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FEATURED ARTICLE

Longitudinal changes in cerebral blood flow and their relation with cognitive decline in patients with dementia: Current knowledge and future directions

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Abstract

The pathophysiology underlying cognitive decline is multifactorial, with increasing literature suggesting a role for cerebrovascular health. Cerebral blood flow (CBF) is an important element of cerebrovascular health, which raises questions regarding the relation between CBF and cognitive decline. Cross-sectional studies demonstrate lower CBF in patients with cognitive decline compared to healthy age-matched peers. Remarkably, longitudinal studies do not support a link between CBF reductions and cognitive decline. These studies, however, are often limited by small sample sizes and may therefore be underpowered to detect small effect sizes. Therefore, through a systematic review and meta-analysis of longitudinal studies, we examined whether longitudinal changes in global CBF are related to cognitive decline in subjects with Alzheimer's disease, and qualitatively described findings on regional CBF. Considering the growing impact of dementia and the lack of treatment options, it is important to understand the role of CBF as a prognostic biomarker and/or treatment target in dementia.

KEYWORDS
Alzheimer's disease, cerebrovascular circulation, cognition, dementia, meta-analysis, single-photon emission computed tomography, systematic review

1 | NARRATIVE

Approximately 50 million people are currently diagnosed with dementia worldwide, and this number is expected to rise dramatically.[1] Dementia accounted for a 38.3% increase in all-age disability-adjusted life-year (DALY) counts worldwide between 2007 and 2017.[2] This highlights the impact of dementia on the quality of life of individual patients, but also the growing global societal impact, making dementia a worldwide public health priority. The pathophysiology underlying dementia is a multifactorial process, with mounting evidence for a role for the cardiovascular system.[3–5] For example, traditional cardiovascular risk factors are independently associated with cognitive decline,[6–9] while peripheral artery endothelial dysfunction is associated with cognitive impairment in older adults.[10,11] Moreover, cerebrovascular injuries[12,13] and cerebrovascular dysfunction[14,15] have been associated with cognitive impairment. These vascular risk factors increase, as expected, the risk of vascular cognitive impairment or vascular dementia, but also the risk of Alzheimer's disease (AD).[3,16]

The brain, with less than 2% of body weight, represents ≈15% to 20% of total body metabolism and consequently receives ≈15% to 20% of total blood flow.[17] Given the importance of cerebral blood flow (CBF) in the regulation of cerebrovascular health,[18] impairments

in CBF may be linked to cognitive decline. Studies that have examined CBF in relation to cognitive decline, typically using modern imaging techniques such as single-photon emission computed tomography (SPECT) and transcranial Doppler, are mostly cross-sectional. The majority of these cross-sectional studies have suggested lower CBF in those with cognitive decline.[14,17] In contrast, studies that adopted a longitudinal design do not support this observation. However, these longitudinal studies are often limited by small sample sizes, making these studies underpowered to detect small effect sizes. Moreover, several of these studies are also subject to a high level of heterogeneity (e.g., etiology, disease stage, measurement techniques). These limitations make it difficult to truly understand the longitudinal relation between changes in CBF and cognitive decline.

Considering the growing global impact of dementia and the current lack of effective treatment options, it is important to better understand the role of CBF as a potential target for prevention and treatment, or as a biomarker to predict cognitive decline or disease progression. Therefore, through a systematic review and meta-analysis of longitudinal studies that repeatedly measured both CBF and cognitive function in patients with probable AD at the time of follow-up, we examined whether longitudinal changes in global CBF (gCBF) are related to cognitive decline in dementia. Moreover, we qualitatively described findings from studies selected by systematic review on longitudinal changes in regional CBF (rCBF) in patients with dementia at the time of follow-up.

By systematically reviewing current literature, our search and selection process yielded 20 studies that adopted a longitudinal design, with measurements of CBF (global and/or regional) and cognitive function at baseline and follow-up in patients with probable AD. Five studies[19–23] that presented longitudinal findings on global CBF (assessed by SPECT), and cognitive function (reported as Mini-Mental State Examination [MMSE] score) were eligible for quantitative synthesis in a meta-analysis, which demonstrated yearly decreases in gCBF (1.32%) and cognitive function (10.8%, representing 2.4 MMSE points) in patients with probable AD. These findings are in line with findings from one previous study[24] that addressed gCBF, although this specific study was not suitable for inclusion in the meta-analysis because it quantified gCBF differently, namely as the cortico-cerebellar ratio. Interestingly, while none of the individual studies included in our meta-analysis demonstrated a significant longitudinal decrease in gCBF in patients with dementia, our meta-analysis revealed an overall significant decline in gCBF in this group. This highlights the strength and importance of a meta-analysis, which confirms that longitudinal decline in gCBF is present in patients with dementia. This also suggests that individual studies are frequently underpowered to detect longitudinal changes in gCBF across a relatively short follow-up period.

Moreover, decreases in gCBF and cognitive function in patients with probable AD seem significantly related across longitudinal follow-up.

1.1 | Reduction in global CBF with normal aging

Only one out of the five studies from our meta-analysis included a control group, comprising 18 cognitively healthy age-matched individuals that underwent gCBF assessments at baseline and after follow-up.[19] This study reported a mean decrease rate of 0.3 mL/100 g/minute per year, reflecting an annual decrease of ≈0.5%. This annual decrease rate is in line with a previous study in the general population, including 34 individuals aged 22 to 82 years, that also demonstrated an annual linear decline of 0.5% in gCBF from early adulthood.[25] More recent work suggests that the rate of decline in gCBF in normal aging may even be lower, at 0.8 mL/100 g/minute per decade (i.e., 0.14% annually).[26] Thus, the average annual decline of 1.32% in gCBF in patients with probable AD is between 3 to 10 times higher than in normal aging. Together with the observation that the decline in gCBF is related to cognitive decline, our observations highlight the potential clinical relevance of measuring and better understanding the longitudinal changes in gCBF in dementia.

RESEARCH IN CONTEXT

1. **Systematic Review**: We identified studies using traditional sources that reported results on longitudinal changes in cerebral blood flow (CBF; assessed by single-photon emission computed tomography imaging) and cognitive function (Mini-Mental State Examination [MMSE]) in patients with dementia. Findings on global CBF (gCBF) changes and their relation to changes in MMSE were included in a meta-analysis. Findings on regional CBF (rCBF) were qualitatively described.
2. **Interpretation**: This article elucidates the presence and amount of longitudinal gCBF reductions in Alzheimer's disease (AD) that are linked to cognitive decline, probably explained by rCBF reductions in areas linked to AD pathology. Therefore, we propose a role for CBF as a biomarker for monitoring and treating dementia, and suggest that CBF reductions are mainly driven by AD pathology, rather than by vascular disease.
3. **Future Directions**: Research should investigate targetable vascular components of CBF reductions in early-stage dementia, and examine the causality among CBF reductions, dementia-related neuropathology, and brain atrophy, regardless of cardiovascular risk.

1.2 | Potential mechanisms

Our meta-regression analysis revealed a significant correlation between the magnitude of decline in gCBF and the magnitude of cognitive decline. To understand the clinical consequences of this substantial decline in gCBF in patients with probable AD, we have to address questions about the potential underlying mechanisms for this close relation between gCBF and cognitive decline. The reduction in gCBF can be partially explained by changes in vascular structure

and function that occur with aging, such as arterial stiffening, wall thickening, and endothelial dysfunction,[27] that even in healthy individuals contribute to decreases in (cerebro)vascular health.[17,28] In patients with probable AD, additional vascular pathology has been observed, such as amyloid angiopathy, blood-brain barrier dysfunction, and altered vascular anatomy (e.g., increased vessel tortuosity).[29] Hence, in AD, both normal vascular aging and dementia-related vascular pathologies can contribute to changes in cerebrovascular structure and function, which might contribute to both decreases in gCBF and cognitive impairment, on top of the effects caused by AD neuropathology. This mechanism could explain the now well-known observations that multiple vascular risk factors and lifestyle factors, such as hypertension, smoking, and physical inactivity, have been linked to AD.[30] In this scenario, the decline in gCBF, explained by a combination of AD pathology and associated vascular risk factors, may be intrinsically linked to cognitive decline.

