moderate-to-severe CAA pathology was 23.0% (95% CI: 17.3-29.1, Figure 3A). CAA according to the (modified) Boston criteria was not assessed in population-based cohorts. The pooled prevalence of strictly lobar cerebral microbleeds detected by MRI was 7.1% (95% CI: 4.9-9.8, Figure 3B). The pooled prevalence of cortical superficial siderosis was 0.8% (95% CI: 0.5-1.2, Figure 3C).

In cognitively normal elderly, the pooled prevalence of moderate-to-severe CAA was 6.4% (95% CI: 3.2-10.5, Figure 4A). The pooled prevalence of probable CAA according to the (modified) Boston criteria was 5.1% (95% CI: 0.0-31.2, Figure 4B). The pooled prevalence of strictly lobar cerebral microbleeds was 6.6% (95% CI: 3.8-10.1, Figure 4C). The

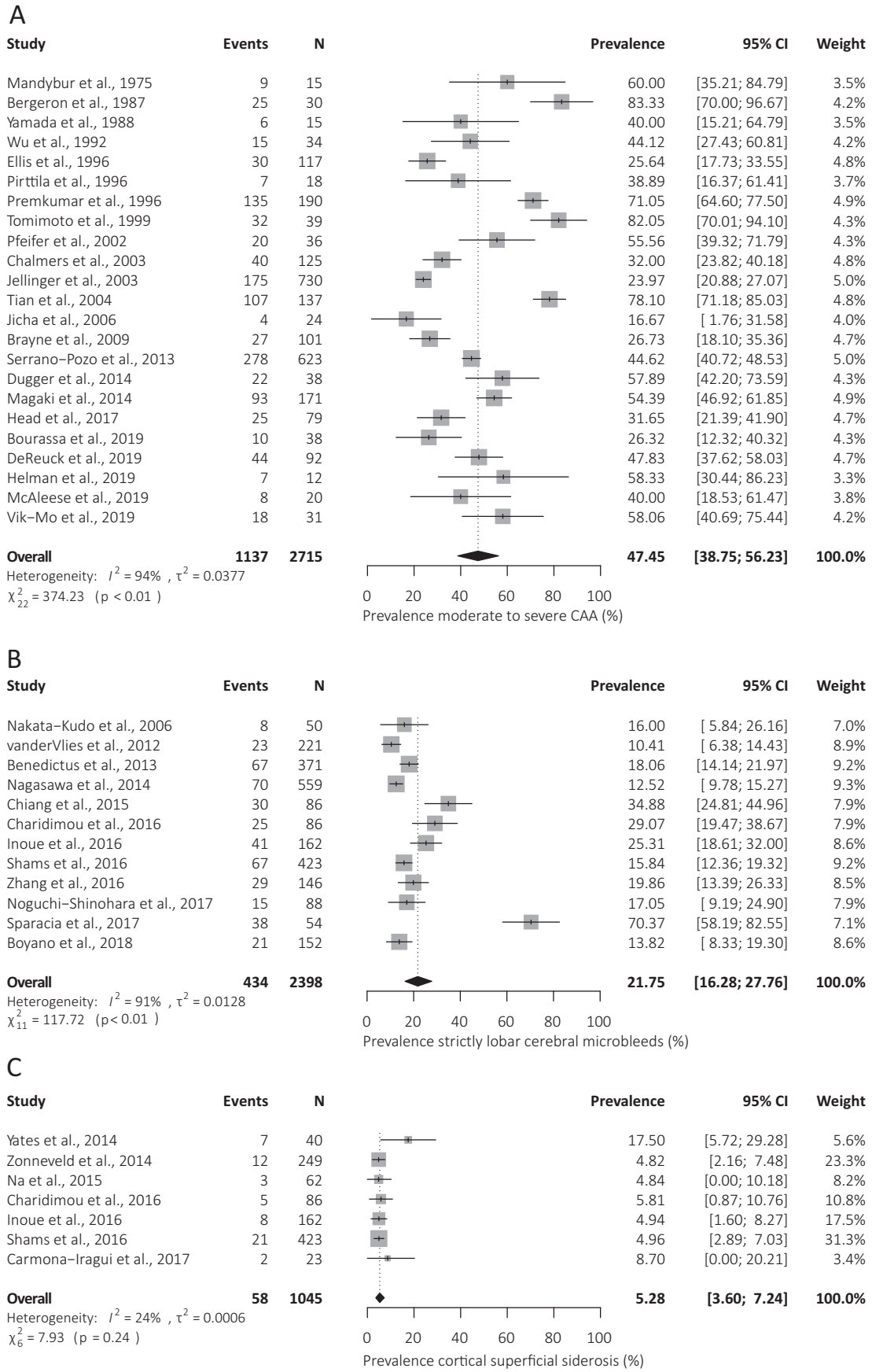


FIGURE 2 Forest plots showing the prevalence in Alzheimer's disease patients of moderate-to-severe cerebral amyloid angiopathy (CAA) pathology (A), strictly lobar cerebral microbleeds (B), and cortical superficial siderosis (C). CAA, cerebral amyloid angiopathy

