

Review Article

Cerebral amyloid- β deposition in patients with heart disease or carotid occlusive disease: A systematic review and meta-analysis

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ABSTRACT

Background: Cardiovascular disease is an important contributor to cognitive impairment. This likely involves prototypical vascular disease mechanisms like ischemia, but cardiovascular disease might also impact the brain by accelerating cerebral amyloid- β accumulation. We aimed to determine whether there is an association between heart disease or carotid occlusive disease (COD) and cerebral amyloid- β burden.

Methods: We conducted a systematic review of studies investigating cerebral amyloid- β burden, measured with positron emission tomography, in adults with and without heart disease or COD. Where possible, we obtained standardized mean differences (SMD) of amyloid- β standardized uptake volume ratios (SUVR) for meta-analysis. **Results:** Eight cross-sectional studies were identified (1478 participants, aged 60–81 years, 51% female). Three studies on heart disease (two on atrial fibrillation (AF) only, one on AF, coronary artery disease and heart failure) did not find a difference in amyloid- β burden between patients and controls. The pooled difference for 746 participants with and without AF did not reach significance (SMD SUVR 0.14, 95%CI -0.06–0.34). Of the five studies on COD (one on differences between participants with and without COD, four on differences between hemispheres in unilateral COD), four did not find a difference in amyloid- β between participants or hemispheres. The pooled difference in amyloid- β load between hemispheres in 24 patients with unilateral COD was not significant (SMD SUVR -0.13, 95%CI -0.70–0.43).

Conclusion: Based on current studies, although limited and heterogeneous, there is insufficient evidence to support the hypothesis that heart disease or COD are associated with increased cerebral amyloid- β burden.

1. Introduction

Dementia is a common public health problem with a cumulative incidence of 1.4 cases of Alzheimer's disease and 0.4 cases of vascular dementia per 100 persons over a period of five years [1,2]. It has a large impact on both patients and relatives. One of the main causes of dementia is amyloid- β accumulation in the brain [3]. Individuals with increased cerebral amyloid- β levels have approximately a twice as high risk of developing amnesic mild cognitive impairment or dementia compared to amyloid- β negative individuals [4]. Cardiovascular disease is another important risk factor for dementia [5]. The risk of dementia in

patients with heart disease or heart failure is increased by 27% and 60% respectively [6]. Similarly, patients with carotid occlusive disease (COD) are at risk for cognitive impairment [7].

Traditionally, amyloid- β accumulation leading to Alzheimer's disease and cardiovascular disease leading to vascular dementia were viewed as separate disease processes. However, the two pathologies often coincide in older individuals [8–10]. Cardiovascular diseases [6], but also cardiovascular risk factors such as hypertension [11,12], not only increase the risk of vascular dementia, but also the risk of a clinical diagnosis of Alzheimer's disease. This raises the question whether both pathologies are linked. Previous systematic reviews focused on a clinical

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diagnosis of dementia instead of the etiology.

Besides prototypical vascular disease mechanisms like ischemia, cardiovascular disease might also impact the brain by accelerating cerebral amyloid- β accumulation [13]. In patients with cardiovascular disease, the structure and function of the blood vessels is affected. While the specific disease processes for heart disease and COD may be different, cerebral blood flow could be compromised in both instances [14]. This may lead to impaired clearance of amyloid- β from the brain, which then results in more cerebral amyloid- β [13]. Positron emission tomography (PET) imaging has made it possible to visualize and quantify the cerebral amyloid- β burden in these patients in vivo and to study this association.

Therefore, we performed a systematic review of studies examining cerebral amyloid- β accumulation as measured using PET in patients with heart disease or COD. We hypothesized that patients with heart disease or COD have more cerebral amyloid- β accumulation than adults without these diseases.

2. Materials and methods

2.1. Eligibility criteria

We formulated the following inclusion criteria: 1) observational studies, 2) adults from the general population or hospital-based populations, 3) patients with a heart disease (i.e. heart failure, myocardial infarction, heart valve diseases, arrhythmias or cardiomyopathies) or COD (i.e. stenosis or occlusion of the extracranial internal carotid artery (ICA)), 4) measurement of the amount of cerebral amyloid- β by a PET-scan and 5) assessment of the heart disease or COD before or at the same time as the cerebral amyloid- β load. Exclusion criteria were: 1) case reports and 2) studies in another language than English.

2.2. Information sources, search strategy and study records

The study team developed the search strategy with help from an information specialist of Utrecht University. The search included the following terms: amyloid or amyloid radiotracers, PET and various heart diseases or COD. For each element, relevant search terms and subject headings (if available) were selected. There were no limits on the search with respect to study design, date or language. The complete search is provided in Supplementary File 1. The search was performed on 29 April 2022 in Pubmed, EMBASE and Scopus. Additionally, the reference lists of the included studies and relevant reviews identified through the search, were scanned.

We exported the retrieved articles, removed duplicates and uploaded the unique articles into an online program for screening [15]. Two authors (NS and NT) independently screened the titles and abstracts for eligibility. Full text articles were retrieved if the article seemed to match the inclusion and exclusion criteria or if there was any uncertainty. The same two authors then read the full text articles and decided whether or not they met the inclusion and exclusion criteria and could be included in the review. Disagreements were resolved by discussion.