An alternative mechanism is that the reduction in gCBF in AD is fully explained by neurodegeneration. In this scenario, amyloid beta (Aß) and tau accumulation lead to neurodegeneration and brain atrophy, which drives the decline in CBF. Because CBF is closely linked to global brain volume, the whole brain atrophy in AD may, at least in part, contribute to the reduction in gCBF. Indeed, the reported average reduction in global brain volume in AD is 1% to 3% per year,[31,32] while in healthy aging, this annual reduction reaches only approximately 0.5%.[32,33] The magnitude of the reduction in brain volume in AD is remarkably similar to the reduction in gCBF that we have identified. Although this would support the hypothesis that the reduction in gCBF is explained by atrophy, there is considerable debate in the literature in which order these mechanisms occur. Some studies support the hypothesis that reductions in gCBF precede global brain atrophy,[29,34] whereas others support the opposite direction.[35] We believe our observations and discussion of regional versus global changes in CBF below may shed more light on this debate.

1.3 | Global versus regional CBF

Our observation of a small, but significant, decline in global CBF begs the question whether this change reflects a true generalized change across the brain or represents a more focal change of specific brain regions. We therefore aimed to qualitatively aggregate and analyze findings from studies examining regional CBF in patients with dementia. Collectively, when further exploring rCBF changes subsequent to gCBF changes, we found that significant longitudinal decreases in rCBF were reported by multiple individual studies at the regional level, either at a more extensive (i.e., lobular) or a small (i.e., specific brain structures such as gyri) level. This indicates that studies are better capable of detecting changes in rCBF compared to detecting changes in gCBF. Our findings support the hypothesis that (minor) changes in gCBF are predominantly explained by changes in rCBF. Importantly, specific brain structures were consistently identified showing decreases in rCBF. Specifically, at a lobular level, the temporal, parietal, and limbic lobes seem to be more pronouncedly subject to cerebral hypoperfusion compared to the frontal and occipital lobes in patients with probable AD. This suggests that decreases in CBF are mostly present in specific small brain structures rather than at a more extensive, that is, lobular or global level.

Combining this with the finding from our meta-analysis of a strong relation between decreases in gCBF and cognitive function, this raises the question whether these specifically affected small brain structures are in coherence with phenotypical manifestations within the cognitive domain in patients with probable AD. The angular gyrus, precuneus, superior temporal gyrus, middle temporal gyrus, parahippocampal gyrus, anterior cingulate, and inferior parietal lobule were consistently found to present longitudinal decreases in CBF. Interestingly, all of these brain structures are linked to relevant functions within the cognitive domain in AD.[36–41] This suggests that regions that show marked reductions in CBF are those that are involved in the phenotypical manifestation of AD neuropathology, which would explain why hypoperfusion in specific brain areas is linked to cognitive decline in patients with probable AD. These observations derived from longitudinal studies are in line with previous cross-sectional observations, also linking lower regional CBF levels to disease status and progression in patients with early-stage dementia (i.e., subjective cognitive impairment, mild cognitive impairment [MCI], and early AD).

Our observations argue against the hypothesis of a generalized reduction in CBF across all regions through the impact of vascular risk factors in AD.[6] In the simplified "chicken or egg" discussion of whether the reduction in CBF is caused by AD, or whether AD is caused by a reduction in CBF (due to vascular disease), one would expect a more global reduction in CBF, or a more random distribution of reductions in regional CBF if the primary insult was vascular. It is unlikely, for example, that general cerebrovascular disease (endothelial dysfunction, embolic stroke, atherosclerosis) would show such a specific regional clustering. Rather, the observation that CBF is reduced in brain areas that are specifically associated with AD pathology (Aß and tau accumulation) strongly suggests that the progressive regional reduction in CBF, that is linked to progressive cognitive decline, is a consequence of AD.

1.4 | Interpretation

The meta-analysis in this study reveals a longitudinal decrease in gCBF in patients with dementia, while the individual study results did not identify such an effect. Potentially, these individual studies were underpowered to detect significant changes in gCBF. This lack of statistical power can be explained by a relatively short follow-up and/or a relatively small effect size in relation to the resolution of SPECT. In addition, measuring CBF is subject to variability, both related to biological and measurement variation. The difficulty of performing these studies, combined with the challenging task of sufficient patient recruitment, may explain the relatively small sample size. In these cases, a meta-analysis may be a powerful tool to reduce the impact of variability of the measurement error and relatively low power of individual

studies. Our findings indicate that in patients with probable AD, progressive reductions in CBF are closely linked to progression in cognitive decline, and that these reductions in CBF are observed in brain areas affected by AD pathology. It is important to acknowledge that our meta-analysis is based on a relatively small number of studies. However, this field exploring the potential link between CBF and cognitive decline is characterized by heterogeneity in methodology, imaging techniques, and methods of evaluating cognitive decline. Therefore, we specifically focused on a single neuroimaging technique to provide robust insight into this question, with SPECT being the technique that yielded the largest volume of studies and individuals. Importantly, it should be realized that even when focusing on a single neuroimaging technique, a certain level of measurement variability is present, for example, the use of different radioactive tracers. Moreover, one limitation of the relatively small sample size is that statistically correcting for potential covariates, such as age and sex, was not allowed. This should be considered when interpreting our results, as potential between-group differences may be present. Last, these studies were not designed to prove causality between cognitive decline and CBF. Still, with these cautions for potential limitations in mind, our observations do suggest that AD pathology, and not vascular disease, is the main driver for these reductions in CBF. This in turn will make it less likely that vascular interventions aimed strictly at restoring or improving CBF can prevent or reduce progressive cognitive decline in AD dementia.

However, our observations do not exclude that vascular disease contributes to AD. We have specifically investigated patients in the stage of AD dementia, and looked at the link between progressive reductions in CBF and progression of cognitive decline. This is clearly different from the early (preclinical and early symptomatic) stages of AD, for which previous studies have shown that CBF is reduced very early in the development of AD.[4,5] Vascular risk factors may aggravate the vascular pathology associated with amyloid angiopathy or blood-brain barrier dysfunction caused by AD, and contribute to the acceleration of the regional neuropathology, causing excessive regional vascular dysfunction and local impairment of the neurovascular unit.[42] We think that such factors play a role mostly in the early stages of disease, which can span decades, and that the contribution of these vascular factors to brain dysfunction and ultimately to cognitive decline takes several years to develop. The potential for vascular prevention aiming at preserving CBF would therefore be strongest in very early stages of AD, but much less so in the dementia stage.

Based on our observations, we propose a role for CBF as a biomarker to monitor disease progression or responses to treatment in dementia, because we provide evidence that the decline in CBF is closely related to cognitive decline in AD.

1.5 | Future directions

We recommend future work to test the following hypotheses: (1) reduced global CBF in the early stages of AD has vascular components amenable to treatment, and (2) reduced global CBF is, regardless of cardiovascular risk, caused by dementia-related neuropathology (e.g., amyloid angiopathy) and/or neuronal loss with concomitant decreases in neuronal demand for blood supply.

2 | METHODS AND RESULTS

A systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[43] The protocol for this study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CDR42019148065.