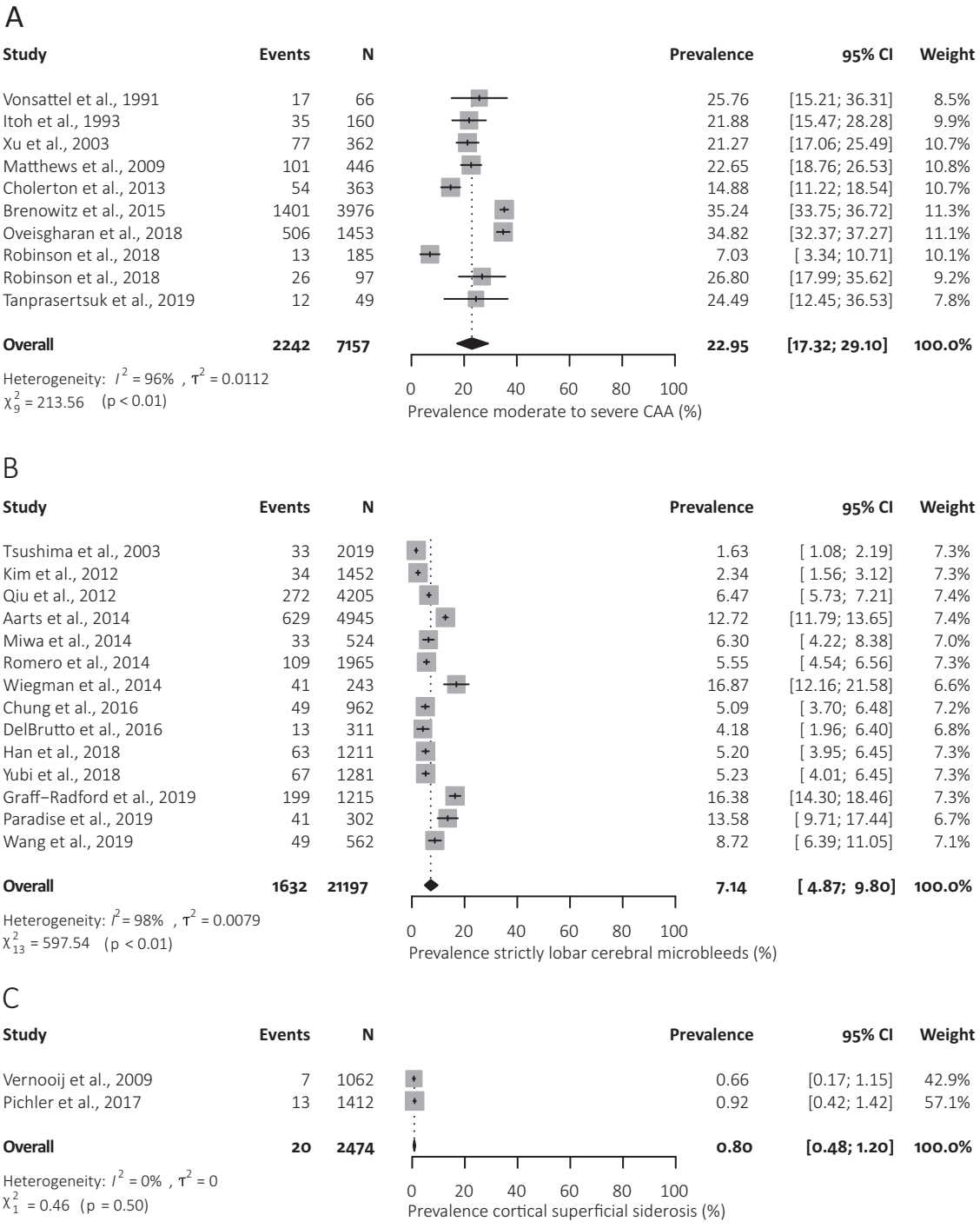


FIGURE 3 Forest plots showing the prevalence in the general population of moderate-to-severe cerebral amyloid angiopathy (CAA) pathology (A), strictly lobar cerebral microbleeds (B), and cortical superficial siderosis (C). CAA, cerebral amyloid angiopathy

pooled prevalence of cortical superficial siderosis was 0.5% (95% CI: 0.0-1.5, Figure 4D).

In patients with ICH, the pooled prevalence of moderate-to-severe CAA was 24.1% (95% CI: 3.8-54.1, Figure 5A). The pooled prevalence of probable CAA according to the (modified) Boston criteria was 20.2% (95% CI: 9.5-33.7, Figure 5B). The pooled prevalence of strictly lobar cerebral microbleeds was 19.2% (95% CI: 14.6-24.1 Figure 5C), and of cortical superficial siderosis 15.6% (95% CI: 8.9-23.7, Figure 5D).

