



Review

The cross-sectional association between amyloid burden and white matter hyperintensities in older adults without cognitive impairment: A systematic review and meta-analysis

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia, characterized by the aggregation of amyloid-beta (A β) proteins into plaques. Individuals with AD frequently show mixed pathologies, often caused by cerebral small vessel disease (CSVD), resulting in lesions such as white matter hyperintensities (WMH). The current systematic review and meta-analysis investigated the cross-sectional relationship between amyloid burden and WMH in older adults without objective cognitive impairment. A systematic search performed in PubMed, Embase, and PsycINFO yielded 13 eligible studies. A β was assessed using PET, CSF, or plasma measurements. Two meta-analyses were performed: one on Cohen's d metrics and one on correlation coefficients. The meta-analyses revealed an overall weighted small-to-medium Cohen's d of 0.55 (95% CI: 0.31–0.78) in CSF, an overall correlation of 0.31 (0.09–0.50) in CSF, and a large Cohen's d of 0.96 (95% CI: 0.66–1.27) in PET. Only two studies assessed this relationship in plasma, with an effect size of –0.20 (95% CI: –0.75 to 0.34). These findings indicate a relationship between both amyloid and vascular pathologies in cognitively normal adults in PET and CSF. Future studies should assess the possible relationship of blood amyloid-beta and WMH for broader identification of at risk individuals showing mixed pathology in preclinical stages.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by declining cognitive functioning and quality of life, accounting for 60–80% of all dementia cases (Alzheimer's, 2022). The pathogenesis of AD begins two to three decades before the onset of clinical symptoms, providing opportunity for prevention and intervention. Further, AD pathology rarely occurs in isolation and is typically due to mixed pathology, in which brain changes are associated with multiple causes contributing to dementia (Schneider et al., 2007).

AD pathology includes aggregation of amyloid-beta (A β) protein in

the brain as well as vascular lesions, where blood vessels in the brain and/or brain tissue are damaged due to not receiving enough oxygen, blood, or nutrients. Cerebral small vessel disease (CSVD) refers to a group of diseases that affect these small cerebral blood vessels (Pantoni, 2010). One marker of CSVD, visualized on magnetic resonance imaging (MRI), includes white matter hyperintensities (WMH). WMH are common in healthy older adults and are associated with increasing age (de Leeuw et al., 2001). Additionally, WMH are more frequently present in individuals with AD (Sarabia-Cobo et al., 2014) and are also associated with an increased risk of AD (Liu et al., 2018). The severity of WMH increases faster over time in individuals with AD compared to healthy

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older adults (Lo and Jagust, 2012) and are also associated with worse cognitive functioning (Diaz et al., 1991; van den Berg et al., 2018). In individuals with AD, amyloid burden is associated with WMH (Liu et al., 2018; Provenzano et al., 2013; van Westen et al., 2016). Moreover, AD is associated with increased WMH long before the expected onset of symptoms (Lee et al., 2016), suggesting WMH may play a role in the preclinical stage of AD. However, previous literature assessing the association between amyloid burden and WMH has shown conflicting results in older adults both with and without cognitive impairment. While some studies found that higher amyloid burden was related to more WMH (Brickman et al., 2015a; Kandel et al., 2016; Osborn et al., 2018; Skoog et al., 2018; van Leijssen et al., 2018; van Westen et al., 2016), other studies did not detect such a relationship (Dupont et al., 2020; Gurol et al., 2013; Hedden et al., 2012; Jonsson et al., 2010; Kaffashian et al., 2014; Schreiner et al., 2018; van Leijssen et al., 2018; van Waalwijk van Doorn et al., 2021; van Westen et al., 2016; Yi et al., 2018). While AD pathology and vascular pathology could be independent processes, a previous literature review (Roseborough et al., 2017) highlighted that a relation may still exist and is blurred by differences in methods between studies. Further, there have been conflicting results when assessing amyloid in different modalities or within different isoforms. For example, van Westen et al. (2016) reported a significant association only for plasma A β 38 and A β 40, but not for plasma A β 42 or when using 18 F positron emission topography (PET). Brickman et al. (2015a) found a significant association only when observing amyloid categorically, not continuously. Therefore, a systematic review and meta-analysis that explores these methodological differences and their impact on the association between amyloid-beta and WMH is warranted.

Three previous systematic reviews (Kim et al., 2020; Liu et al., 2018; Roseborough et al., 2017), one including a meta-analysis (Liu et al., 2018), investigated the cross-sectional association between amyloid and WMH in older adults without cognitive impairment. Two reviews found no association between amyloid and WMH in cognitively unimpaired older adults (Liu et al., 2018; Roseborough et al., 2017). However, one review (Roseborough et al., 2017) only included studies using PET imaging to assess amyloid burden; while the other review (Liu et al., 2018) only included two studies in the meta-analysis. The most recent review (Kim et al., 2020) included 14 studies that assessed amyloid, and all but two found a significant relationship between the two pathologies. Further, only three studies solely focused on cognitively unimpaired individuals. By focusing on cognitively unimpaired individuals in the current review and multiple modalities of amyloid assessment, we can better quantify the relationship between the two leading pathologies of AD during its extended preclinical stage. In this current systematic review and meta-analysis, we investigated the cross-sectional relationship between amyloid burden and WMH in older adults without objective cognitive impairment. Systematic evidence for the presence or absence of an association between amyloid and WMH in cognitively unimpaired older adults could provide more insight into the pathogenesis of AD and its relationship with CSVD in the preclinical stage of AD.

2. Methods

This systematic review and meta-analysis was performed following the PRISMA guidelines (Moher et al., 2009) (Supplementary Info 1).

2.1. Search and study selection

A search string for studies that investigated the association between amyloid and WMH in older adults without cognitive impairment was developed in consultation with a librarian (P.W., acknowledgments) for PubMed, and it was subsequently translated to Embase and PsycINFO (Supplementary Info 2). On May 7, 2021, the MEDLINE, Embase and PsycINFO databases were searched, after which duplicates were removed with EndNote (v. 20.2) (The EndNote Team, 2013) reference management software. Subsequently, two reviewers (E.T. and B.M.)

independently screened titles and abstracts using the Rayyan app (Ouzzani et al., 2016) to assess eligibility. Full texts of the remaining articles were retrieved and screened against eligibility criteria. Any disagreements were resolved by discussion. Snowballing and reverse snowballing were performed by scanning the reference lists of the included articles for any other publications of interest as well as searching Scopus for other works that cited the included articles.