2.3. Data collection process, data items and outcomes and prioritization

Data were extracted into a standardized form and included information on sample size, study design, demographics, disease, PET-scan procedures and analyses, outcomes on amyloid- β accumulation in the brain, and potential sources of bias. One author (NS) extracted the data, after which a second author (NT) checked if this was done correctly. In case of missing data, we contacted the corresponding author to ask for additional information. We received additional data of three studies [16–18].

The primary outcome was amyloid- β accumulation in the brain, expressed as the global or hemispheric amyloid- β load. Differences between patients with or without heart disease or COD were recorded. In

studies only including patients with unilateral COD the difference in amyloid- β load between the two hemispheres was recorded.

2.4. Risk of bias in individual studies

The STROBE checklist was used to assess if the studies reported all the relevant items for an observational study [19]. We adapted the Newcastle-Ottawa Quality Assessment Scale (NOS) to assess the quality and risk of bias of the included studies (Supplementary Table 2) [20].

2.5. Data synthesis

Studies were pooled if they were sufficiently homogenous in terms of study population, determinant and outcome. Studies on heart disease and COD were assessed separately. Review Manager version 5.4 was used to perform a meta-analysis assessing standardized mean differences in amyloid- β with a random effects model. The results are presented in a forest plot. Heterogeneity was tested using the Chi² test ($p < 0.05$ indicated heterogeneity) and I² statistic (25% indicated low heterogeneity; 50% moderate heterogeneity and 75% high heterogeneity).

3. Results

The literature search yielded a total of 1385 unique articles, of which 27 articles were read in full-text to assess their eligibility (Fig. 1). Eight articles could be included in this review [16–18,21–25]. The estimated quality of the included studies varied from weak to moderate with studies receiving between 3 and 7 stars out of 10 on the NOS assessment (Table 1). Completed STROBE checklists are provided in Supplementary Table 3.

3.1. Heart disease

We found three cross-sectional studies of moderate quality on the association between heart disease and amyloid- β accumulation (Table 2) [16,22,25].

One study studied a hospital-based cohort of participants with normal cognitive function, mild cognitive impairment and Alzheimer's disease [22]. This study examined the association between self-reported atrial fibrillation (AF) and amyloid- β load, as determined by static PET-scans [22]. All participants were combined into one group instead of performing the analyses stratified by cognitive status [22]. Participants of this cohort without AF served as reference participants [22]. Crude coefficients were not provided, but there was no significant association between AF and amyloid- β load after adjustment for confounders [22].

The other two studies were population-based studies and determined the difference in amyloid- β load between patients with and without heart disease [16,25]. The first study investigated differences between participants with and without AF [16]. The second study considered multiple heart diseases (i.e. cardiac arrhythmias (AF and atrial flutter), coronary artery disease and congestive heart failure), and compared participants with and without these diseases [25]. Diagnoses were ascertained by the presence of a related ICD-code [16,25]. Reference participants without these diagnoses were derived from the same cohort as the patients with heart disease [16,25]. Both studies performed static PET-scans, providing standardized uptake volume ratios (SUVR) to determine amyloid- β load [16,25].

We pooled the analyses on AF and atrial flutter from the two population-based studies in a meta-analysis, including 746 participants of which 123 had AF or atrial flutter (49% female, mean age between 75 and 76 years) (Fig. 2) [16,25]. The other study on AF could not be included in the meta-analyses, because the required data (i.e. SUVR of amyloid- β PET in participants with and without AF) was not available [22]. The pooled difference did not reach significance (standardized mean difference in amyloid- β SUVR of 0.14, 95% confidence interval (CI) -0.06–0.34, $p = 0.17$). Meta-analysis on heart disease as a composite