In patients with lobar ICH, the pooled prevalence of moderate-to-severe CAA was 56.7% (95% CI: 41.7-71.0, Figure 6A). The prevalence of probable CAA according to the (modified) Boston criteria was 49.6% (95% CI: 29.1-70.3 Figure 6B). No studies evaluated the prevalence of strictly lobar cerebral microbleeds in patients with lobar ICH. The

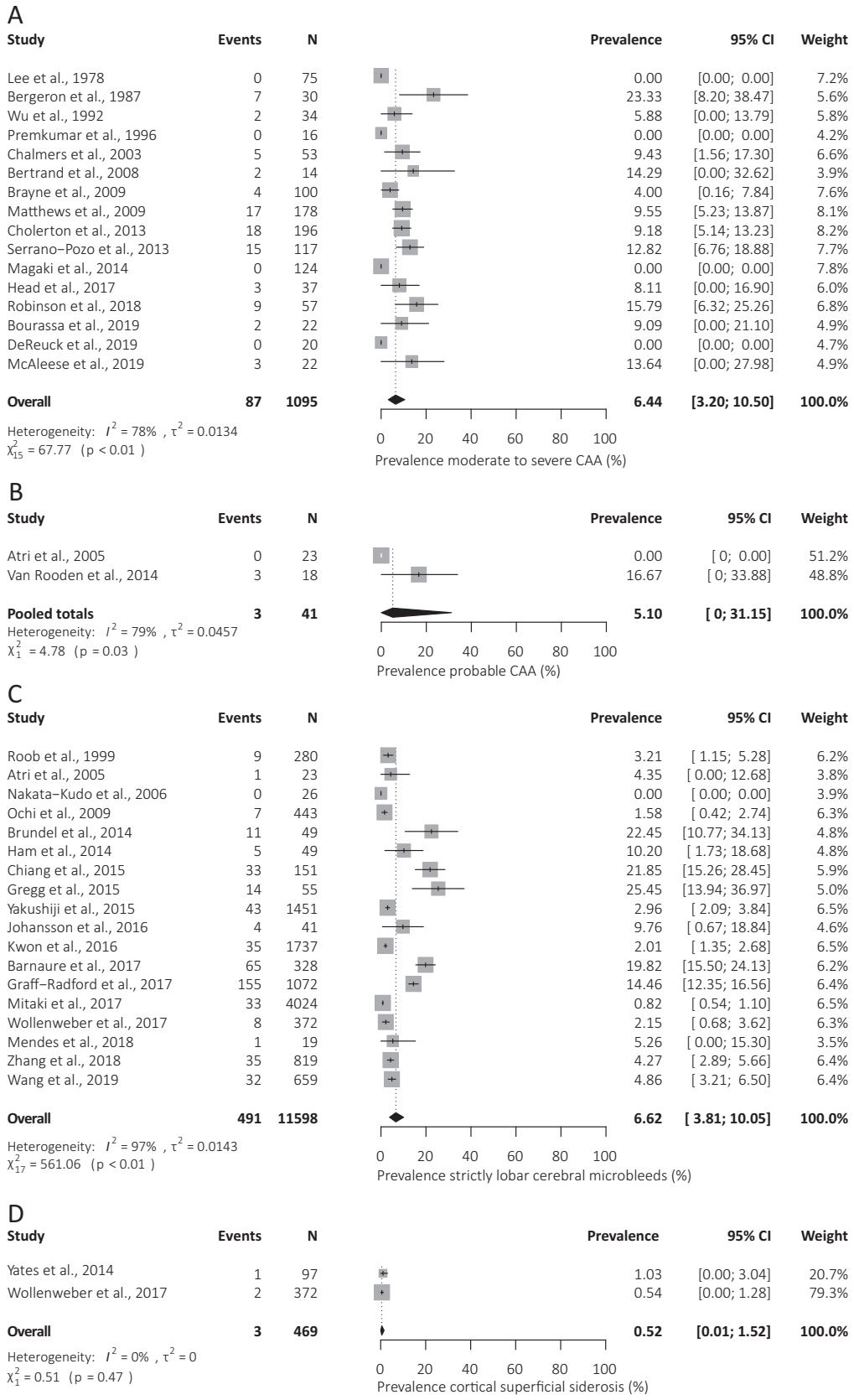


FIGURE 4 Forest plots showing the prevalence in cognitively normal elderly of moderate-to-severe cerebral amyloid angiopathy (CAA) pathology (A), probable CAA according to the (modified) Boston criteria (B), strictly lobar cerebral microbleeds (C), and cortical superficial siderosis (D). CAA, cerebral amyloid angiopathy