An updated search was performed on February 7, 2022 and the same procedures as listed above were performed independently by two reviewers (E.T. and M.B.) for the additional articles.

2.2. Eligibility criteria

Studies eligible for inclusion reported a cross-sectional association between amyloid burden—measured by PET imaging, cerebrospinal fluid (CSF), or blood plasma assays—and WMH, as measured by MRI or CT scan. Studies had an observational cross-sectional or longitudinal design with reported baseline characteristics and associations. Clinical trials were excluded. Only articles reporting associations in older adults without objective cognitive impairment were included. Therefore, studies on individuals who reported subjective cognitive impairment may have been included. No criteria for age of the participants, language, or publication date were set.

Studies reporting only spatial (e.g., only deep or periventricular) measurements of WMH on MRI, as our focus was on total WMH volume, or only longitudinal associations were excluded. Moreover, studies were excluded if they included only participants with the same amyloid status or if there was insufficient information to calculate an effect size. If the same study cohort was used in multiple articles, the study with the largest sample size was included.

2.2.1. Data extraction and risk of bias assessment

Information about the size of the cohort, participant demographics and characteristics, measurements, amyloid method (PET, CSF, or plasma), amyloid isoforms (A β 40 and A β 42), metrics (continuous or categorical), WMH assessment, and associations between amyloid and WMH were extracted from the selected articles.

The risk of bias assessment was performed using an adjusted version of the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (Supplementary Info 3), where the included studies were rated with stars based on nine criteria within the following sections: quality of participant selection, comparability of cohorts based on the design or analysis, and quality of outcome assessment.

2.3. Statistical analysis

Statistical analysis was performed using R version 4.0.3 (RStudio, 2020). The outcomes of the individual studies were transformed into Cohen's d using means and standard deviations, point-biserial correlations, and Cohen's f using the *esc* package in R (Lüdtke, 2019), if the data was available. If correlation coefficients were reported, they were included in a separate meta-analysis. Effect sizes were reversed if amyloid burden was measured by CSF or blood plasma, as lower amyloid levels in CSF or plasma represent a higher amyloid burden in the brain (Blennow et al., 2015; Janelidze et al., 2016). Therefore, all studies with a positive effect size (i.e., Cohen's d or correlation) represent a relation between more WMH with higher amyloid burden. A random-effects model was used to calculate the pooled estimates from the Cohen's d and correlation coefficients separately using the *meta* and *metafor* packages (Balduzzi et al., 2019; Viechtbauer, 2010). We chose a random-effects model over a fixed-effects model because in the presence of heterogeneity, a random-effects meta-analysis weights the studies relatively more equally than a fixed-effect analysis (Borenstein et al., 2010).

As some studies had multiple amyloid metrics from the same subjects (i.e., reporting both A β 40 and A β 42, reporting continuous and

categorical scales, reporting both adjusted and unadjusted results), some analyses were not included in the calculation of the pooled estimate for the overall meta-analysis to avoid those studies getting weighted multiple times in the meta-analysis. Preference was given to continuous data, the isoform A β 42, and analyses adjusted for covariates.

Heterogeneity was tested using Cochran's Q test and I^2 statistic. Moderate heterogeneity was rated as 30–60%, substantial heterogeneity as 50–90%, and considerable heterogeneity as more than 75% based on the Cochrane Handbook (Higgins et al., 2019). The risk of publication bias was assessed by visual inspection of funnel plots and the Egger's t-test. To explore heterogeneity, subgroup analyses were performed based on amyloid assessment method (PET, CSF, or plasma), covariate adjustment, amyloid classification (continuous or categorical), and WMH assessment (Fazekas score or volumetric). As APOE e4 genotype can influence the relation between AD pathology and WMH (Roseborough et al., 2017), we also performed a meta-regression on prevalence of APOE e4 genotype per study. The statistical significance threshold was set at $p < 0.05$.

3. Results

3.1. Search results

A total of 1287 articles were found after duplicate removal, of which 43 full-text articles were assessed for eligibility (Fig. 1). After full-text screening, 13 studies were included in the meta-analysis (Abner et al., 2020; Brickman et al., 2015a; Gokcal et al., 2022; Hedden et al., 2012;

Jonsson et al., 2010; Kaffashian et al., 2014; Kandel et al., 2016; Kester et al., 2014; Osborn et al., 2018; Schreiner et al., 2018; Skoog et al., 2018; van Waalwijk van Doorn et al., 2021; Yi et al., 2018) (Fig. 1).

The demographics of the subjects of the included studies are shown in Table 1. The included studies consisted of a total of 2649 participants, with a mean age ranging from 59 to 85 years, the percentage of females ranging from 13% to 65%, and a mean education ranging from 14 to 18 years, if reported. Six studies (46.2%) reported APOE ϵ 4 allele positivity, with a range of 21–34% of participants having at least one APOE ϵ 4 allele. Six studies (46.2%) measured amyloid with PET imaging, two studies (15.4%) measured amyloid in plasma, and five studies (38.5%) measured amyloid in CSF. In the studies that used PET imaging, half of the studies used the 11 C-PiB PET tracer and the other half used a 18 F PET tracer. Most of the studies looked globally with the cerebellar cortex as reference. All CSF studies used an ELISA assay. For plasma, one study assessed amyloid via endothelial-derived exosomes, and the other used the Luminex xMAP assay. Nine of the 13 studies (69.2%) assessed WMH volumes using automated procedures. Three (42.9%) of the seven studies using CSF or blood plasma measured only A β 42, while four studies (57.1%) measured both A β 40 and A β 42. Eleven studies (84.6%) reported a continuous scale for amyloid burden, two studies (15.4%) reported only a categorical scale, and one study (7.7%) reported both. For the categorical studies, Kaffashian et al. (2014) used tertiles to assess amyloid-beta levels and Kandel et al. (2016) reported that 31% of the sample was amyloid-positive. All studies determined WMH on MRI, except for one study (7.7%) that used a CT scan. Moreover, five studies (38.5%) separated participants into groups based on their WMH burden,