2.1 | Search

Supervised by DT and coordinated by an information specialist from the university library, two authors (RW and DS) constructed search strategies for searching MEDLINE (index period 1946—2020), Embase (index period 1974—2020), and Web of Science Core Collection (index period 1945—2020). Each database was searched for free text and index terms associated with (1) measures of cerebrovascular function (e.g., CBF), (2) disease of interest and measures of cognitive function (e.g., MMSE), and (3) imaging techniques that can be used for indicating measures of cerebrovascular function (e.g., SPECT). Based on our in- and exclusion criteria, restrictions were only applied on advice by the information specialist, differing for each database. The detailed search strategies and restrictions for searching each of the three databases can be found in Appendix A. The primary search (July 31, 2019) yielded 6945 unique records available for title and abstract screening, with another 575 when performing a final search update (March 30, 2020).

2.2 | Eligibility criteria and study selection

Eligible studies were selected based on predefined eligibility criteria. During the first screening and selection rounds, it was found that the original eligibility criteria were too unbounded. Therefore, the original eligibility criteria were modified during the course of this study. Ultimately, only studies with a longitudinal study design were selected that included patients with a clinical diagnosis of AD, vascular dementia (VaD), or mixed-type dementia at the time of follow-up, according to the Association Internationale pour la Recherche et l'Enseignement en Neurosciences[44] and/or National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[45] and/or Diagnostic and Statistical Manual of Mental Disorders (any edition; latest 5th edition[46]) criteria. Patients with MCI at baseline, who did not progress to dementia during the follow-up period, were not considered. Studies were excluded that only selected patients based on one specific comorbidity (e.g., diabetes), that could potentially interfere with outcomes of interest (e.g., effects of diabetes on CBF). If, however, these comorbidities were present in only a subset of patients, representative of the prevalence of this comorbidity in a clinical dementia population, the study was included. At least one patient group had to be studied observationally or was

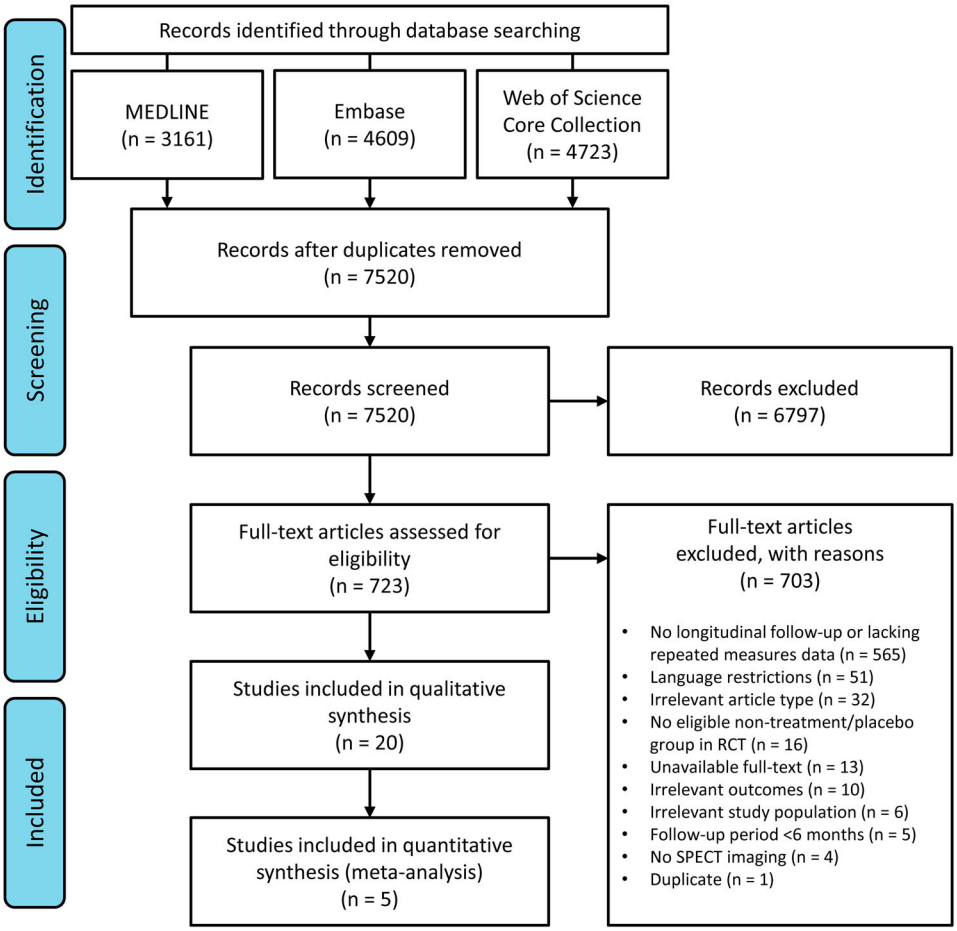

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart of the literature search, screening, and selection process

subjected to a placebo or non-treatment condition. Patients receiving medication as part of routine care, such as acetylcholinesterase inhibitors, were acceptable for inclusion. Studies had to report results on measures of both global cognitive function (assessed by MMSE, Montreal Cognitive Assessment, Cambridge Cognitive Examination, or Alzheimer's Disease Assessment Scale-Cognitive subscale) and CBF (assessed by SPECT) at baseline and (the change) after at least 6 months of follow-up. For CBF, only studies using SPECT were included. Initially, a broader search was used, but this led to a too heterogeneous set of studies with widely varying imaging modalities and small sample sizes. Therefore, the inclusion criteria were restricted by only including studies that used the imaging technique that was found to be used most, that is, SPECT. For the purpose of the meta-analysis on the relation between longitudinal changes in global CBF and cognitive function, studies had to quantitatively report numbers of either means and variances or effect sizes and appropriate statistics. For qualitative descriptive analyses on regional CBF, studies had to provide data (quantitative and/or graphical) or statements that ensured whether regional CBF significantly changed across follow-up. Reasons for exclusion of studies were (1) unavailable full text; (2) publication language other than English, Dutch, German, French, or Russian; (3) conference abstracts; or (4) double reporting. After deduplication of the records yielded by the search, the selection of studies comprised a round of title and abstract screening and a subsequent round of full-text screening. Each screening round was independently performed *in duplo* by two authors (RW and DS). For consensus, disagreements were resolved by discussion and/or by consulting a third reviewer (JC). Eventually, 20 studies[19–24,47–60] were included in this systematic review, including five studies[19–23] eligible for quantitative synthesis. A flowchart of the study identification and selection process can be found in Figure 1.

To provide a complete overview of studies that aimed to observationally examine longitudinal changes in cerebral hemodynamics and cognitive function in patients with a diagnosis of AD at follow-up, we have added a table in Appendix B with general study characteristics of four additional studies addressing this aim using an imaging technique other than SPECT.

2.3 | Risk of bias

Study quality was assessed for all included studies using the National Heart, Lung, and Blood Institute "Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group."[61] Independent *in duplo* appraisal by two authors (RW and AB) was