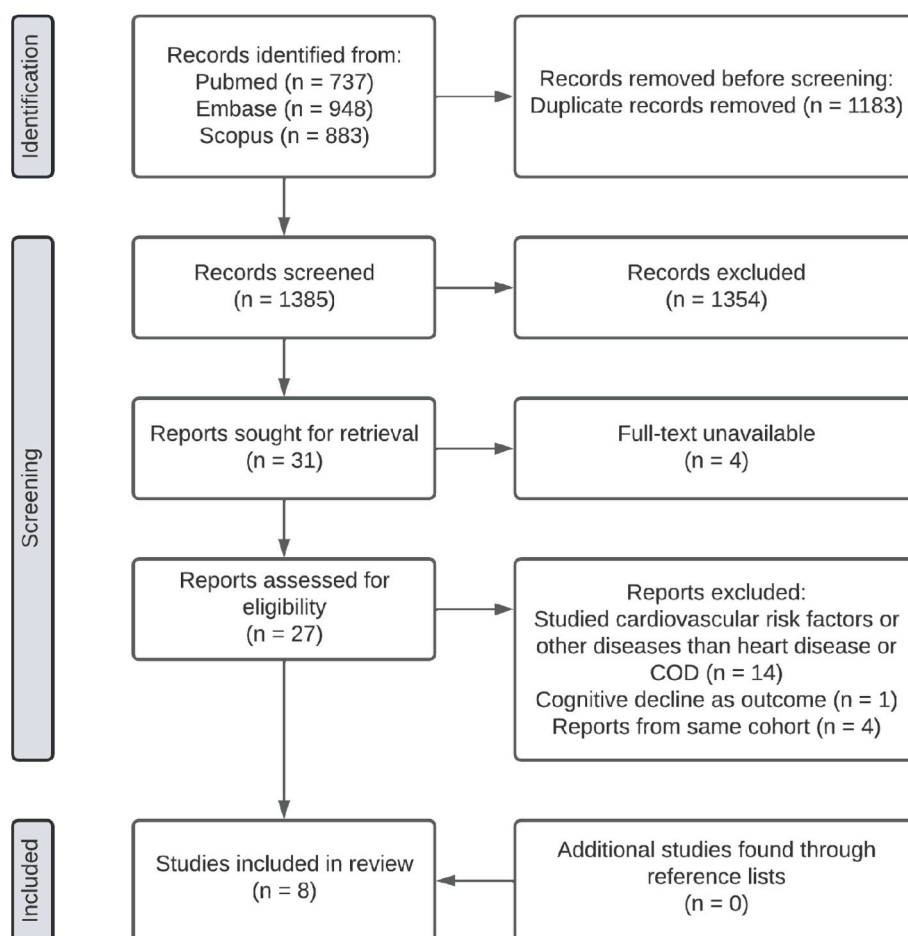


Fig. 1. Flowchart of the study selection process.
COD indicates carotid occlusive disease.

Table 1

Assessment of the quality and risk of bias of the included studies using an adapted version of the Newcastle-Ottawa Quality Assessment Scale.

Study	Selection			Comparability	Outcome		Total
	Representativeness of the participants with the disease	Selection of the participants without the disease	Ascertainment of the determinant	Comparability of participants on the basis of the design or analysis	Assessment of outcome	Statistical test	
Hansson 2018	1	1	2	0	1	1	6
Huang 2012	0	0	2	0	1	1	4
Johansen 2020	1	1	1	2	1	1	7
Kang 2020	1	0	2	0	1	1	5
Koncz 2022	1	1	0	2	1	1	6
Ogasawara 2019	0	1	2	NA	0	NA	3
Vemuri 2017	1	1	1	1	1	1	6
Yamauchi 2019	1	1	2	0	2	1	7

NA indicates not applicable.

A maximum of 10 stars could be earned per study: 5 stars for selection, 2 stars for comparability and 3 stars for outcome.

outcome could not be performed since the analyses on coronary artery disease and congestive heart failure were performed in the same population as the AF and atrial flutter analyses [25].

3.2. Carotid occlusive disease

We included five cross-sectional studies on the association between COD and amyloid- β accumulation (Table 2).

We found one population-based study of 477 participants (59% female, mean age 71 years), that looked at the difference in global amyloid- β accumulation, determined by static PET-scans, between participants with or without COD [23]. Most patients had a mild ICA stenosis on MRA with only two patients having a stenosis of 50% or more [23]. Reference participants without COD were drawn from the same cohort [23]. In both participants with and without mild cognitive impairment, the global burden of amyloid- β did not differ between

Table 2

Characteristics of the included studies.

Study	Cohort	Disease studied	Ascertainment of heart disease or COD	Ascertainment of amyloid- β load	Participants	Female	Age, years	Cognition	Amyloid load, SUVR	Amyloid load, SUVR
					N (patients/controls)	N (%)	Mean \pm SD		Mean \pm SD	Mean \pm SD
Heart disease (between subject comparisons)									Patients	Controls
Johansen 2020	Population based, USA	Atrial fibrillation	ECG or ICD-codes	18F-Florbetapir static PET	316 (17/299)	177 (56)	76 \pm 5	228 CN and 88 MCI	1.36 \pm 0.39	1.29 \pm 0.25
Vemuri 2017	Population based, USA ^a	Atrial fibrillation or atrial flutter	ICD-codes	11C-PiB static PET	430 (106/324) ^b	190 (44)	75 \pm 8	389 CN, 33 MCI, 5 dementia (3 AD and 2 mixed) and 3 no diagnosis	1.62 \pm 0.44	1.57 \pm 0.43
		Coronary artery disease			430 (79/351) ^c				1.67 \pm 0.47	1.56 \pm 0.42
		Congestive heart failure			430 (12/418) ^d				1.79 \pm 0.49	1.57 \pm 0.43
Koncz 2022	Hospital based, USA & Canada	Atrial fibrillation	Self-reported	18F-Florbetapir static PET	216 (7/209)	91 (42)	73 \pm 7	47 CN, 123 MCI and 46 AD	$\beta = -0.245$ (SE 0.332) ^e	
COD (between subject comparisons)									Patients	Controls
Kang 2020	Population based, Korea	ICA stenosis	MRA	11C-PiB static PET	281 (23/258)	146 (52)	69 \pm 8	CDR of 0	1.19 \pm 0.25	1.17 \pm 0.16
					196 (22/174)	134 (67)	73 \pm 7	CDR of 0.5–1	1.63 \pm 0.53	1.61 \pm 0.41
Unilateral COD (within subject comparisons)									Ipsilateral hemisphere	Contralateral hemisphere
Hansson 2018	Hospital based, Sweden	Unilateral ICA or MCA (near) occlusion	MRA, CTA or Doppler ultrasound	18F-Flutemetamol static PET	11	6 (55)	68 \pm 10	CN	1.37 \pm 0.29	1.38 \pm 0.27
Huang 2012	Hospital based, Taiwan	Unilateral ICA stenosis	–	18F-Florbetapir static PET	11 (5/6) ^f	5 (45)	–	6 CN and 5 vascular dementia	More uptake in the ipsilateral frontal, anterior cingulate, temporal, precuneus and occipital ROI * ^g	
Ogasawara 2019	Hospital based, Japan	Unilateral ICA stenosis with lateralized hypoperfusion	MRA, CTA or conventional angiography	18F-Florbetapir static PET	4	1 (25)	69 \pm 3	–	Ratio ipsilateral to contralateral hemisphere: 1.0 \pm 0.0 ^h	
Yamauchi 2019	Hospital based, Japan	Unilateral ICA or MCA occlusion or stenosis	MRA or conventional angiography	18F-FPYBF-2 dynamic PET	13	4 (31)	69 \pm 8	–	1.08 \pm 0.13	1.11 \pm 0.14