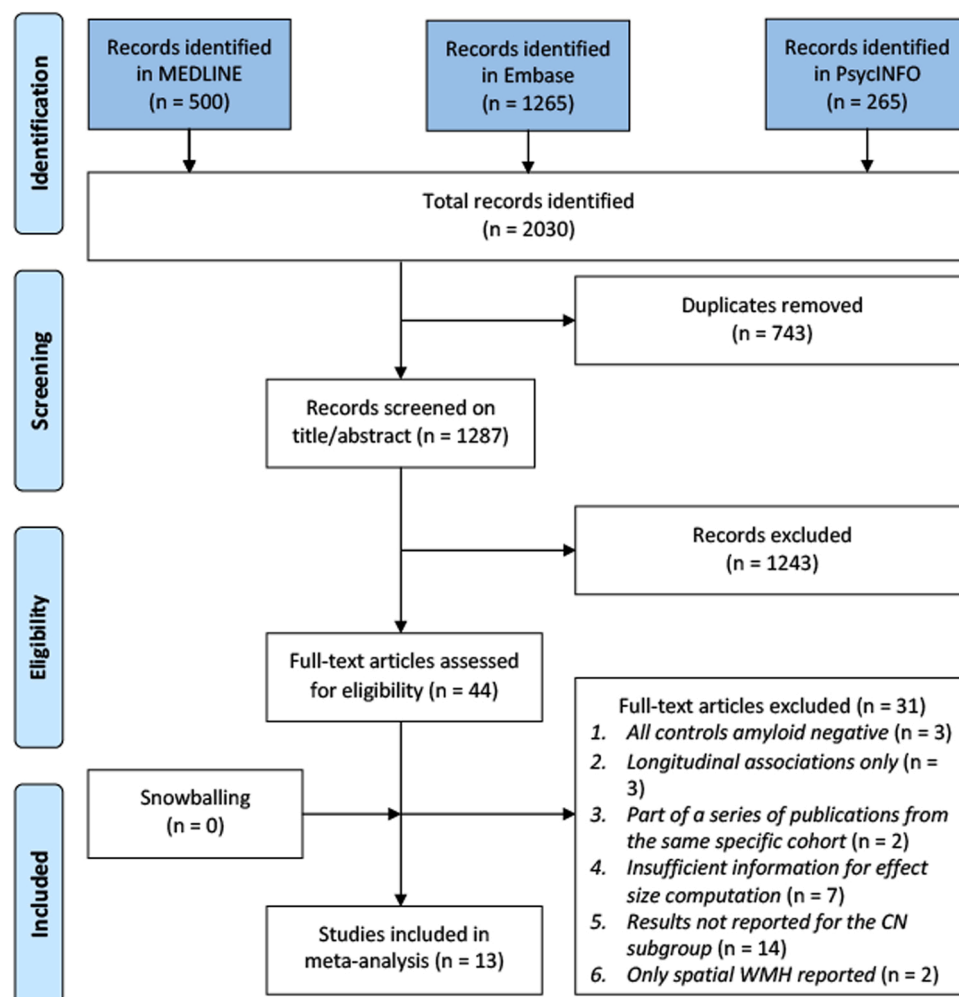


Fig. 1. PRISMA flow chart of the original literature search.

Table 1

Characteristics of the participants of the included studies in the meta-analysis.

Study	Cohort	Cohort origin	Sample size	Age (Mean \pm SD in years)	Sex/gender distribution (% women)	Education (Mean \pm SD in years)	APOE ϵ 4 positive, %	Vascular burden
Abner et al. (2020)	Sander-Browns Center on Aging of University of Kentucky, Memory and Aging Center of University of California	Memory clinic	42	73.5 \pm 1.6	52%	18 \pm 1	-	52% deemed having CSVD based on Fazekas
Brickman et al. (2015a)	Washington Heights Inwood Columbia Aging Program (WHICAP)	Population	14	82.5 \pm 3.3	43%	-	-	Participants had an average of 1.8 vascular risk factors (i.e., diabetes, hypertension, or heart disease)
Gokcal et al. (2022)	Massachusetts General Hospital	Research center	38	70 \pm 7.1	13%	-	-	All participants had CAA, 64% having hypertension
Hedden et al. (2012)	Harvard Aging Brain Study	Population	109	73.5 \pm 5.8	-	-	-	-
Jonsson et al. (2010)	Leukoaraiosis and disability in the elderly (LADIS) project	Hospital	53	74 \pm 4.8	47%	-	-	-
Kaffashian et al. (2014)	Three-City Dijon Study	Population	1693	72.4 \pm 4.1	61%	60% high school or less	21%	77% had hypertension, 8% had diabetes, 6% had prior cardiovascular disease
Kandel et al. (2016)	Alzheimer's Disease Neuroimaging Initiative (ADNI)	Population	158	73.5 \pm 6.1	52%	16 \pm 3	30%	-
Kester et al. (2014)	Amsterdam Dementia Cohort	Memory clinic	337	59 \pm 9	42%	-	34%	26% had hypertension, 10% had diabetes, 3% had myocardial infarction
Osborn et al. (2018)	Vanderbilt Memory & Aging Project	Population	77	72 \pm 7	29%	17 \pm 2	29%	48% on anti-hypertensives, 13% had diabetes
Schreiner et al. (2018)	Hospital for Psychogeriatric Medicine at University of Zurich	Hospital	27	70.3 \pm 5.7	41%	16 \pm 2	30%	Vascular risk factors were low (no uncontrolled hypertension/hyperlipidemia, no diabetes, no smoking)
Skoog et al. (2018)	Individuals living in Gothenburg	Population	30	85.4 \pm 0.1	53%	-	-	13% had a stroke
van Waalwijk van Doorn et al. (2021)	Biomarkers for Alzheimer's and Parkinson's Disease (BiomarkAPD) project	Hospital	52	61.1 \pm 8.9	65%	-	-	-
Yi et al. (2018)	Keimyung University Dongsan Medical Center	Memory clinic	19	62.5 \pm 5.5	63%	14 \pm 3	21%	-

Note: CSVD = cerebral small vessel disease; CAA = cerebral amyloid angiopathy.

while the other studies (61.5%) used WMH burden as a continuous outcome. While three studies (23.1%) used the Fazekas score for WMH assessment, the other 10 studies (76.9%) used volumes. Covariates (e.g., age, sex/gender, education, or other factors) were controlled for in eight

studies (61.5%). Five studies (38.5%) reported correlation coefficients, whereas the rest of the studies reported metrics that could be converted into a Cohen's d.