TABLE 1 Overview of the study characteristics of the included studies

Study (ID. First author, year)	Patient (sub)group(s) of interest	N (m:f)	Age at baseline (years)	FU type	FU period (months)	Measure(s) of cognitive function	SPECT radioactive tracer
1. Philpot, 1991[47]	AD	10 (8:3)[c]	69 ± 10[c]	Obs	15 ± 2[b]	MMSE; CAMCOG	^{99m}Tc-HMPAO
2. Brown, 1995[48]	AD	24 (NR)	74 ± 7[d]	Obs	24 ± NR[b]	CAMCOG	^{99m}Tc-HMPAO
3. Celsis, 1997[19]	AD	18 (11:7)	64 ± 7	Obs	36 ± 18[b]	MMSE	^{133}Xe
	AD – ARCD at baseline	5 (13:11)[c]	62 ± 9[c]	Obs	24 ± 12[b,c]	MMSE	^{133}Xe
4. Sachdev, 1997[24]	AD	10 (4:6)	71 ± 13	Obs	24 ± 5	MMSE	^{99m}Tc-HMPAO
5. Kogure, 2000[20]	AD	32 (13:19)	72 ± 8[a]	Obs	15 ± 4[a]	MMSE	^{99m}Tc-ECD
6. Nakano, 2001[21]	AD	20 (13:7)	71 ± 6	RCT – PbO	12 ± NR	MMSE	^{99m}Tc-ECD
7. Nobili, 2002[49]	AD	13 (4:9)	71 ± 6	RCT – PbO	13 ± 1	MMSE	^{99m}Tc-HMPAO
8. Lojkowska, 2003[50]	AD and VaD	8 (NR)	65 ± 10	RCT – NT	12 ± NR	MMSE	^{99m}Tc-HMPAO
9. Sakamoto, 2003[22]	AD – ε4 carriers	11 (6:5)	71 ± 4	Obs	24 ± 1	MMSE	^{99m}Tc-ECD
	AD – ε4 non-carriers	12 (5:7)	70 ± 8	Obs	24 ± 2	MMSE	^{99m}Tc-ECD
10. Tonini, 2003[51]	AD	13 (7:6)	78 ± 6	Obs	6 ± NR[e]	MMSE	^{99m}Tc-HMPAO
11. Lee, 2004[52]	AD	15 (5:10)	70 ± 5	Obs	19 ± 7	MMSE	^{99m}Tc-HMPAO
12. Huang, 2007[53]	AD – MCI at baseline	16 (8:8)	62 ± 7	Obs	19 ± 9	MMSE	^{99m}Tc-HMPAO
13. Hanyu, 2010[54]	AD – rapid progression	24 (10:14)	76 ± 7	Obs	37 ± 7	MMSE	[^{123}I]IMP
	AD – slow progression	24 (9:15)	76 ± 6	Obs	37 ± 6	MMSE	[^{123}I]IMP
14. Hirao, 2011[55]	AD – DM	11 (5:6)	78 ± 6	Obs	30 ± 8	MMSE	[^{123}I]IMP
	AD – no DM	12 (6:6)	79 ± 5	Obs	28 ± 4	MMSE	[^{123}I]IMP
15. Kume, 2011[56]	AD – no VRF	24 (9:15)	77 ± 7	Obs	41 ± 10	MMSE	[^{123}I]IMP
	AD – single VRF	27 (12:15)	76 ± 5	Obs	41 ± 8	MMSE	[^{123}I]IMP
	AD – multiple VRFs	17 (8:9)	76 ± 7	Obs	40 ± 10	MMSE	[^{123}I]IMP
16. Alegret, 2012[57]	AD	35 (9:29)[c]	76 ± 5[c]	Obs	24 ± NR[b]	MMSE	^{99m}Tc-ECD
17. Ogomori, 2013[58]	AD – rapid progression	24 (NR)	72 ± 9	Obs	16 ± 16[b]	MMSE	^{99m}Tc-ECD
	AD – slow progression	13 (NR)	75 ± 7	Obs	16 ± 10[b]	MMSE	^{99m}Tc-ECD
18. Sakurai, 2013[59]	AD	9 (1:8)	79 ± 7	RCT – NT	6 ± NR	MMSE; ADAS-Jcog	[^{123}I]IMP
19. Hanaoka, 2016[23]	AD – no WML	14 (7:7)	75 ± 7	Obs	26 ± 5	MMSE	^{99m}Tc-ECD
	AD – WML	24 (9:15)	77 ± 8	Obs	26 ± 4	MMSE	^{99m}Tc-ECD
20. Yoshii, 2018[60]	AD	32 (8:24)	70 ± 8	Obs	30 ± 6	ADAS-Jcog	^{99m}Tc-ECD

Abbreviations: [^{123}I]IMP, N-isopropyl-(^{123}I)-p-iodoamphetamine; ^{133}Xe, Xenon-133; ^{99m}Tc-ECD, technetium-99 m-ethyl-cysteinate dimer; ^{99m}Tc-HMPAO, technetium-99 m-hexamethyl-propylenamine oxime; AD, Alzheimer's disease; ADAS-J-cog, Alzheimer's Disease Assessment Scale-cognitive subscale Japanese version; ARCD, age related cognitive decline; CAMCOG, Cambridge Cognitive Examination; DM, diabetes mellitus; FU, follow-up; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; N, number of patients; NR, not reported; NT, non-treatment condition; Obs, observational; PbO, placebo condition; RCT, randomized controlled trial; SD, standard deviation; SEM, standard error of the mean; VaD, vascular dementia; VRF, vascular risk factor; WML, white matter lesions; ε4, apolipoprotein E epsilon 4 allele.

[a]Estimated SD based on range (= [maximum – minimum]/4).

[b]Mean and SD estimated in months based on follow-up duration reported in weeks or years (1 month = 1/12 year = 4 weeks).

[c]Based on originally included patients at baseline, not taking loss to follow-up into account.

[d]Estimated SD based on standard error of the mean and sample size (SD = $\sqrt{}$SEM*n).

[e]Also measurements after 3 months of follow-up.

followed by discussion to meet consensus on disagreements. None of the studies scored "poor," 1 study scored "fair," and 19 studies scored "good." Specific scores for each quality item can be found in Appendix C.

2.4 | Overview of studies

The 20 studies included in this review originate from 1991 to 2018, cumulatively describing 34 patient groups of interest for review, as some study populations were divided in multiple subgroups based on patient characteristics.[22,23,54–56,62] Patients across all groups of interest were diagnosed with probable AD at the time of follow-up. Only one study included patients with a diagnosis other than probable AD, that is, VaD, which were part of a mixed group comprising eight patients with VaD or probable AD.[50] Considering the negligible proportion of patients with VaD and complete lack of patients with mixed type dementia, the discussion of this study is solely focused on AD dementia. Most patient groups (28/34) were followed observationally, whereas six patient groups were part of a randomized controlled trial, where we included those individuals who were subjected to a non-treatment or placebo condition. Table 1 provides an overview of the general study

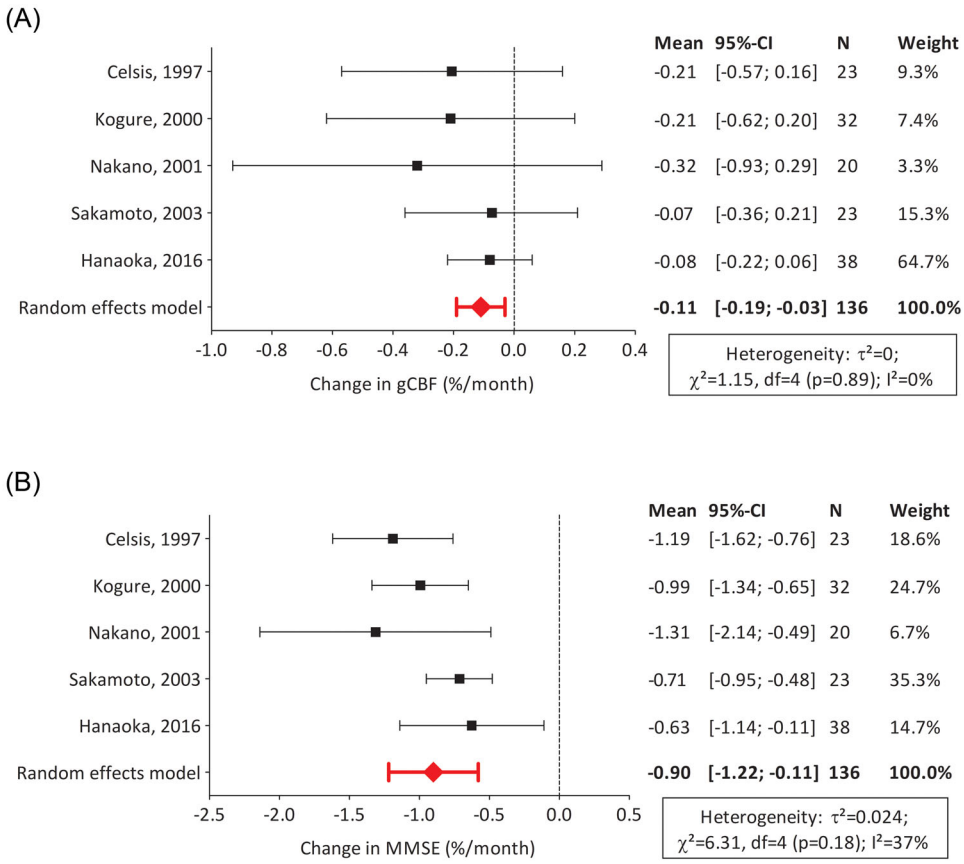

FIGURE 2 Forest plots of the meta-analyses on monthly relative changes in gCBF (A) and MMSE (B). CI, confidence interval; gCBF, global cerebral blood flow; MMSE, Mini-Mental State Examination; N, number of patients

and demographic patient characteristics for each included study in this review.