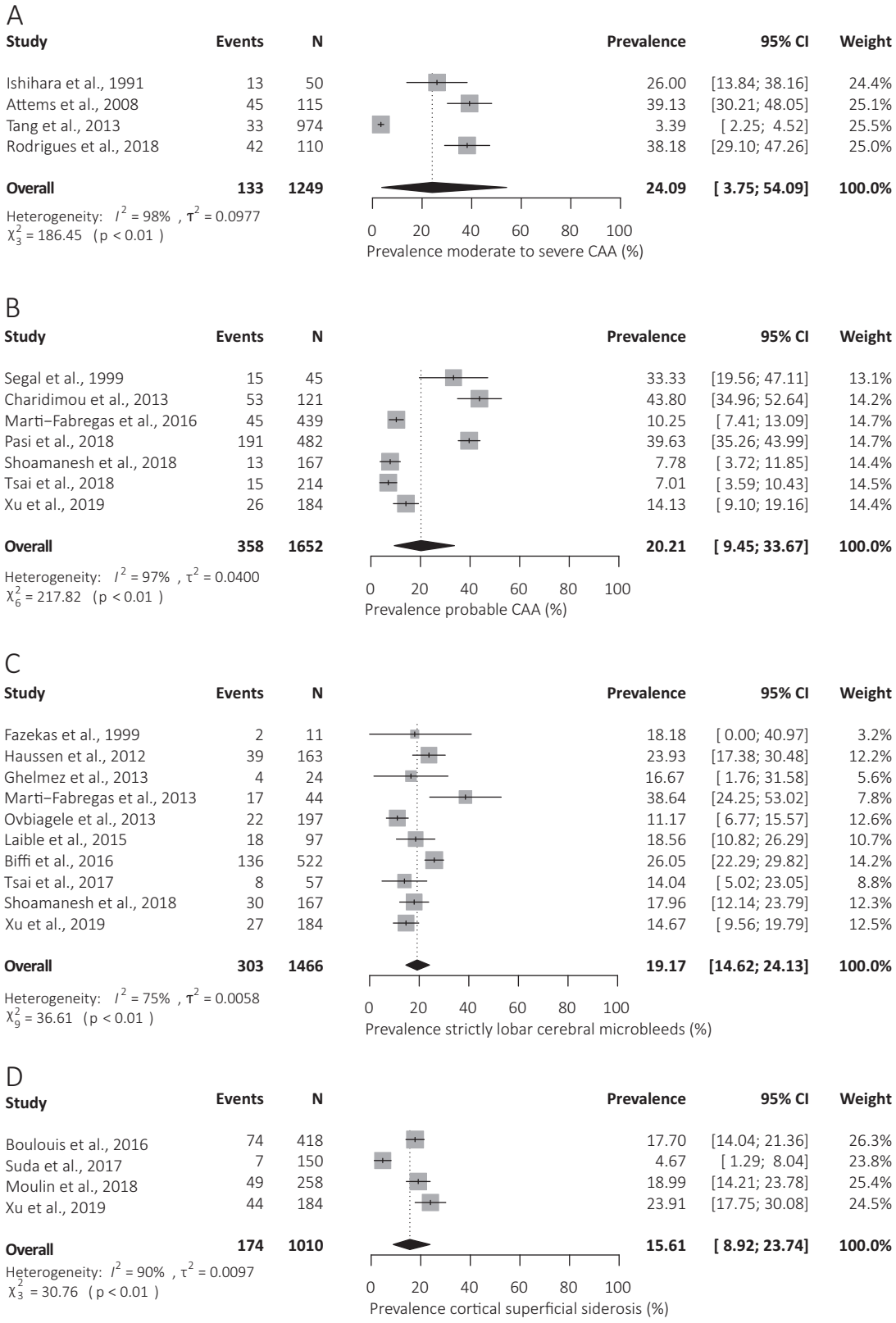


FIGURE 5 Forest plots showing the prevalence in patients with intracerebral hemorrhage of moderate-to-severe cerebral amyloid angiopathy (CAA) pathology (A), probable CAA according to the (modified) Boston criteria (B), strictly lobar cerebral microbleeds (C), and cortical superficial siderosis (D). CAA, cerebral amyloid angiopathy