Table 2

Risk of bias assessment using the adjusted Newcastle-Ottawa Quality Assessment Scale Cohort Studies.

Study	Selection			Comparability				Outcome		Overall (max. 9)
	Representative	Selection	Exposure	Age	Sex/gender	Education	Other factors	Outcome	Same method	
Abner et al. (2020)	-	*	*	-	-	-	-	*	*	4
Brickman et al. (2015a)	*	*	*	-	-	-	-	*	*	5
Gokcal et al. (2022)	-	*	*	*	*	-	*	*	*	7
Hedden et al. (2012)	*	*	*	*	-	-	-	*	*	6
Jonsson et al. (2010)	*	*	*	-	-	-	-	*	*	5
Kaffashian et al. (2014)	*	*	-	*	*	*	*	*	*	7
Kandel et al. (2016)	*	*	*	*	*	*	-	*	*	8
Kester et al. (2014)	-	*	*	*	*	-	-	*	*	6
Osborn et al. (2018)	*	*	*	*	*	*	*	*	*	9
Schreiner et al. (2018)	*	*	*	-	-	-	-	*	*	5
Skoog et al. (2018)	*	*	*	-	-	-	-	-	*	4
van Waalwijk van Doorn et al. (2021)	*	*	*	*	*	-	*	*	*	8
Yi et al. (2018)	-	*	*	*	*	-	-	*	*	6

Note: In Gokcal et al. (2022), presence of intracerebral hemorrhage was also included as a confounder. In Kaffashian et al. (2014), adjustments were also done for prior cardiovascular disease, diabetes mellitus, body mass index, hypertension, low-density and high-density lipoprotein cholesterol, triglycerides, uric acid, serum creatinine, and APOE ϵ 2 and ϵ 4 allele presence. In Osborn et al. (2018), models were also adjusted for race/ethnicity, intracranial volume, cognitive diagnosis, a modified Framingham Stroke Risk Profile, and APOE ϵ 4 allele presence. In van Waalwijk van Doorn et al. (2021), models were also corrected for research center.

3.2. Risk of bias within and across studies

Studies scored between four and nine stars on the risk of bias assessment (Table 2). Regarding selection criteria, four studies lost stars as their sample was not representative of an older community-dwelling adult without dementia (30.8%). Moreover, five studies (38.5%) did not adjust for any covariates (e.g., age, sex/gender, education, or other). One study (7.7%) did not measure WMH via MRI; therefore, it lost a star regarding ascertainment of the outcome. One study (7.7%) used median cut-offs for amyloid assessment, losing a star regarding the exposure. One study scored all nine stars. The funnel plot to assess publication bias was not fully symmetric with Cohen's d metrics as four dots lie outside the funnel. However, there was a symmetrical funnel plot for the studies reporting correlation coefficients (Fig. 2). The Egger's t statistic did not confirm a publication bias (Cohen's d: bias = 1.95, SE = 1.37, $t(6) = 1.42$, $p = 0.20$; correlation coefficient: bias = 1.60, SE = 1.08, $t(3) = 1.48$, $p = 0.24$).

3.3. Meta-analysis

The study characteristics and effect sizes (Cohen's d and correlation coefficients) of the included studies are shown in Table 3. The meta-analysis of the eight studies resulted in an overall weighted Cohen's d of 0.45 (95% CI: 0.07–0.82, $p = 0.02$). An overall weighted correlation coefficient on the four other studies was 0.17 (95% CI: 0.03–0.31, $p = 0.02$) (Fig. 3). There was substantial heterogeneity in the pooled estimate for Cohen's d ($Q(7) = 50.83$, $p < 0.001$, $I^2 = 86.2\%$) (University et al., 2018). However, there was little to no heterogeneity for the studies reporting correlation coefficients ($Q(4) = 3.40$, $p = 0.49$, $I^2 = 0.0\%$).

Six out of the 13 studies reported information regarding the prevalence of APOE e4 genotype. There were too little studies reporting APOE e4 genotype in the correlation coefficient meta-analysis to perform a meta-regression. However, for the meta-analysis on Cohen's d studies, a meta-regression on those studies did not reveal that the prevalence of an APOE e4 allele had an impact on the meta-analysis ($p = 0.05$).

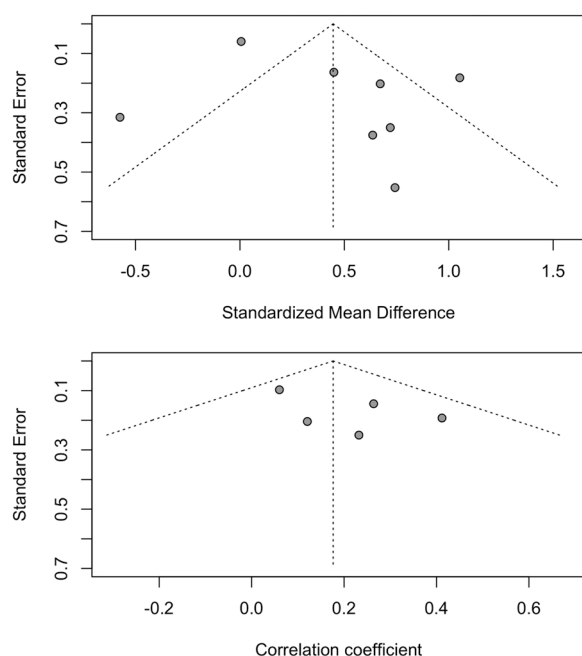


Fig. 2. Funnel plot of the 8 studies converted to Cohen's d and the 5 studies using correlation coefficients.