2.5 | Global CBF

Original detailed data were collected from six studies that reported results on gCBF at baseline and (the change) after a median follow-up of 24 months[19–24] (Appendix D). To minimize extraction errors, data extraction was independently performed *in duplo* by two authors (RW and AB), and subsequently compared to resolve discrepancies. Five of these studies,[19–23] which used the most widely methods for quantifying global CBF (i.e., absolute mean CBF across the whole cerebrum in millilitres per 100 gram brain weight per minute) and cognitive function (i.e., MMSE), were used for meta-analyses. All meta-analyses were performed using R Statistical Software with "General Package for Meta-analysis" (meta), version 4.19-0. First, the data was processed to calculate data for the relative monthly change from baseline (%). These calculated outcomes were subsequently pooled for subgroups within the same study. Random-effects meta-analyses on these final outcomes indicated a significant overall monthly relative decrease in gCBF (MD = −0.11; 95% confidence interval [CI] = −0.19, −0.03; $P = 0.023$) with no heterogeneity (Cochran's Q = 1.15; $I^2 = 0\%$; $P = 0.89$). This indicates an estimated 1.32% reduction in CBF per year. Furthermore, random-effects meta-analyses also revealed a significant overall monthly relative decrease in MMSE (MD = −0.90; 95% CI = −1.22, −0.58; $P = 0.0014$) with moderate heterogeneity (Cochran's Q = 6.31; $I^2 = 37\%$; $P = 0.18$), indicating an average 10.8% reduction, reflecting 2.4 points, in MMSE per year. Forest plots of the meta-analyses on monthly relative changes in gCBF and MMSE can be found in Figure 2. By visually inspecting the Funnel plots (Appendix E) for the change in either gCBF and MMSE, we assumed that publication bias was not present.

Both variables in the meta-analysis, that is, gCBF and MMSE, are assumed to be subject to proportional measurement errors. Therefore, Deming regression analysis, a method that accounts for errors in two dimensions (i.e., x-axis and y-axis),[63] was used for describing the relationship between the relative monthly changes from baseline in gCBF and MMSE, showing a significant relationship with an intercept of 0.375 (SE = 0.145; 95% CI = 0.091, 0.658) and a slope of 3.445 (SE = 0.984; 95% CI = 1.518, 5.373).

In one study,[24] gCBF was quantified as the corticocerebellar ratio (CCR), representing a perfusion index that is calculated by dividing the mean counts per pixel in the cortical region (i.e., whole cerebrum in case of gCBF) by the mean counts per pixel for the cerebellum. In line with the meta-analysis, this study found significant longitudinal decreases in

TABLE 2 Studies reporting on baseline and (change after) follow-up data on rCBF in large cortical areas

Study	Patient (sub)group	N	Frontal lobe				Temporal lobe				Parieto-temporal lobe	Parietal lobe			Occipital lobe
			Superior part	Inferior part	Anterior part	Posterior part	Lateral part	Medial part	Anterior part	Posterior part		Anterior part	Posterior part	Superior part	
1[47]	AD	10			●		◐	○				●	●		
2[48]	AD	24	○	○				○					○		
3[19]	AD	18									○				
3[19]	AD - ARCD at baseline	5									○				
4[24]	AD	10			○			○					●		○
7[49]	AD	13			○			◐					○		◐
8[50]	AD	8			●	●			●	●					
10[51]	AD	13			●		○	●					●		●
12[53]	AD - MCI at baseline	16						●			○			●	
16[57]	AD	35			●			●					●		◐

Abbreviations: AD, Alzheimer's disease; ARCD, age-related cognitive decline; MCI, mild cognitive impairment; N, number of patients; rCBF, regional cerebral blood flow.
Overview of the presence of significant longitudinal changes in regional CBF in large cortical areas for each patient (sub)group from a study. A symbol ○ indicates no significant change in either hemisphere. The symbols ◐, ◑, and ● indicate a significant decrease in only the left hemisphere, only the right hemisphere, or bilaterally, respectively. Grey cells indicate that the presence of a significant change was not reported or studied.

both MMSE ($P < 0.001$) and whole cerebrum perfusion ratio ($P < 0.03$) in 10 patients with probable AD after 24 months of follow-up.

2.6 | Regional CBF

Due to lacking comparability and consistency, data from included studies that reported findings on regional CBF were not suitable for aggregation in a meta-analysis. Therefore, findings on rCBF are quantitatively described here, categorized into rCBF findings in large (e.g., lobes) and small (e.g., gyri) cortical areas. Nine studies[19,24,47–51,53,57] examined changes across longitudinal follow-up in rCBF in larger cortical regions, that is, the frontal, temporal, parietal, and occipital lobes (Table 2).

No studies reported on changes in rCBF in the limbic region. Celsis et al.[19] only studied parietotemporal rCBF and found no significant change across follow-up in either the group with AD at baseline and the group with age-related cognitive decline (ARCD) at baseline who progressed to AD at follow-up, which is in line with the findings from one other study examining parietotemporal rCBF in patients with MCI at baseline.[53]

Four studies examined longitudinal changes in rCBF in the occipital lobe. Only one study reported a significant bilateral decrease,[51] whereas two other studies found this decrease to be only present in the left occipital lobe.[49,57] No changes were reported in the occipital lobe in the remaining study.[24]

The frontal, temporal, and parietal lobes were studied more frequently. Brown et al.[48] reported no significant decrease in rCBF in any of these three lobar regions, although a significant decline was reported when pooling these lobular regions. Moreover, consistent declines in rCBF were found in most other studies that examined (extensive areas of) the frontal (4 out of 6[47,50,51,57]), temporal (6 out of 7[47,49–51,53,57]) and parietal (5 out of 6[24,47,51,53,57]) lobes.