AD indicates Alzheimer's disease, CDR clinical dementia rating scale, CN cognitively normal, COD carotid occlusive disease, CTA computed tomography angiography, ECG electrocardiography, ICA internal carotid artery, ICD-codes International Classification of Diseases codes, MCA middle cerebral artery, MCI mild cognitive impairment, MRA magnetic resonance angiography, PET positron emission tomography, PiB Pittsburgh compound B, ROI region of interest, SUVR standardized uptake value ratio.

- Indicates missing information.

* Indicates a p -value of <0.05 .

^a The same cohort was subdivided three times into participants with and without a certain disease.

^b The patients were significantly older (79 \pm 8 versus 73 \pm 8 years), were more often male (64% versus 53%) and had lower cognitive scores (global z-score of -0.31 versus 0.29) than the controls.

^c The patients were significantly older (80 \pm 8 versus 74 \pm 8 years), were more often male (80% versus 50%) and had lower cognitive scores (global z-score of -0.37 versus 0.26) than the controls.

^d The patients were significantly older (81 \pm 5 versus 75 \pm 8 years) than the controls.

^e Coefficient for the association between the presence of atrial fibrillation and the amyloid- β SUVR. Adjusted for age, sex, education, APOE E4 carrier status, history of hypertension, cardiovascular disease, smoking, body mass index, fasting total cholesterol and fasting glucose levels.

^f The patients were significantly older (70 \pm 6 versus 60 \pm 3 years) than the controls. All the patients had vascular dementia and all the controls were cognitively normal.

^g P -value of <0.05 for the difference in amyloid SUVR between the ROIs in the hemisphere ipsilateral to ICA stenosis and the same ROIs in the healthy controls.

^h Ratio of amyloid load in the hemisphere ipsilateral to the ICA stenosis divided by the amyloid load in the contralateral hemisphere. Statistical tests were not performed.

participants with or without COD [23]. Overall effects were not assessed.

Four small, hospital-based studies included 33 patients with unilateral COD (39% female, mean age ranging from 68 to 70 years), of which one study also recruited 6 healthy controls without COD (50% female, mean age of 60 years) [17,18,21,24]. MRA was most frequently performed to establish the COD, but Doppler ultrasound, CT-angiography or conventional angiography were used as well [17,18,21,24]. Amyloid- β

accumulation was determined using static PET-scans [18,21,24], except for one study that used dynamic PET-scans [17]. The first study compared the amount of amyloid- β in the hemisphere ipsilateral to the COD of patients with vascular dementia to the amount of amyloid- β in the same hemisphere of healthy control participants without COD, who were 10 years younger on average [21]. They found that the hemisphere ipsilateral to the COD had significantly more amyloid- β than the hemisphere of healthy controls [21]. Differences between hemispheres

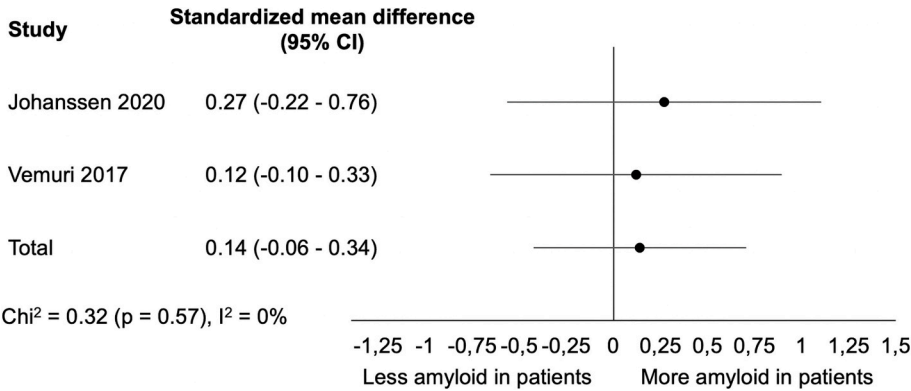


Fig. 2. Forest plot for atrial fibrillation and atrial flutter. The forest plots shows the association between the presence of atrial fibrillation or atrial flutter and the cortical amyloid- β standardized uptake value ratio. Data were pooled using a random effects model. A positive standardized mean difference indicates that participants with atrial fibrillation or atrial flutter have more amyloid- β than participants without atrial fibrillation or atrial flutter.