3.4. Subgroup analyses

To explore heterogeneity, subgroup analyses were performed. When assessing a difference across methods for amyloid burden, there was a significant subgroup difference in the Cohen's d studies ($Q(2) = 13.97$, $p < 0.001$). The meta-analysis of the three studies in CSF resulted in an overall weighted effect size of 0.55 (95% CI: 0.31–0.78, $p < 0.001$) (Fig. 4). For the three PET studies, an overall weighted effect size of 0.96 (95% CI: 0.66–1.27, $p < 0.001$) was found. For the two plasma studies, an effect size of -0.20 (95% CI: -0.75 to 0.34 , $p = 0.47$) was found. There was substantial heterogeneity in the plasma studies ($Q(1) = 3.27$, $p = 0.07$, $I^2 = 69.5\%$) (University et al., 2018). There was no heterogeneity found in the CSF studies ($Q(2) = 0.79$, $p = 0.64$, $I^2 = 0\%$) or in the PET studies ($Q(2) = 0.88$, $p = 0.64$, $I^2 = 0\%$).

For the studies reporting correlation coefficients, there was not a subgroup difference between studies using PET or CSF ($Q(1) = 2.58$, $p = 0.11$). The overall weighted correlation coefficient for CSF studies was 0.31 (95% CI: 0.09; 0.50, $p = 0.01$). The overall weighted correlation coefficient for PET studies was 0.09 (95% CI: -0.07 ; 0.25, $p = 0.28$) (Fig. 4). Neither PET nor CSF studies showed heterogeneity.

The studies that adjusted for covariates showed more variance compared to studies that did not adjust for covariates (Supplementary Figure 1). The confidence interval of the pooled effect size as well as the heterogeneity of the studies using a categorical scale were greater than studies using a continuous scale (Supplementary Figure 2); however, this subgroup analysis could only be performed in the Cohen's d meta-analysis. This pattern was also seen for studies using the Fazekas score compared to studies assessing WMH volumes (Supplementary Figure 3). This pattern could be explained by less studies in the subgroups with wider confidence intervals and larger heterogeneity.

Nonetheless, no significant subgroup differences were found when the studies were stratified by covariate adjustment (Cohen's d: 3 vs. 5 study groups, $Q(1) = 0.44$, $p = 0.51$; correlation coefficients: 2 vs. 3 study groups, $Q(1) = 0.65$, $p = 0.42$), amyloid scale (Cohen's d: 2 vs. 6 study groups, $Q(1) = 0.03$, $p = 0.87$), or WMH assessment (Cohen's d: 6 vs. 2 study groups, $Q(1) = 0.55$, $p = 0.46$).

As WMH are more common in women (Fatemi et al., 2018), we also performed a sensitivity analysis removing Hedden et al. (2012), as they did not report the sex distribution in the analytical sample on WMH. However, our meta-analysis on correlation coefficients remained similar (0.26; 95% CI: 0.08–0.42). Further, we performed a sensitivity analysis removing the studies that did not adjust for age (Abner et al., 2020; Brickman et al., 2015a; Jonsson et al., 2010; Schreiner et al., 2018; Skoog et al., 2018). Results remained similar in the overall Cohen's d (Cohen's d: 0.45, 95% CI: 0.07–0.82). However, in the overall correlation meta-analysis, there was only a trend towards significance ($r: 0.14$, 95% CI: -0.02 to 0.29).

4. Discussion

This systematic review and meta-analysis included 13 studies that explored the cross-sectional association between amyloid burden in CSF, PET, and plasma and WMH in older adults without objective cognitive impairment. The meta-analysis using Cohen's d yielded an overall effect size of 0.45, which is considered small- to medium-sized (Cohen, 1988). The meta-analysis on correlation coefficients yielded a pooled correlation of 0.17. When stratified by amyloid assessment method, a Cohen's d of 0.55 for the CSF studies and 0.96 was found for the PET studies and a pooled correlation of 0.31 was found for the CSF studies. No association was found for the plasma studies. Almost half of the studies did not adjust for covariates which increased the risk of bias regarding comparability. The funnel plot and Egger's t-test did not reveal evidence for publication bias. Moreover, subgroup analysis revealed that the overall substantial heterogeneity (University et al., 2018) in the Cohen's d meta-analysis was driven by amyloid burden assessment method. However, substantial heterogeneity remained in the plasma studies.

Table 3
Study characteristics and effect sizes.

Study	N	Amyloid scale	Amyloid method	WMH assessment	Covariate controlled	Cohen's d \pm SE or correlation coefficient
Abner et al. (2020)	42	Continuous	Plasma, endothelial-derived exosomes, ELISA assay	Fazekas score	No	-0.24 \pm 0.31 (A β 40)
Brickman et al. (2015a)	14	Continuous Categorical	18 F PET in either frontal, temporal, parietal, posterior cingulate, or occipital cortices	Volumetric, automated	No	-0.57 \pm 0.31 (A β 42) 0.74 \pm 0.55 2.31 \pm 0.69
Gokcal et al. (2022)	38	Continuous	11 C-PiB PET, globally with cerebellar cortex as reference	Volumetric, automated	Age, sex, presence of intracerebral hemorrhage	0.72 \pm 0.35
Hedden et al. (2012)	109	Continuous	11 C-PiB PET, only in the frontal, lateral parietal and temporal, retrosplenial cortices	Volumetric, automated	Age	0.06 \pm 0.10
Jonsson et al. (2010)	53	Continuous	CSF, MSD Multi-Array (A β 40) & Luminex xMAP (A β 42)	Volumetric, automated	No	0.05 \pm 0.19 (A β 40) 0.64 \pm 0.19 (A β 42)
Kaffashian et al. (2014)	1693	Categorical	Plasma, Luminex xMap	Volumetric, automated	Age and sex	0.02 \pm 0.06 (A β 40) 0.01 \pm 0.06 (A β 42) -0.08 \pm 0.06 (A β 42/40)
Kandel et al. (2016)	158	Categorical	18 F PET, globally with cerebellar cortex as reference	Volumetric, automated	Age, sex/gender, education	1.05 \pm 0.18
Kester et al. (2014)	337	Continuous	CSF, ELISA	Fazekas score	Age, sex, medial temporal lobe atrophy	0.67 \pm 0.20 (A β 42)
Osborn et al. (2018)	77	Continuous	CSF, ELISA	Volumetric, automated then confirmed manually	Age, sex, race/ethnicity, education, intracranial volume, cognitive diagnosis, APOE4, vascular risk factors	0.45 \pm 0.16 (A β 42)
Schreiner et al. (2018)	27	Continuous	11 C-PiB PET, posterior cingulate and precuneus	Volumetric, automated	No	0.12 \pm 0.19
Skoog et al. (2018)	30	Continuous	CSF, ELISA	Volumetric, via CT scan	No	0.46 \pm 0.15 (A β 40) 0.39 \pm 0.16 (A β 42)
van Waalwijk van Doorn et al. (2021)	52	Continuous	CSF, ELISA	Volumetric, automated with a ML algorithm then checked manually	Age, sex, and research center	0.26 \pm 0.13 (A β 42)
Yi et al. (2018)	19	Continuous	18 F PET, globally with cerebellar cortex as reference	Fazekas score	Age and sex	0.23 \pm 0.22