Fourteen studies,[20–23,50,52–60] including 21 patient (sub)groups, reported on longitudinal changes in rCBF in smaller brain regions

TABLE 3 Studies reporting on baseline and (change after) follow-up data on rCBF on the gyric level

Study	Patient (sub)group	N	Frontal lobe										Parietal lobe						Temporal lobe					Occipital lobe					Limbiclobe								
			Superior frontal gyrus	Middle frontal gyrus	Inferior frontal gyrus	Medial frontal gyrus	Orbital gyrus	Rectal gyrus	Paracentral lobule	Precentral gyrus	Subcallosal gyrus	Superior parietal lobule	Inferior parietal lobule	Angular gyrus	Postcentral gyrus	Precuneus	Supramarginal gyrus	Superior temporal gyrus	Middle temporal gyrus	Inferior temporal gyrus	Transverse temporal gyrus	Hippocampus	Superior occipital gyrus	Middle occipital gyrus	Inferior occipital gyrus	Cuneus	Fusiform gyrus	Lingual gyrus	Thalamus	Parahippocampal gyrus	Cingulate gyrus	Anterior cingulate	Posterior cingulate	Uncus	Insula
5[20]	AD	32	◑	●	○	○	○	○	◑	◑	○	○	◐	○	●	◑	○	○	○	●	○	◐	○	◐	◐	◑	○	○	○	◐	○	○	◑	○	○
6[21]	AD	20	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
8[50]	AD	8								●																										
9[22]	AD - ε4 carriers	11	○	○	◑	◑	○	○	○	◑	○	○	○	○	○	○	○	◑	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	◑
	AD - ε4noncarriers	12	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
11[52]	AD	15	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	◐	●	◑	○	○	○	○	○	○	◑	○	○	○	○	○	○	○	○
12[53]	AD-MCIatbaseline	16																															○		
13[54]	AD - rapidly progressing	24	◐	◐	◐	●	○	◐	○	○	○	◐	●	●	◐	●	●	●	●	●	◐		○	○	○	○	●	○	○	●	●	●	○	●		
	AD-slowlyprogressing	24	○	○	○	○	○	○	○	○	○	○	○	◐	○	◐	○	◐	◑	○	○		○	○	○	○	◑	○	○	◑	○	○	◑	◑		
14[55]	AD - DM	11	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○		○	○	○	○	○	○	○	○	○	◑	○	○		
	AD-noDM	12	○	○	○	◑	○	○	◐	○	○	○	●	●	○	○	◐	◑	●	○	○		○	○	○	○	○	○	○	○	●	◐	○	○		
15[56]	AD - no VRF	24	○	○	○	○	○	○	○	○	○	○	○	○	○	◐	○	●	◐	○	○		○	○	○	○	○	○	○	○	○	○	○	○		
	AD-singleVRF	27	○	○	○	◐	○	●	○	○	●	◑	◑	●	○	◐	◑	●	●	○	●		○	○	○	○	○	○	○	●	●	◐	○	●		
	AD - multiple VRFs	17	◐	●	●	◐	○	○	○	○	●	◑	●	●	○	●	●	◑	●	●	◑		○	◑	○	○	◑	○	○	◑	●	●	◐	○		
16[57]	AD	35	○	○	○	○	○	○	○	●	○	○	○	○	●	●	●	○	○	○	○	○	○	○	○	●	○	○	○	○	○	●	●	○	●
17[58]	AD - rapidly progressing	24	○	○	○	○	○	○	○	○	○	◑	◑	●	○	●	○	○	◑	○	○	○	○	◑	○	○	○	○	○	○	○	○	○	○	○
	AD-slowlyprogressing	13	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
18[59]	AD	9	○	○	○	○	○	○	○	○	○	○	○	○	◑	○	○	○	◐	○	○		○	○	○	○	○	○	○	○	○	○	○	○		
19[23]	AD-noWML	14	○	○	○					○								○												○	○	○	○			
	AD - WML	24	○	◐	○					○								○												○	●	◐	●			
20[60]	AD	32		○	○							●	●	●		●	○	●	●	●											○	○	○			

Abbreviations: AD, Alzheimer's disease; DM, diabetes mellitus; MCI, mild cognitive impairment; N, number of patients; rCBF, regional cerebral blood flow; VRF, vascular risk factor; WML, white matter lesions.
Notes: Overview of the presence of significant longitudinal changes in rCBF in small brain areas for each patient (sub)group from a study. A symbol ○ indicates no significant change in either hemisphere. The symbols ◐, ◑, and ● indicate that the change was significant in only the left, only the right, or bilaterally, respectively. Green symbols indicate an increase in rCBF, whereas red symbols indicate a decrease in rCBF. Grey cells indicate that the presence of a significant change was not reported or studied.

(Table 3), such as specific gyri that have been associated with AD pathology. Although longitudinal increases in rCBF have been rarely observed, two studies found an increase in the postcentral gyrus.[20,59] Decreases in rCBF were consistently found in small brain areas located across the parietal, temporal, and limbic lobes, mostly in the angular gyrus, precuneus, superior temporal gyrus, middle temporal gyrus, parahippocampal gyrus, anterior cingulate, and inferior parietal lobule. Regions located within the frontal and occipital lobes did not show consistent changes in rCBF.

3 | CONCLUSIONS

This paper addressed the question whether longitudinal changes in (global and/or regional) CBF are related to cognitive decline in patients with probable AD. First, we demonstrated that both global CBF and cognitive function decrease across longitudinal follow-up in patients with probable AD. Specifically, we found an annual decline in global CBF of −1.32% and a decrease of −10.8% for cognitive function across 1 year, with both the annual decline in global CBF and decline in cognitive function being substantially higher than in normal aging. Second, meta-regression analysis shows a positive correlation between the decrease in global CBF and cognitive decline, suggesting that both endpoints are intrinsically linked. Third, at the regional level, reduced CBF was reported in both larger and smaller regions, though most consistently in specific brain structures located across the parietal, temporal, and limbic lobes. Interestingly, these brain structures are affected specifically by AD neuropathology and have been linked to functions within the cognitive domain. These regional CBF decreases are responsible for the observed reduction in global CBF, and are related to the progression of cognitive decline in dementia. Our systematic review and meta-analysis provides strong support for the hypothesis that decreases in CBF are the consequence of pronounced changes at regional level, rather than a generalized process that affects all brain regions.

Taken together, our study supports the hypothesis that in the dementia stage of AD, longitudinal decreases in both global and regional CBF are linked to the progression of dementia, most likely through neuropathological changes in specific brain areas involved in AD. Future research is required to explore the role of global or regional CBF as a potential target for the prevention and treatment of cognitive decline in earlier stages of AD. For this, we present several testable hypotheses and recommendations for future research:

- Given the assumption that specific small brain structures are more pronouncedly subject to decreases in CBF rather than more extensive regions (i.e., lobes or whole brain), we recommend future studies to focus on specific small brain structures using suitable imaging techniques with appropriate spatial resolutions. This approach likely improves the detectability of CBF changes, enabling relatively smaller sample sizes to detect effect sizes.
- To examine the causal links among cerebral hypoperfusion, cortical atrophy, and cognitive decline, and to better understand the role of CBF as a prognostic factor for predicting future cognitive decline and/or as a potential target for the prevention and treatment of cognitive decline in earlier stages of AD, we recommend randomized controlled trials using interventions that specifically target CBF in large study populations phenotyped with AD biomarkers across longitudinal follow-up.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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APPENDIX A

SEARCH STRATEGIES

Table A.1, A.2, A.3, B.1, C.1, D.1, Figure E.1.