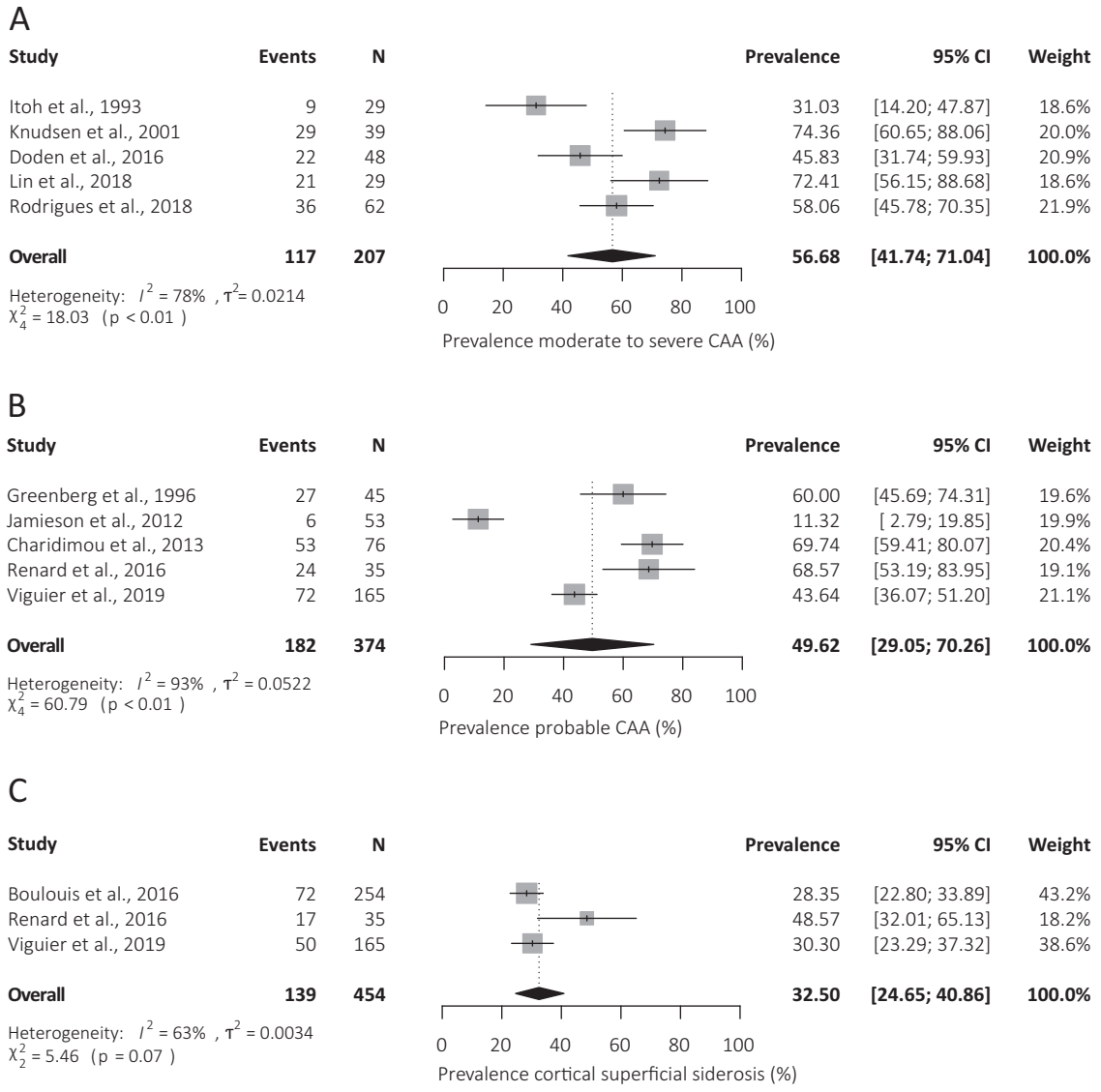


FIGURE 6 Forest plots showing the prevalence in patients with lobar intracerebral hemorrhage of moderate-to-severe cerebral amyloid angiopathy (CAA) pathology (A), probable CAA according to the (modified) Boston criteria (B), and cortical superficial siderosis (C). CAA, cerebral amyloid angiopathy

pooled prevalence of cortical superficial siderosis was 32.5% (95% CI: 24.7-40.9, Figure 6C).

For the results of meta-regression analyses of pathology studies, we refer to Appendix G, Table 3, and for the results of meta-regression analyses of MRI studies, we refer to Appendix H, Table 4. Part 2: Consolidated methods and results contains a discussion on the statistically significant modifiers of CAA prevalence in pathology and MRI studies. Here, we discuss results for modifiers that did not significantly affect CAA prevalence. We found that in pathology studies, neither the number of investigated cortical regions, type of amyloid staining, type of study design, definition (clinical vs neuropathological) of AD or cognitively normal elderly, nor publication year affected the prevalence of moderate-to-severe CAA. In imaging studies, we found no effect of the use of SWI or T2* sequence, or the percentage of individuals with hypertension, on the prevalence of strictly lobar cerebral microbleeds.

Meta-analyses using generalized linear mixed models yielded similar pooled estimates (the 95% CIs substantially overlapped and point estimates of prevalence were comparable) as the main random effects model using the double arsine transformation (Appendix J). Leave-one-out analyses and removal of multiple outliers only slightly altered the overall pooled estimates in some groups (Appendix K).

ACKNOWLEDGMENTS

We thank Alice Tillema for her help in designing the search strategies. We thank Janna Schulze for her help with translating the Japanese articles and Mengfei Cai for his assistance with translating the Chinese articles. We thank Rodin Aarssen for his assistance with

R programming, and Jan Willem van Dalen for his advice on statistical methods. This work was supported by the BIONIC project (no. 733050822, which has been made possible by ZonMW as part of "Memorabel," the research and innovation program for dementia, as part of the Dutch national "Deltaplan for Dementia": zonmw.nl/dementiaresearch), the CAFÉ project (the National Institutes of Health, USA, grant number 5R01NS104147-02), and a grant from the Selfridges Group Foundation (NR170024). The BIONIC project is a consortium of Radboudumc, LUMC, ADX Neurosciences, and Rhode Island University. CJM Klijn is supported by a clinical established investigator grant of the Dutch Heart Foundation (grant 2012T077) and an ASPASIA grant from The Netherlands Organization for Health Research and Development, ZonMW (grant 015008048). F.H.B.M. Schreuder is supported by a senior clinical scientist grant of the Dutch Heart Foundation (grant 2019T060).