within the patients with dementia were smaller than between the patients and the healthy controls [21]. The exact SUVR was not reported or retrieved, but displayed in figures. The other three studies compared the burden of amyloid- β in the hemisphere ipsilateral to the COD to the contralateral hemisphere within patients. The individual studies did not find a significant difference in amyloid- β burden between hemispheres [17,18,24].

We were able to pool data of two out of four studies on unilateral COD, including 24 participants (Fig. 3) [17,18]. Both studies were of moderate quality. The other two studies could not be pooled because the necessary data (i.e. SUVR of amyloid- β PET in the ipsilateral and contralateral hemisphere) were not available [21,24]. There was no significant difference in the amyloid- β load between the hemisphere ipsilateral and contralateral to the COD in the pooled analyses (standardized mean difference in amyloid- β SUVR of -0.13, 95% CI -0.70–0.43, $p = 0.65$). One other study on COD could not be included in the meta-analyses, because this study compared the amyloid- β burden in participants with and without COD rather than comparing the amyloid- β burden between the hemispheres in patients with unilateral COD [23].

4. Discussion

This systematic review assessed studies on cerebral amyloid- β accumulation in patients with heart disease or COD. We did not find supportive evidence for the hypothesis that patients with heart disease or COD have more cerebral amyloid- β accumulation than adults without these diseases, although the quantity and quality of available data was limited.

Studies show that cardiovascular disease and cardiovascular risk factors increase the risk of dementia and also the risk of a clinical diagnosis of Alzheimer's disease [6,11], which might be attributed to increased amyloid- β accumulation. A number of studies have investigated whether cardiovascular risk factors are associated with an

increased burden of amyloid- β , but results were mixed. The Atherosclerosis Risk in Communities study found that participants with obesity or a higher number of cardiovascular risk factors in midlife had a higher chance of being amyloid- β positive on PET in late-life [26]. Similarly, the Alzheimer's Disease Neuroimaging Initiative reported that the presence of hypertension predisposed to an elevated amyloid- β SUVR after two years of follow-up [22]. In contrast, Insight 46, a population-based cohort study, reported no significant association between blood pressure or the Framingham Heart study-cardiovascular risk score and a positive amyloid- β PET in late-life [27,28]. As cardiovascular disease is a downstream effect of cardiovascular risk factors, the association between cardiovascular disease and amyloid- β burden might be stronger than the association with cardiovascular risk factors. Therefore, we focused on cardiovascular disease rather than cardiovascular risk factors, but did not find a significant association with amyloid- β burden.

One of the main methodological considerations influencing the findings is the number of studies and study quality. There were only eight studies that determined the association between cardiovascular disease and the cerebral burden of amyloid- β . These studies investigated populations of limited sample size and in case of the population-based cohorts also with a low burden of disease. There were relatively few patients in comparison to controls and patients in population-based cohorts tend to have milder pathology than patients from hospital-based cohorts. This hampers their power to detect a significant association. In addition, studies on heart valve disease, another common type of heart disease, are lacking. Lastly, the cognitive status of the participants is not always described or properly assessed with a full neuropsychological assessment, while this can influence the association between cardiovascular disease and amyloid- β burden [29].

The selection of the reference participants is also important, as differences in age or cognitive impairment are strongly associated with the amount of cerebral amyloid- β , with more cognitive impairment and higher amyloid- β load in older subjects [4]. All but one included study

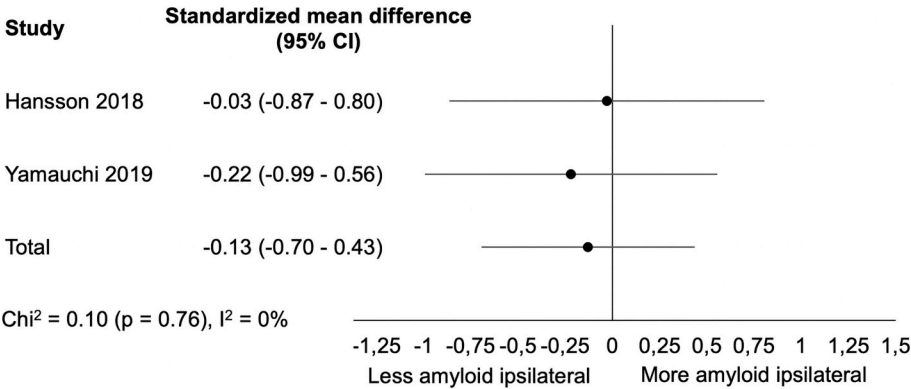


Fig. 3. Forest plot for unilateral carotid occlusive disease. The forest plots shows the association between the hemispheres ipsilateral and contralateral to the carotid occlusive disease and the cortical amyloid- β standardized uptake value ratio. Data were pooled using a random effects model. A positive standardized mean difference indicates that there is more amyloid- β in the hemisphere ipsilateral to the carotid occlusive disease than in the contralateral hemisphere.