TABLE A.1 Search strategy for conducting the searches in MEDLINE

Free text and index terms associated with	Search string in MEDLINE (1946–2020)
Measures of cerebrovascular function	(blood flow velocity/ or carbon dioxide/ or exp cerebral arteries/ or exp cerebrovascular circulation/ or exp vascular resistance/ or hemodynamics/ or hypercapnia/ or hypocapnia/ or hypoxia/ or vascular capacitance/ or vasoconstriction/ or vasodilation/ or vasomotor system/ or ((breath adj3 hold* adj3 index) or (autoregulat* and index) or blood carbon dioxide or blood co2 or ((brain or cortical) adj3 (blood flow or circulation or h?emodynamic* or perfusion or reactivit*)) or carbon dioxide reactivit* or cbf or cbv or (cerebr* adj3 (autoregulation or blood flow or circulation or dysfunction* or function* or h?emodynamic* or hypoperfusion or perfusion or stiffness or vasomotor reactivity)) or cerebral blood vol* or cerebrovascular capacitance* or cerebrovascular circulation* or cerebrovascular conduct* or cerebrovascular reactivit* or cerebrovascular resistanc* or co2 reactivit* or gcbf or hypercapni* or hypocapni* or hypoxemi* or hypoxi* or neurovascular coupling* or neuro-vascular coupling* or pulsatility or pulsatility index or pulse wave velocit* or rcbf or rcbv or resistance index or serum carbon dioxide or vascular capacitance* or vascular conduct* or vascular reactivit* or vascular resistanc* or vascular stiffness or vasoconstriction* or vasodilat* or vasomotor* or vasoreact* or vasorelaxation*).ti,ab,kf.)
AND	
Disease of interest and measures of cognitive function	(alzheimer disease/ or dementia/ or exp cognitive aging/ or exp cognitive dysfunction/ or exp dementia, vascular/ or (lzheimer* or cognitive ageing or cognitive aging or cognitive decline* or cognitive disorder* or cognitive dysfunction* or (cognitive function* adj3 (decline* or diminish* or impair*)) or cognitive impairment* or dementia* or impaired cognit* or neurocognitive decline* or neurocognitive disorder* or neurocognitive dysfunction* or neurocognitive impairment*).ti,ab,kf.)
AND	
Imaging techniques that can be used for indicating measures of cerebrovascular function	(exp optical imaging/ or exp spectroscopy, near-infrared/ or exp tomography, emission-computed/ or exp ultrasound, doppler/ or *magnetic resonance imaging/mt or middle cerebral artery/dg or pulse wave analysis/ or xenon radioisotopes/ or (133xe or arterial spin* or asl or blood oxygen* level dependent or bold fmri or bold functional mr* or bold imag* or bold magnetic resonance imaging or bold mr* or ((doppler or duplex) adj3 (sonograph* or transcranial or ultraso*)) or dsc magnetic resonance or dsc-mr* or dynamic susceptibility contrast or fmr imaging or fmri or fnir* or functional mr* or kety-schmidt or near-infrared spectroscop* or neurosonolog* or nir spectroscop* or nirs or optical coherence tomograph* or optical imaging or optical tomography or perfusion imaging or perfusion magnetic imag* or perfusion magnetic resonance or perfusion mr* or perfusion weighted imag* or pet or phase-contrast magnetic or phase-contrast mr* or positron emission tomograph* or pulse wave analys* or pulse wave assessment* or pulse wave velocity analys* or pulse wave velocity assessment* or quantitative magnetic resonance or quantitative mr* or single photon emission or spect or tcd or (transcranial adj3 (sonograph* or ultraso*)) or xe-133 or xenon enhanced).ti,ab,kf.)
NOT	
Restrictions/filters	(exp animals/ not humans/)

TABLE A.2 Search strategy for conducting the searches in Embase

Free text and index terms associated with	Search string in Embase (1974–2020)
Measures of cerebrovascular function	(blood flow velocity/ or blood vessel capacitance/ or brain hypoxia/ or brain perfusion/ or carbon dioxide blood level/ or carbon dioxide breathing/ or exp blood vessel function/ or exp brain artery/ or exp brain blood flow/ or exp brain capillary/ or exp brain circulation/ or experimental hypoxia/ or hemodynamics/ or hypercapnia/ or hypocapnia/ or vasomotor system/ or ((autoregulat* and index) or blood carbon dioxide or blood co2 or ((brain or cortical) adj3 (blood flow or circulation or h?emodynamic* or perfusion or reactivit*)) or (breath adj3 hold* adj3 index) or carbon dioxide reactivit* or cbf or cbv or (cerebr* adj3 (autoregulation or blood flow or circulation or dysfunction* or function* or h?emodynamic* or hypoperfusion or perfusion or stiffness or vasomotor reactivity)) or cerebral blood vol* or cerebrovascular capacitance* or cerebrovascular circulation* or cerebrovascular conduct* or cerebrovascular reactivit* or cerebrovascular resistanc* or co2 reactivit* or gcbf or hypercapni* or hypocapni* or hypoxemi* or hypoxi* or neurovascular coupling* or neuro-vascular coupling* or pulsatility or pulsatility index or pulse wave velocit* or rcbf or rcbv or resistance index or serum carbon dioxide or vascular capacitance* or vascular conduct* or vascular reactivit* or vascular resistanc* or vascular stiffness or vasoconstriction* or vasodilat* or vasomotor* or vasoreact* or vasorelaxation*).ti,ab,kw.)
AND	
Disease of interest and measures of cognitive function	(*alzheimer disease/ or *dementia/ or exp *cognitive aging/ or *mild cognitive impairment/ or *multiinfarct dementia/ or (alzheimer* or cognitive ageing or cognitive aging or cognitive decline* or cognitive disorder* or cognitive dysfunction* or (cognitive function* adj3 (decline* or diminish* or impair*)) or cognitive impairment* or dementia* or impaired cognit* or neurocognitive decline* or neurocognitive disorder* or neurocognitive dysfunction* or neurocognitive impairment*).ti,ab,kw.)
AND	
Imaging techniques that can be used for indicating measures of cerebrovascular function	(arterial spin labeling/ or b scan/ or doppler ultrasonography/ or duplex doppler ultrasonography/ or exp computer assisted emission tomography/ or exp near infrared spectroscopy/ or functional magnetic resonance imaging/ or nuclear magnetic resonance imaging/ or optical coherence tomography/ or perfusion weighted imaging/ or transcranial doppler ultrasonography/ or transcranial doppler/ or xenon 133/ or (133xe or arterial spin* or asl or blood oxygen* level dependent or bold fmri or bold functional mr* or bold imag* or bold magnetic resonance imaging or bold mr* or ((doppler or duplex) adj3 (sonograph* or transcranial or ultraso*)) or dsc magnetic resonance or dsc-mr* or dynamic susceptibility contrast or fmr imaging or fmri or fnir* or functional mr* or kety-schmidt or near-infrared spectroscop* or neurosonolog* or nir spectroscop* or nirs or optical coherence tomograph* or optical imaging or optical tomography or perfusion imaging or perfusion magnetic imag* or perfusion mr* or pet or phase-contrast magnetic or phase-contrast mr* or positron emission tomograph* or pulse wave analys* or pulse wave assessment* or pulse wave velocity analys* or pulse wave velocity assessment* or quantitative magnetic resonance or quantitative mr* or single photon emission or spect or tcd or (transcranial adj3 (sonograph* or ultraso*)) or xe-133 or xenon enhanced).ti,ab,kw.)
NOT	
Restrictions/filters†	((animal tissue/ or animal model/ or animal experiment/ or exp animal/ or exp experimental animal/ or nonhuman/) not exp human/)

†Yielded hits with an conference abstract status identified by Embase were manually excluded.

TABLE A.3 Search strategy for conducting the searches in Web of Science Core Collection