Note: WMH = white matter hyperintensities. ELISA = enzyme-linked immunosorbent assay. PiB = Pittsburgh compound B. PET = positron emission tomography. SUVR = standardized uptake value ratio. CSF = cerebrospinal fluid. A β = amyloid-beta.

Although many of the included studies did not find evidence for an association between amyloid burden and WMH, this meta-analysis revealed the presence of a small-to-medium sized cross-sectional relationship between the two pathologies which is also in line with the findings of a recent systematic review (Kim et al., 2020). Among the included studies, one reported a negative association and the remaining 12 reported a positive association. However, 8 of the 13 studies reported non-significant associations. By reducing the variance of the individual studies and increasing power, this meta-analysis was able to reach more precision, whereas most of the individual studies could not. Further, our findings are in line with a recent study of more than 500 individuals that also found an association between WMH and amyloid-beta burden in cognitively unimpaired individuals (Habes et al., 2021). These findings suggest a possible role in the prevention of CSVD in delaying AD and pathological aging.

In the meta-analysis on correlation coefficients, studies measuring amyloid in CSF showed a significantly higher association with WMH than amyloid measured with PET imaging or in plasma. Amyloid in CSF is a more sensitive marker for early disease stages of AD than amyloid PET imaging (Mattsson et al., 2015)—the current meta-analysis only included cognitively unimpaired older adults, which may explain this subgroup difference. Low but present amyloid burden may not have been accurately detected with PET imaging, resulting in only detecting a relationship of WMH with amyloid pathology using CSF in cognitively unimpaired older adults. This hypothesis might also explain why Roseborough et al. (2017) did not find a cross-sectional association between amyloid burden and WMH in cognitively unimpaired older adults, as they only included studies assessing amyloid burden with PET in their systematic review. This could also explain the discrepancy in results

between PET and CSF modalities. However, this was only seen in the meta-analysis using correlation coefficients. For the meta-analysis on studies where Cohen's d could be calculated, PET studies showed a slightly higher effect size. This could have been due to the large effect size from Kandel et al. (2016), which may be explained by their categorical classification of amyloid burden. Lastly, while the largest included study that used plasma assessment (Kaffashian et al., 2014) did not find a cross-sectional association, a longitudinal association was found. With the development of more sensitive assays for plasma A β since this study was performed, future studies should assess if plasma amyloid burden may be a more prognostic marker for vascular burden.

Further, substantial heterogeneity was found within the studies using plasma assessment in the Cohen's d meta-analysis. This may be due to differing performance between plasma amyloid assays (Janelidze et al., 2021) leading to different results. In addition, while plasma and CSF amyloid have shown positive correlations amongst varying assays (Janelidze et al., 2016; Janelidze et al., 2021), some differences have been seen in the relationship between plasma amyloid and AD and plasma amyloid and vascular disease. For example, one study reported higher plasma amyloid in association with vascular risk factors and lower plasma amyloid across the continuum of subjective cognitive decline, mild cognitive impairment, and AD, whereas consistent results were seen with CSF (Janelidze et al., 2016). However, as there were only two studies that assessed amyloid in plasma, we could not perform further subgroup analysis. As assessing amyloid burden through plasma is a relatively new modality, further studies need to be done to fully understand the relationship between plasma amyloid burden and WMH.

Some studies could not be included in the meta-analysis due to insufficient information for effect size calculation. Although, these