had an appropriate reference group either by comparing patients and controls drawn from the same population-based cohort [16,23,25], by including age-matched reference participants in the hospital-based cohort [22], or by making within subject comparisons, i.e. comparing one hemisphere to the other [17,18,24]. The importance of this selection is supported by the only study that found a difference in amyloid- β between the hemispheres in patients with unilateral COD [21]. In this study, the affected hemisphere of patients with vascular dementia was compared with the same hemisphere of healthy reference participants without COD, who were 10 years younger on average [21]. Although differences between hemispheres within the patients with dementia were not reported by numbers, the figures show considerable smaller differences within the patients with dementia than between the patients and the healthy controls [21].

The last important methodological factor is the type of PET-protocol. Only one study performed dynamic PET-scans, while most used static PET-scans. For a static PET-scan, only a few frames are recorded approximately one hour after the injection of the radioactive tracer. In so called dynamic PET-scans, frames are made from the time of injection to approximately 90 min afterwards. Dynamic scanning enables full quantification of the amyloid- β load while simultaneously correcting for cerebral blood flow (CBF). For scans that are obtained with a static method, this is not possible and only semi-quantitative measurements like SUVR can be done, without correction for CBF. This is especially important in patients in whom CBF could be reduced, such as in patients with heart disease or COD. Cerebral hypoperfusion is likely to affect the distribution of the PET-tracer by changing the delivery to and clearance from the brain [30]. In other words, the tracer might not be transported as fast or in the same concentration in patients or regions with hypoperfusion as compared to participants with a normal perfusion. So the absence of cerebral amyloid- β could be the result of low perfusion rather than a true low amyloid- β burden. This means that studies that have performed static PET-scans may have missed differences in amyloid- β between patients with and without heart disease or COD. Only one study performed dynamic PET-scans and reported no significant difference in amyloid- β accumulation between the hemisphere ipsilateral and contralateral to the ICA stenosis or occlusion [17]. However, this study was small and warrants replication in a larger cohort.

Based on the observation that cardiovascular disease is associated with a clinical diagnosis of Alzheimer's disease [6], we hypothesized that heart disease and COD could be associated with increased cerebral amyloid- β burden. Both diseases could result in impaired cerebral perfusion [14] and hypoperfusion has been suggested to cause an increase in amyloid- β burden [13]. We did not find supportive evidence for our hypothesis. Therefore, the association between cardiovascular disease and a clinical diagnosis of Alzheimer's disease may be explained by concomitant vascular brain injury, such as white matter hyperintensities [31,32]. Subtle vascular brain injury may not preclude a participant to meet the clinical criteria for Alzheimer's disease [33,34]. This means that the reported association between cardiovascular disease and Alzheimer's disease, may not reflect pure Alzheimer's disease, but rather dementia of mixed origin.

Strengths of our study include a comprehensive literature search that was built by an information specialist with input from the study team. Additionally, we formally assessed the quality of the included studies according to the recommendations for evaluating bias in observational studies and tailored the criteria to fit our research question. Some limitations should be taken into account. There was a limited number of published studies on cerebral amyloid- β accumulation in patients with heart disease or COD. The studies that were performed, had considerable heterogeneity in their methodology and reporting of outcomes. We contacted the corresponding author for additional data, but did not receive a response from all authors. Nonetheless, we pooled data in a meta-analysis where possible.

5. Conclusions

We did not find supportive evidence for the notion that cardiovascular diseases increase cerebral amyloid- β accumulation, although the quantity and quality of available studies was limited. Future research should aim to include more patients, derived from representative populations, and should use dynamic PET-scans to account for the differences in cerebral perfusion between patients and reference participants. Alternatively, the association between cardiovascular disease and dementia could be explained by factors other than amyloid- β [28,35,36], such as cerebral ischemia [37–39] or a proinflammatory state [40].

Author contributions

Conception and design: all authors. Collection and assembly of data: NS, NT. Quality assessment: NS, NT. Data analysis: NS. Results interpretation: NS, NT, AL, WF. Manuscript writing: NS, NT, AL, WF. Critical and intellectual revision of manuscript: all authors. Final approval of manuscript: all authors.

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Declaration of Competing Interest

None.

Data availability

The data that supports the findings of this study are included in the article or supplementary material, further inquiries can be directed to the corresponding author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jns.2023.120551>.