REFERENCES

1. Attems J, Jellinger K, Thal DR, Van Nostrand W. Review: sporadic cerebral amyloid angiopathy. *Neuropathol Appl Neurobiol*. 2011;37:75-93.
2. van Etten ES, Gurol ME, van der Grond J, et al. Recurrent hemorrhage risk and mortality in hereditary and sporadic cerebral amyloid angiopathy. *Neurology*. 2016;87:1482-1487.
3. 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;16:30-42.
4. Glenner GG, Henry JH, Fujihara S. Congophilic angiopathy in the pathogenesis of Alzheimer's degeneration. *Ann Pathol*. 1981;1:120-129.
5. Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature*. 2016;537:50-56.
6. Greenberg SM, Vonsattel JP, Stakes JW, Gruber M, Finklestein SP. The clinical spectrum of cerebral amyloid angiopathy: presentations without lobar hemorrhage. *Neurology*. 1993;43:2073-2079.
7. Wermer MJH, Greenberg SM. The growing clinical spectrum of cerebral amyloid angiopathy. *Curr Opin Neurol*. 2018;31:28-35.
8. Yakupova EI, Bobyleva LG, Vikhlyantsev IM, Bobylev AG. Congo Red and amyloids: history and relationship. *Biosci Rep*. 2019;39:BSR20181415.
9. Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology*. 2010;74:1346.
10. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. *Neurology*. 2001;56:537-539.
11. Vernooij MW, van der Lugt A, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. *Neurology*. 2008;70:1208-1214.
12. Kim SW, Chung SJ, Oh YS, et al. Cerebral microbleeds in patients with dementia with Lewy bodies and Parkinson disease dementia. *AJNR Am J Neuroradiol*. 2015;36:1642-1647.
13. 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.
14. Vernooij MW, Ikram MA, Hofman A, Krestin GP, Breteler MM, van der Lugt A. Superficial siderosis in the general population. *Neurology*. 2009;73:202-205.
15. Genisman RV, Oksova EE. [Morphologic diagnosis of vascular and senile dementia (the significance of Congophilic angiopathy)]. *Zh Nevropatol Psikhiatr Im S S Korsakova*. 1988;88:35-39.
16. Joachim CL, Morris JH, Selkoe DJ. Clinically diagnosed Alzheimer's disease: autopsy results in 150 cases. *Ann Neurol*. 1988;24:50-56.
17. Parker JC Jr, Philpot J. Postmortem evaluation of Alzheimer's disease. *South Med J*. 1985;78:1411-1413.
18. Ritter MA, Droste DW, Hegedüs K, et al. Role of cerebral amyloid angiopathy in intracerebral hemorrhage in hypertensive patients. *Neurology*. 2005;64:1233-1237.
19. De Reuck J. The impact of cerebral amyloid angiopathy in various neurodegenerative dementia syndromes: a neuropathological study. *Neurol Res Int*. 2019;2019:7247325.
20. Tanskanen M, Mäkelä M, Myllykangas L, et al. Prevalence and severity of cerebral amyloid angiopathy: a population-based study on very elderly Finns (Vantaa 85+). *Neuropathol Appl Neurobiol*. 2012;38:329-336.
21. Robinson JL, Corrada MM, Kovacs GG, et al. Non-Alzheimer's contributions to dementia and cognitive resilience in The 90+ Study. *Acta Neuropathol*. 2018;136:377-388.
22. Nicoll JA, Wilkinson D, Holmes C, Steart P, Markham H, Weller RO. Neuropathology of human Alzheimer disease after immunization with amyloid-beta peptide: a case report. *Nat Med*. 2003;9:448-452.
23. Patton RL, Kalback WM, Esh CL, et al. Amyloid-beta peptide remnants in AN-1792-immunized Alzheimer's disease patients: a biochemical analysis. *Am J Pathol*. 2006;169:1048-1063.
24. Nicoll JA, Barton E, Boche D, et al. Abeta species removal after abeta42 immunization. *J Neuropathol Exp Neurol*. 2006;65:1040-1048.
25. Sperling RA, Jack CR Jr, Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement*. 2011;7:367-385.
26. Pettersen JA, Sathiyamoorthy G, Gao FQ, et al. Microbleed topography, leukoaraiosis, and cognition in probable Alzheimer disease from the Sunnybrook dementia study. *Arch Neurol*. 2008;65:790-795.
27. Nakata-Kudo Y, Mizuno T, Yamada K, et al. Microbleeds in Alzheimer disease are more related to cerebral amyloid angiopathy than cerebrovascular disease. *Dement Geriatr Cogn Disord*. 2006;22:8-14.
28. Cordonnier C, van der Flier WM. Brain microbleeds and Alzheimer's disease: innocent observation or key player? *Brain*. 2011;134:335-344.
29. Noguchi-Shinohara M, Komatsu J, Samuraki M, et al. Cerebral amyloid angiopathy-related microbleeds and cerebrospinal fluid biomarkers in Alzheimer's disease. *J Alzheimers Dis*. 2017;55:905-913.
30. Verbeek MM, Kremer BP, Rikkert MO, Van Domburg PH, Skehan ME, Greenberg SM. Cerebrospinal fluid amyloid beta(40) is decreased in cerebral amyloid angiopathy. *Ann Neurol*. 2009;66:245-249.
31. Goos JD, Kester MI, Barkhof F, et al. Patients with Alzheimer disease with multiple microbleeds: relation with cerebrospinal fluid biomarkers and cognition. *Stroke*. 2009;40:3455-3460.
32. Boyle PA, Yu L, Nag S, et al. Cerebral amyloid angiopathy and cognitive outcomes in community-based older persons. *Neurology*. 2015;85:1930-1936.
33. Pfeifer LA, White LR, Ross GW, Petrovitch H, Launer LJ. Cerebral amyloid angiopathy and cognitive function: the HAAS autopsy study. *Neurology*. 2002;58:1629-1634.
34. Case NF, Charlton A, Zwiers A, et al. Cerebral amyloid angiopathy is associated with executive dysfunction and mild cognitive impairment. *Stroke*. 2016;47:2010-2016.
35. 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;69:320-327.
36. Banerjee G, Wilson D, Ambler G, et al. Cognitive impairment before intracerebral hemorrhage is associated with cerebral amyloid angiopathy. *Stroke*. 2018;49:40-45.
37. Charidimou A, Peeters A, Fox Z, et al. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis. *Stroke*. 2012;43:2324-2330.