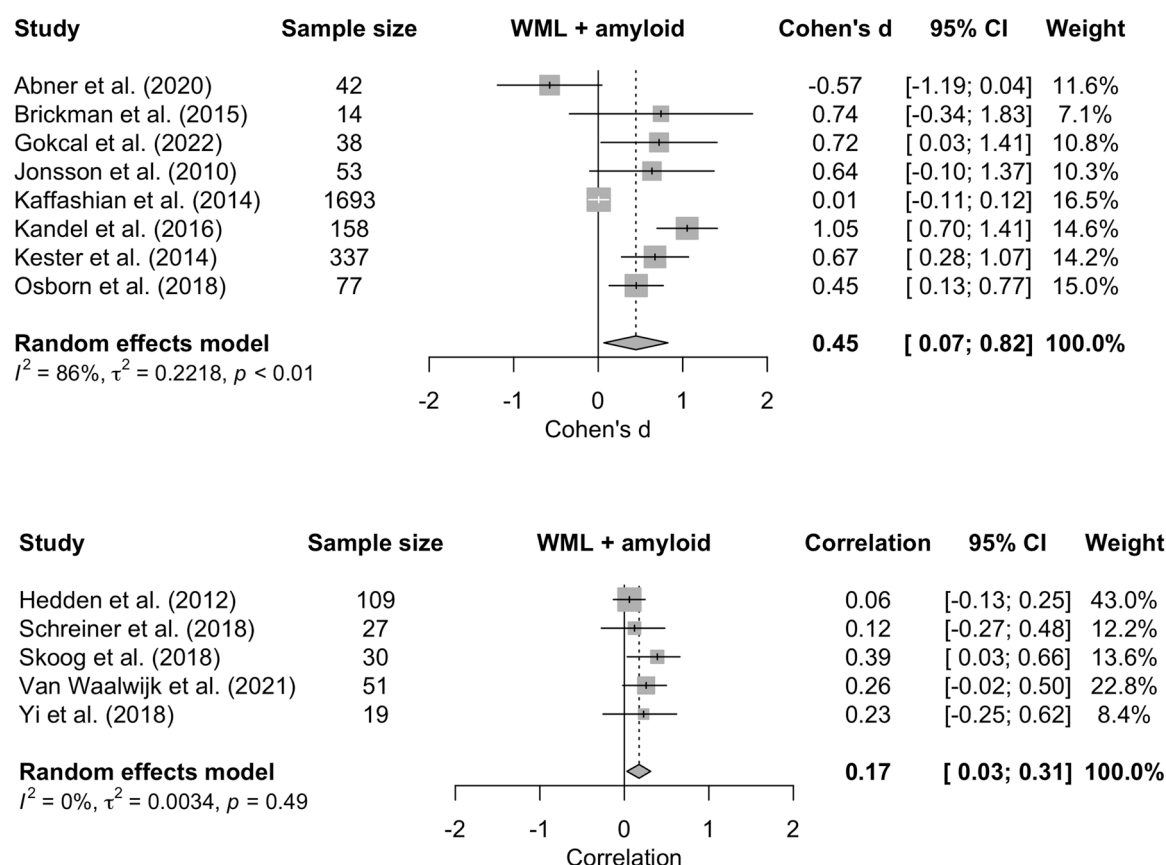


Fig. 3. Forest plot of the two meta-analyses for a total of 13 studies of the relationship between amyloid and WMH in cognitively normal older adults. The effect sizes of the individual studies are represented by the squares, of which the size is proportional to the weight of the study. The diamond represents the pooled estimate. The effect sizes of analyses using continuous data, A β 42, and adjusted for covariates were used for the meta-analysis, when a study reported multiple analyses.

studies also reported higher WMH associated with amyloid burden in PET (Garnier-Crussard et al., 2022; Gurol et al., 2013; Pålhaugen et al., 2021) and CSF (Morrison et al., 2022; Pålhaugen et al., 2021; van Westen et al., 2016; Walsh et al., 2020). However, some studies found no association (Dupont et al., 2020; Koncz et al., 2022; Marchant et al., 2012). As a previous study found that 18 F predominantly labels vascular amyloid (Gurol et al., 2016), we reason that the null finding in Koncz et al. (2022) could be due to that they combined 11 C and 18 F PET tracers in their methodology. Further, Dupont et al. (2020) measured amyloid with 11 C PET, possibly explaining the null finding. Methodological discrepancies could also explain the null finding in Marchant et al. (2012), as they characterized vascular burden by not only WMH but also by infarct presence. Studies that only reported spatial WMH also confirmed our findings on PET (Graff-Radford et al., 2019; Marnane et al., 2016) and CSF (Marnane et al., 2016). However, one study assessing plasma amyloid burden did find an association with periventricular and subcortical WMH (van Dijk et al., 2004); whereas, in our meta-analysis no association was found for amyloid burden in plasma and WMH. Longitudinal studies also reported similar findings (Dadar et al., 2020; Lo and Jagust, 2012), where baseline A β 42 predicted WMH (Dadar et al., 2020) as well as baseline WMH predicting amyloid PET (Lo and Jagust, 2012).

There are some limitations of the current review and meta-analysis. Only one article (van Waalwijk van Doorn et al., 2021) included participants with subjective cognitive decline, thus no subgroup analysis could be performed based on cognitive status. Moreover, only a small number of studies could be analyzed in some subgroup analyses (amyloid assessment scale, covariate adjustment, and WMH assessment), giving less precise estimates of the effect sizes and less power for determining significant subgroup differences. There is also a possibility

that the association of amyloid burden on WMH is mediated by other vascular factors, such as hypertension. However, as we focused on cross-sectional studies, mediation analyses would have limitations and none of the included studies assessed possible mediation through other factors. Further, as we chose to focus on cross-sectional associations to reduce complexity and heterogeneity, future research should explore the longitudinal relationship between amyloid burden and WMHs to assess their temporal relationship as well as any additive effects. Due to some studies reporting multiple metrics, such as continuous and categorical data, some subjective decisions methodologically were made for the meta-analysis which could have introduced some bias. There was some discrepancy for A β 40 and A β 42 in Abner et al. (2020) and Jonsson et al. (2010), with stronger associations found for A β 42. This difference is in line with previous studies showing stronger associations with A β 42 than A β 40 with cognitive decline and later dementia. However, most studies that reported multiple metrics showed similar directional associations between them. Of note, most of the included studies did not report education level of the participants or included those mostly highly educated. Further, only one study (Osborn et al., 2018) reported the ethnicity of participants, which was 93% White. This is of importance as these findings are not generalizable due to the homogeneity of included individuals regarding education and ethnicity. As most research has traditionally focused on White participants with high education, future studies should include historically marginalized individuals to ensure generalizability. This systematic review and meta-analysis also was not registered on PROSPERO as data extraction had already been performed. However, one of the key reasons for review registration is to prevent duplication, and no current protocols in PROSPERO were on the same topic as the current review. Lastly, the current study did not have an age restriction, and as WMH are common with aging, the age range