References

- [1] G. Livingston, J. Huntley, A. Sommerlad, D. Ames, C. Ballard, S. Banerjee, et al., Dementia prevention, intervention, and care: 2020 report of the lancet commission, *Lancet*. 396 (2020) 413–446.
- [2] C.L. Satizabal, A.S. Beiser, V. Chouraki, G. Chêne, C. Dufouil, S. Seshadri, Incidence of dementia over three decades in the Framingham heart study, *N. Engl. J. Med.* 374 (2016) 523–532.
- [3] P. Scheltens, B. De Strooper, M. Kivipelto, H. Holstege, G. Chételat, C.E. Teunissen, et al., Alzheimer's disease, *Lancet*. 397 (2021) 1577–1590.
- [4] R.O. Roberts, J.A. Aakre, W.K. Kremers, M. Vassilaki, D.S. Knopman, M.M. Mielke, et al., Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting, *JAMA Neurol.* 75 (2018) 970–979.
- [5] W.M. Van der Flier, I. Skoog, J.A. Schneider, L. Pantoni, V. Mok, C.L.H. Chen, et al., Vascular cognitive impairment, *Nat Rev Dis Primers*. 4 (2018) 18003, <https://doi.org/10.1038/nrdp.2018.3>.
- [6] F.J. Wolters, R.A. Segufa, S.K.L. Darweesh, D. Bos, M.A. Ikram, B. Sabayan, et al., Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis, *Alzheimers Dement.* 14 (2018) 1493–1504.