38. Charidimou A, Baron J-C, Werring DJ. Transient focal neurological episodes, cerebral amyloid angiopathy, and intracerebral hemorrhage risk: looking beyond TIAs. *Int J Stroke*. 2013;8:105-108.
39. Illsley A, Ramadan H. Cerebral amyloid angiopathy: a transient ischaemic attack mimic. *Clin Med (Lond)*. 2014;14:255-259.
40. Chung CP, Chou KH, Chen WT, et al. Strictly lobar cerebral microbleeds are associated with cognitive impairment. *Stroke*. 2016;47:2497-2502.
41. Poels MMF, Ikram MA, van der Lugt A, et al. Cerebral microbleeds are associated with worse cognitive function: the Rotterdam Scan Study. *Neurology*. 2012;78:326-333.
42. Akoudad S, Portegies ML, Koudstaal PJ, et al. Cerebral microbleeds are associated with an increased risk of stroke: the Rotterdam study. *Circulation*. 2015;132:509-516.
43. Wilson D, Charidimou A, Ambler G, et al. Recurrent stroke risk and cerebral microbleed burden in ischemic stroke and TIA: a meta-analysis. *Neurology*. 2016;87:1501-1510.
44. Gregg NM, Kim AE, Gurol ME, et al. Incidental cerebral microbleeds and cerebral blood flow in elderly individuals. *JAMA Neurol*. 2015;72:1021-1028.
45. Altmann-Schneider I, Trompet S, de Craen AJ, et al. Cerebral microbleeds are predictive of mortality in the elderly. *Stroke*. 2011;42:638-644.
46. Greenberg SM, Charidimou A. Diagnosis of cerebral amyloid angiopathy: evolution of the Boston criteria. *Stroke*. 2018;49:491-497.
47. Martinez-Ramirez S, Romero J-R, Shoamanesh A, et al. Diagnostic value of lobar microbleeds in individuals without intracerebral hemorrhage. *Alzheimers Dement*. 2015;11:1480-1488.
48. Jolink WMT, Wiegertjes K, Rinkel GJE, Algra A, de Leeuw F-E, Klijn CJM. Location-specific risk factors for intracerebral hemorrhage: systematic review and meta-analysis. *Neurology*. 2020;95:e1807-e1818.
49. Tsai HH, Pasi M, Tsai LK, et al. Microangiopathy underlying mixed-location intracerebral hemorrhages/microbleeds: a PiB-PET study. *Neurology*. 2019;92:e774-e781.
50. Blanc C, Viguier A, Calviere L, et al. Underlying small vessel disease associated with mixed cerebral microbleeds. *Front Neurol*. 2019;10:1126.
51. Charidimou A, Boulouis G, Xiong L, et al. Cortical superficial siderosis and first-ever cerebral hemorrhage in cerebral amyloid angiopathy. *Neurology*. 2017;88:1607-1614.
52. Cordonnier C, Leys D, Dumont F, et al. What are the causes of pre-existing dementia in patients with intracerebral haemorrhages? *Brain*. 2010;133:3281-3289.
53. Viswanathan A, Patel P, Rahman R, et al. Tissue microstructural changes are independently associated with cognitive impairment in cerebral amyloid angiopathy. *Stroke*. 2008;39:1988-1992.
54. van Opstal AM, van Rooden S, van Harten T, et al. Cerebrovascular function in presymptomatic and symptomatic individuals with hereditary cerebral amyloid angiopathy: a case-control study. *Lancet Neurol*. 2017;16:115-122.
55. Schultz AP, Kloet RW, Sohrabi HR, et al. Amyloid imaging of dutch-type hereditary cerebral amyloid angiopathy carriers. *Ann Neurol*. 2019;86:616-625.
56. Charidimou A, Friedrich JO, Greenberg SM, Viswanathan A. Core cerebrospinal fluid biomarker profile in cerebral amyloid angiopathy: a meta-analysis. *Neurology*. 2018;90:e754-e762.
57. Banerjee G, Ambler G, Keshavan A, et al. Cerebrospinal fluid biomarkers in cerebral amyloid angiopathy. *J Alzheimers Dis*. 2020;74:1189-1201.
58. Kuiperij HB, Hondius DC, Kersten I, et al. Apolipoprotein D: a potential biomarker for cerebral amyloid angiopathy. *Neuropathol Appl Neurobiol*. 2020;46:431–440.
59. Greenberg SM, Al-Shahi Salman R, Biessels GJ, et al. Outcome markers for clinical trials in cerebral amyloid angiopathy. *Lancet Neurol*. 2014;13:419-428.