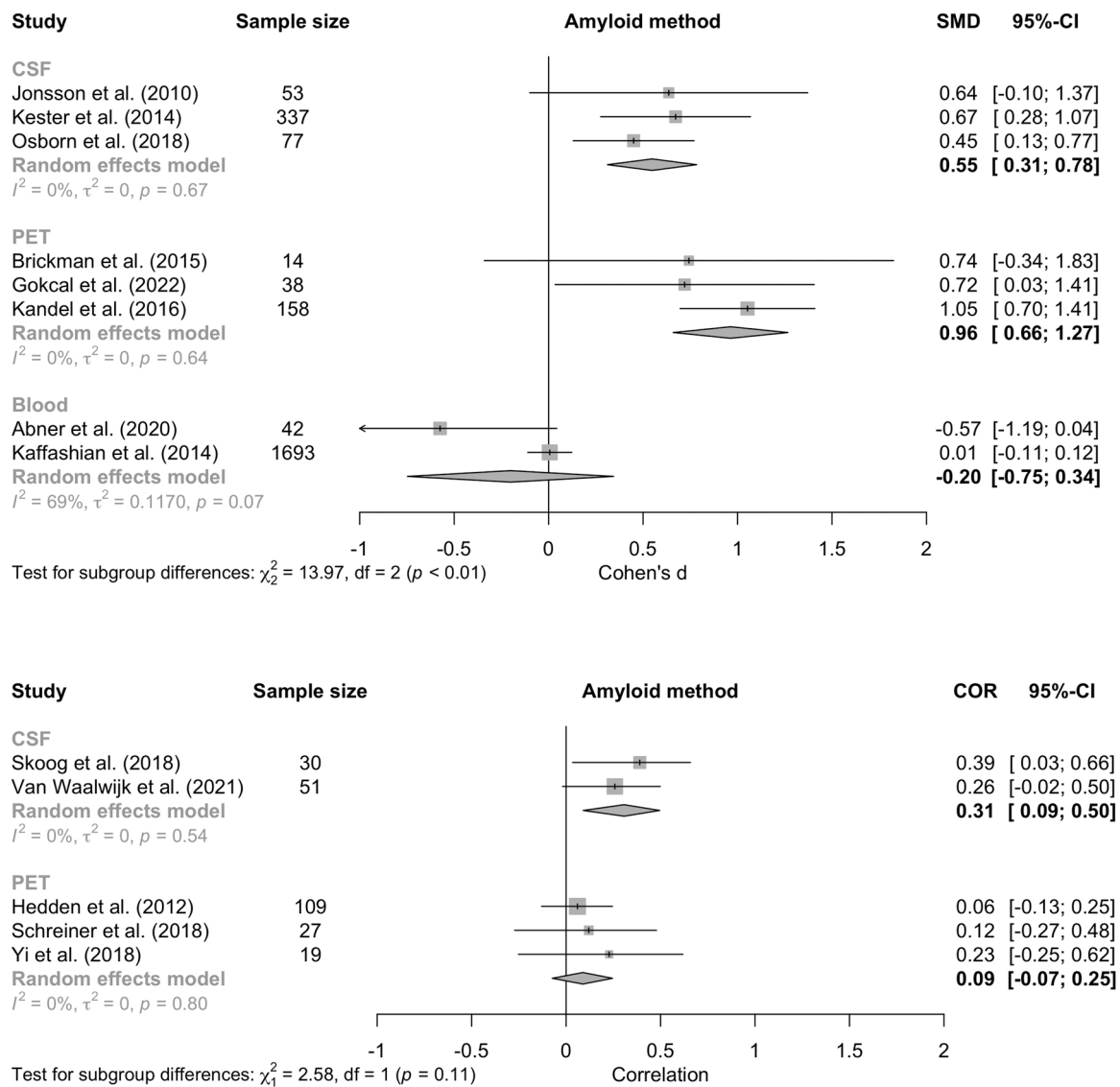


Fig. 4. Forest plot of the subgroup meta-analyses based on amyloid assessment method (PET, CSF, or plasma) for a total of 13 studies. The effect sizes of the individual studies are represented by the squares, of which the size is proportional to the weight of the study. The diamond represents the pooled estimate. The horizontal lines represent the 95% confidence intervals of the individual effect sizes. The effect sizes of analyses using continuous data, Aβ42, and adjusted for covariates were used for the meta-analysis, when a study reported multiple analyses.

could have obscured the relation between amyloid burden and WMH.

A suggestion for future studies is to further investigate the nature of the relationship between amyloid burden and WMH and to determine the underlying mechanisms of how vascular damages to small cerebral vessels may affect amyloid burden in early stages of AD, or vice versa. Future research should also examine other pathologies of AD (e.g., tau and neurodegeneration) and their association with CSVD neuroimaging markers (e.g., WMH, lacunes, cerebral microbleeds, enlarged perivascular spaces). Since it is hypothesized that the impairment of the glymphatic system, which includes perivascular spaces, plays a role in amyloid burden (Tarasoff-Conway et al., 2015), a future direction could be to investigate the relationship between enlarged perivascular spaces and amyloid burden. To increase the number of possible included studies, we decided to only include studies that reported total WMH volume. However, we realize that this choice could have introduced bias into the study towards the null. Previous studies have highlighted region-specific associations between parietal WMH and amyloid-beta burden (Brickman et al., 2015b; Phuah et al., 2022; Yoshita et al., 2006). We assume if we would have differentiated between spatial regions of WMH that we would have a higher effect estimate.

Interestingly, previous studies have found that the spatial topography of WMH matches the deposition of cortical amyloid. Future studies could also assess if parietal WMH hold stronger associations with CSF and plasma amyloid burden. Moreover, examining the longitudinal association between amyloid and WMH could provide more insight in the progression of amyloid burden and WMH over time and their mechanistic pathways in the development of AD (Grimmer et al., 2012; Moscoso et al., 2020; Wang et al., 2021).

In conclusion, this meta-analysis demonstrated a small to medium-sized cross-sectional association between amyloid burden and WMH in CSF and PET in older adults without objective cognitive impairment. As the number of individuals suffering from dementia is expected to increase over the next decades, studying the preclinical stage of AD is of great importance for prevention and potential intervention. The current study highlights the possible use of CSF and PET to assess comorbid amyloid and vascular pathology during the preclinical stage of AD. While no association was found between amyloid burden in blood and WMH, future studies should still consider estimating a possible relation for broader implementation using a cost-effective assessment for amyloid burden. The continued study of the mixed pathologies across the

continuum from healthy aging to dementia may provide more insight in the development of the disease and the origins of its heterogeneity.

Declaration of Competing Interest

The authors have no conflict of interest to report.

Data Availability

No data was used for the research described in the article.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.arr.2023.101952](https://doi.org/10.1016/j.arr.2023.101952).

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