- [7] E.A. Oudeman, L.J. Kappelle, R.M. Van den Berg-Vos, H.C. Weinstein, E. Van den Berg, C.J.M. Klijn, Cognitive functioning in patients with carotid artery occlusion; a systematic review, *J. Neurol. Sci.* 394 (2018) 132–137.
- [8] R. Ossenkoppele, W.J. Jansen, G.D. Rabinovici, D.L. Knol, W.M. Van der Flier, B.N. M. Van Berckel, et al., Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis, *JAMA*. 313 (2015) 1939–1949.
- [9] Z. Arvanitakis, A.W. Capuano, S.E. Leurgans, D.A. Bennett, J.A. Schneider, Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study, *Lancet Neurol.* 15 (2016) 934–943.
- [10] J. Ryan, P. Fransquet, J. Wrigglesworth, P. Lacaze, Phenotypic heterogeneity in dementia: a challenge for epidemiology and biomarker studies, *Front. Public Health* 6 (2018) 181, <https://doi.org/10.3389/fpubh.2018.00181>.
- [11] D.E. Barnes, K. Yaffe, The projected effect of risk factor reduction on Alzheimer's disease prevalence, *Lancet Neurol.* 10 (2011) 819–828.
- [12] J.T. Yu, W. Xu, C.C. Tan, S. Andrieu, J. Suckling, R. Evangelou, et al., Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials, *J. Neurol. Neurosurg. Psychiatry* 91 (2020) 1201–1209.
- [13] A. Gupta, C. Iadecola, Impaired A β clearance: a potential link between atherosclerosis and Alzheimer's disease, *Front. Aging Neurosci.* 7 (2015) 115, <https://doi.org/10.3389/fnagi.2015.00115>.
- [14] A.E. Leeuwis, A.M. Hooghiemstra, E.E. Bron, S. Kuipers, E.A. Oudeman, T. Kalay, et al., Cerebral blood flow and cognitive functioning in patients with disorders along the heart-brain axis, *Alzheimers Dement.* 6 (2020), e12034, <https://doi.org/10.1002/trc2.12034>.
- [15] M. Ouzzani, H. Hammady, Z. Fedorowicz, A. Elmagarmid, Rayyan - a web and mobile app for systematic reviews, *Syst Rev.* 5 (2016) 210, <https://doi.org/10.1186/s13643-016-0384-4>.
- [16] M.C. Johansen, T.H. Mosley, D.S. Knopman, D.F. Wong, C. Ndumele, A.M. Shah, et al., Associations between atrial cardiopathy and cerebral amyloid: the ARIC-PET study, *J. Am. Heart Assoc.* 9 (2020), e018399, <https://doi.org/10.1161/JAHA.120.018399>.
- [17] H. Yamauchi, S. Kagawa, M. Takahashi, N. Oishi, M. Ono, T. Higashi, Misery perfusion and amyloid deposition in atherosclerotic major cerebral artery disease, *Neuroimage Clin.* 22 (2019), 101762, <https://doi.org/10.1016/j.nicl.2019.101762>.
- [18] O. Hansson, S. Palmqvist, H. Ljung, T. Cronberg, D. Van Westen, R. Smith, Cerebral hypoperfusion is not associated with an increase in amyloid β pathology in middle-aged or elderly people, *Alzheimers Dement.* 14 (2018) 54–61.
- [19] J.P. Vandembroucke, E. Von Elm, D.G. Altman, P.C. Göttsche, C.D. Mulrow, S. J. Pocock, et al., Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration, *Epidemiology*. 18 (2007) 805–835.
- [20] G.A. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, et al., The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, Available online at, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, 2000.
- [21] K.L. Huang, K.J. Lin, M.Y. Ho, Y.J. Chang, C.H. Chang, S.P. Wey, et al., Amyloid deposition after cerebral hypoperfusion: evidenced on [(18)F]AV-45 positron emission tomography, *J. Neurol. Sci.* 319 (2012) 124–129.
- [22] R. Koncz, W. Wen, S.R. Makkar, B.C.P. Lam, J.D. Crawford, C.C. Rowe, et al., The interaction between vascular risk factors, cerebral small vessel disease, and amyloid burden in older adults, *J. Alzheimers Dis.* 86 (2022) 1617–1628.
- [23] K.M. Kang, M.S. Byun, J.H. Lee, D. Yi, H.J. Choi, E. Lee, et al., Association of carotid and intracranial stenosis with Alzheimer's disease biomarkers, *Alzheimers Res. Ther.* 12 (2020) 106, <https://doi.org/10.1186/s13195-020-00675-6>.
- [24] K. Ogasawara, S. Fujiwara, K. Chida, K. Terasaki, M. Sasaki, Y. Kubo, Reduction in amyloid β deposition on 18F-florbetapir positron emission tomography with correction of cerebral hypoperfusion after endarterectomy for carotid stenosis, *Am J Nucl Med Mol Imaging*. 9 (2019) 316–320.
- [25] P. Vemuri, T.G. Lesnick, S.A. Przybelski, D.S. Knopman, V.J. Lowe, J. Graff-Radford, et al., Age, vascular health, and Alzheimer's disease biomarkers in an elderly sample, *Ann. Neurol.* 82 (2017) 706–718.
- [26] R.F. Gottesman, A.L.C. Schneider, Y. Zhou, J. Coresh, E. Green, N. Gupta, et al., Association between midlife vascular risk factors and estimated brain amyloid deposition, *JAMA*. 317 (2017) 1443–1450.
- [27] C.A. Lane, J. Barnes, J.M. Nicholas, C.H. Sudre, D.M. Cash, T.D. Parker, et al., Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (insight 46): an epidemiological study, *Lancet Neurol.* 18 (2019) 942–952.
- [28] C.A. Lane, J. Barnes, J.M. Nicholas, C.H. Sudre, D.M. Cash, I.B. Malone, et al., Associations between vascular risk across adulthood and brain pathology in late life: evidence from a British birth cohort, *JAMA Neurol.* 77 (2020) 175–183.
- [29] P.J. Visser, F. Verhey, D.L. Knol, P. Scheltens, L.O. Wahlund, Y. Freund-Levi, et al., Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study, *Lancet Neurol.* 8 (2009) 619–627.
- [30] B.N.M. Van Berckel, R. Ossenkoppele, N. Tolboom, M. Yaqub, J.C. Foster-Dingley, A.D. Windhorst, et al., Longitudinal amyloid imaging using 11C-PiB: methodologic considerations, *J. Nucl. Med.* 54 (2013) 1570–1576.
- [31] C. Qiu, L. Fratiglioni, A major role for cardiovascular burden in age-related cognitive decline, *Nat. Rev. Cardiol.* 12 (2015) 267–277.
- [32] J.M. Wardlaw, C. Smith, M. Dichgans, Small vessel disease: mechanisms and clinical implications, *Lancet Neurol.* 18 (2019) 684–696.
- [33] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, E.M. Stadlan, Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease, *Neurology*. 34 (1984) 939–944.
- [34] G.M. McKhann, D.S. Knopman, H. Chertkow, B.T. Hyman, C.R. Jack Jr., C. H. Kawas, et al., The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimers Dement.* 7 (2011) 263–269.
- [35] R.F. Gottesman, T.H. Mosley, D.S. Knopman, Q. Hao, D. Wong, L.E. Wagenknecht, et al., Association of intracranial atherosclerotic disease with brain β -amyloid deposition: secondary analysis of the ARIC study, *JAMA Neurol.* 77 (2020) 350–357.
- [36] A.M. Gustavsson, D. Van Westen, E. Stomrud, G. Engström, K. Nägga, O. Hansson, Midlife atherosclerosis and development of Alzheimer or vascular dementia, *Ann. Neurol.* 87 (2020) 52–62.
- [37] J. Sundbøll, E. Horváth-Puhó, K. Adelborg, M. Schmidt, L. Pedersen, H.E. Bøtker, et al., Higher risk of vascular dementia in myocardial infarction survivors, *Circulation*. 137 (2018) 567–577.
- [38] R.F.A.G. De Bruijn, J. Heeringa, F.J. Wolters, O.H. Franco, B.H.C. Stricker, A. Hofman, et al., Association between atrial fibrillation and dementia in the general population, *JAMA Neurol.* 72 (2015) 1288–1294.
- [39] J.L. Dearborn, Y. Zhang, Y. Qiao, M.F.K. Suri, L. Liu, R.F. Gottesman, et al., Intracranial atherosclerosis and dementia: the atherosclerosis risk in communities (ARIC) study, *Neurology*. 88 (2017) 1556–1563.
- [40] M.T. Heneka, M.J. Carson, J. El Khoury, G.E. Landreth, F. Brosseron, D.L. Feinstein, et al., Neuroinflammation in Alzheimer's disease, *Lancet Neurol.* 14 (2015) 388–405.