60. van Rooden S, van Opstal AM, Labadie G, et al. Early magnetic resonance imaging and cognitive markers of hereditary cerebral amyloid angiopathy. *Stroke*. 2016;47:3041-3044.
61. Martinez-Ramirez S, van Rooden S, Charidimou A, et al. Perivascular spaces volume in sporadic and hereditary (Dutch-Type) cerebral amyloid angiopathy. *Stroke*. 2018;49:1913-1919.
62. Jäkel L, Kuiperij HB, Gerding LP, et al. Disturbed balance in the expression of MMP9 and TIMP3 in cerebral amyloid angiopathy-related intracerebral haemorrhage. *Acta Neuropathologica Communications*. 2020;8:99.
63. Poels MM, Vernooij MW, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. *Stroke*. 2010;41:S103-S106.
64. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol*. 2009;8:165-174.
65. Nandigam RNK, Viswanathan A, Delgado P, et al. MR imaging detection of cerebral microbleeds: effect of susceptibility-weighted imaging, section thickness, and field strength. *AJNR Am J Neuroradiol*. 2009;30:338-343.
66. Cheng AL, Batool S, McCreary CR, et al. Susceptibility-weighted imaging is more reliable than T2*-weighted gradient-recalled echo MRI for detecting microbleeds. *Stroke*. 2013;44:2782-2786.
67. Shams S, Martola J, Cavallin L, et al. SWI or T2*: which MRI sequence to use in the detection of cerebral microbleeds? The Karolinska Imaging Dementia Study. *AJNR Am J Neuroradiol*. 2015;36:1089-1095.
68. Love S, Chalmers K, Ince P, et al. Development, appraisal, validation and implementation of a consensus protocol for the assessment of cerebral amyloid angiopathy in post-mortem brain tissue. *Am J Neurodegener Dis*. 2014;3:19-32.
69. Olichney JM, Hansen LA, Galasko D, et al. The apolipoprotein E epsilon 4 allele is associated with increased neuritic plaques and cerebral amyloid angiopathy in Alzheimer's disease and Lewy body variant. *Neurology*. 1996;47:190-196.
70. Ellis RJ, Olichney JM, Thal LJ, et al. Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD experience, Part XV. *Neurology*. 1996;46:1592-1596.
71. Vonsattel JPG, Myers RH, Hedley-whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. *Ann Neurol*. 1991;30:637-649.
72. Misra UK, Kalita J, Ranjan P, Mandal SK. Mannitol in intracerebral hemorrhage: a randomized controlled study. *J Neurol Sci*. 2005;234:41-45.
73. Charidimou A, Gang Q, Werring DJ. Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum. *J Neurol Neurosurg Psychiatry*. 2012;83:124-137.
74. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol*. 2012;65:934-939.
75. Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 25, 2019.
76. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health*. 2013;67:974-978.
77. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *The Annals of Mathematical Statistics*. 1950;21:607-611.

78. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. *Res Synth Methods*. 2019;10:476-483.
79. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
80. Viechtbauer W, Cheung MW. Outlier and influence diagnostics for meta-analysis. *Res Synth Methods*. 2010;1:112-125.
81. Baujat B, Mahé C, Pignon JP, Hill C. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. *Stat Med*. 2002;21:2641-2652.
82. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group, The PG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.

SUPPORTING INFORMATION

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

How to cite this article: Jäkel L, De Kort AM, Klijn CJM, Schreuder FHBM, Verbeek MM. Prevalence of cerebral amyloid angiopathy: A systematic review and meta-analysis. *Alzheimer's Dement*. 2022;18:10–28.
https://doi.org/10.1002/alz.12366