Free text and index terms associated with	Search string in Web of Science Core Collection (1945–2020)
Measures of cerebrovascular function	ts = ("autoregulat* index" or "blood carbon dioxide" or "blood co2" or "breath hold* index*" or "carbon dioxide reactivit*" or cbf or cbv or (cerebr* near/3 (dysfunction* or function* or "blood flow" or autoregulation or hemodynamic* or perfusion or "vasomotor reactivity" or circulation or hypoperfusion or stiffness)) or "cerebral blood vol*" or "cerebrovascular capacitance*" or "cerebrovascular circulation*" or "cerebrovascular conduct*" or "cerebrovascular reactivit*" or "cerebrovascular resistanc*" or "co2 reactivit*" or gcbf or hypercapni* or hypocapni* or hypoxemi* or hypoxi* or "kety schmidt" or "neurovascular coupling*" or "neuro-vascular coupling*" or pulsatility or "pulsatility index" or "pulse wave velocit*" or rcbf or rcbv or "resistance index" or "serum carbon dioxide" or "vascular capacitance*" or "vascular conduct*" or "vascular reactivit*" or "vascular resistanc*" or "vascular stiffness" or vasoconstriction* or vasodilat* or vasomotor* or vasoreact* or vasorelaxation*)
AND	
Disease of interest and measures of cognitive function	ts = (alzheimer* or ((cogniti* or neurocogniti*) near/2 (decline* or diminish* or impair*)) or "cognitive ageing" or "cognitive aging" or "cognitive disorder*" or "cognitive dysfunction*" or dementia* or mci or "neurocognitive ageing" or "neurocognitive aging" or "neurocognitive disorder*" or "neurocognitive dysfunction*")
AND	
Imaging techniques that can be used for indicating measures of cerebrovascular function	ts = (133xe or "arterial spin*" or asl or "blood oxygen* level dependent" or "bold fmri" or "bold imag*" or "bold magnetic resonance imaging" or (bold and (mri or "mr imaging")) or ((doppler or duplex) near/3 (sonograph* or transcranial or ultraso*)) or "dsc magnetic resonance" or "dsc-mri" or "dynamic susceptibility contrast" or fmri or "fmr imaging" or fnir* or (functional and (mri or "mr imaging")) or "near-infrared spectroscop*" or neurosonolog* or "nir spectroscop*" or nirs or "optical coherence tomograph*" or "optical imaging" or "optical tomography" or "perfusion imaging" or "perfusion magnetic imag*" or "perfusion magnetic resonance" or (perfusion and (mri or "mr imaging")) or "perfusion weighted imag*" or pet or "phase-contrast magnetic" or ("phase-contrast" and (mri or "mr imaging")) or "positron emission tomograph*" or "pulse wave analys*" or "pulse wave assessment*" or "pulse wave velocity analys*" or "pulse wave velocity assessment*" or "quantitative magnetic resonance" or (quantitative and (mri or "mr imaging")) or "single photon emission" or spect or tcd or (transcranial near/3 (sonograph* or ultraso*)) or "xe-133" or "xenon enhanced")
NOT	
Restrictions/filters	*None*

APPENDIX B

Studies that were excluded based on imaging technique(s)

TABLE B.1 Study characteristics of studies that were excluded based on used imaging technique(s)

Study (First author, year[ref])	Patient (sub)group	N	Mean age at baseline (years)	FU period (months)	Measure(s) of cognitive function	Measure(s) of cerebral hemodynamics	Imaging technique
Viola, 2013[64]	AD – NT group in RCT	10	74	12	MMSE	TOI	NIRS
Lim, 2017[65]	AD	51	72	12	MMSE; ADAS-Cog	CBFV; PI	TCD
Leuzy, 2018[66]	AD	16	71*	96	MMSE	rCBF	PET
De Jong, 2019[67]	AD – PbO group in RCT	22	73	6	MMSE	CBF; CBFV	ASL; TCD

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; ASL, arterial spin labeling; CBF, cerebral blood flow; CBFV, cerebral blood flow velocity; FU, follow-up; MMSE, Mini-Mental State Examination; N, number of patients; NIRS, near-infrared spectroscopy; NT, non-treatment condition; PbO, placebo condition; PET, positron emission tomography; PI, pulsatility index; rCBF, regional cerebral blood flow; RCT, randomized controlled trial; TCD, transcranial Doppler; TOI, tissue oxygenation index.
Median age.

APPENDIX C

Quality assessment

TABLE C.1 Quality assessment of studies included in the quantitative synthesis

Study (ID)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Overall quality rating
1[47]	Y	Y	Y	NR	NR	NA	Y	Y	N	Y	N	NA	Good
2[48]	Y	Y	Y	NR	NR	NA	Y	NR	N	Y	N	NA	Good
3[19]	Y	Y	Y	NR	NR	NA	Y	Y	Y	N	N	NA	Good
4[24]	N	N	Y	NA	NR	NA	Y	NA	N	Y	N	NA	Fair
5[20]	Y	Y	Y	NR	NR	NA	Y	NA	NR	Y	N	NA	Good
6[21]	Y	Y	Y	NR	NR	Y	Y	NR	NR	Y	N	NA	Good
7[49]	Y	Y	Y	Y	NR	Y	Y	NA	Y	Y	N	NA	Good
8[50]	Y	Y	Y	NR	NR	Y	Y	NR	NR	N	N	NA	Good
9[22]	Y	Y	Y	NR	NR	NA	Y	NA	NA	Y	N	NA	Good
10[51]	Y	Y	Y	NR	NR	NA	Y	NA	NR	Y	N	NA	Good
11[52]	Y	Y	Y	NR	NR	NA	Y	NA	NA	Y	N	NA	Good
12[53]	Y	Y	Y	NR	NR	NA	Y	NA	Y	Y	N	NA	Good
13[54]	Y	Y	Y	NR	NR	NA	Y	NA	NR	Y	N	NA	Good
14[55]	Y	Y	Y	NR	NR	NA	Y	Y	NA	Y	N	NA	Good
15[56]	Y	Y	Y	NR	NR	NA	Y	NA	NR	Y	N	NA	Good
16[57]	Y	Y	Y	NR	NR	NA	Y	NA	Y	Y	N	NA	Good
17[58]	Y	Y	Y	NR	NR	NA	Y	NA	NA	Y	N	NA	Good
18[59]	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	NA	Good
19[23]	Y	Y	Y	NR	NR	NA	Y	Y	Y	Y	N	NA	Good
20[60]	Y	Y	Y	NR	NR	NA	Y	NA	NR	Y	N	NA	Good

Abbreviations: N, no; NA, not applicable; NR, not reported; Q, question; Y, yes.

APPENDIX D

Extracted data on gCBF and MMSE

TABLE D.1 Data extracted from studies that reported baseline and (change after) follow-up data on global CBF and MMSE

					gCBF			MMSE		
Study (ID)	Patient (sub)group	N	Mean FU duration (months)	Measure of gCBF	Baseline	Follow-up	Change after FU	Baseline	Follow-up	Change after FU
3[19]	AD	18	36	Absolute gCBF (mL/100g/min)	47 ± 9	43 ± 6	−1.3 ± 4.2*	14.5 ± 7.4	NR	−2.3 ± 2.0*
	AD - ARCD at BL	5	24		55 ± 5	51 ± 15	−0.8 ± 8.8*	26.5 ± 1.3	21.5 ± 1.7	−2.3 ± 1.6*
4[24]	AD	10	24	Mean CCR	0.828 ± 0.05	0.792 ± 0.02	NR	22.75 ± 4.31	16.05 ± 6.85	NR
5[20]	AD	32	15	Absolute gCBF (mL/100g/min)	38.4 ± 4.6	37.2 ± 5.0	NR	26.2 ± 1.5	22.3 ± 3.6	NR
6[21]	AD	20	12	Absolute gCBF (mL/100g/min)	36.8 ± 4.3	35.4 ± 4.4	NR	22.2 ± 3.4	18.7 ± 3.7	NR
9[22]	AD - ε4 carriers	11	24	Absolute gCBF (mL/100g/min)	39.8 ± 4.5	39.2 ± 3.9	NR	26.2 ± 1.8	22.8 ± 3.7	NR
	AD - ε4 noncarriers	12	24		36.8 ± 5.5	36.1 ± 3.4	NR	26.0 ± 1.4	20.7 ± 2.6	NR
19[23]	AD - no WML	14	26	Absolute gCBF (mL/100g/min)	37.8 ± 2.1	37.8 ± 2.8	NR	21.6 ± 5.0	19.6 ± 7.3	NR
	AD - WML	24	26		38.6 ± 3.3	37.3 ± 3.3	NR	19.4 ± 4.8	15.5 ± 6.5	NR

Abbreviations: AD, Alzheimer's disease; ARCD, age related cognitive decline; CCR, cortico-cerebellar ratio; FU, follow-up; gCBF, global cerebral blood flow; MMSE, Mini-Mental State Examination; N, number of patients; NR, not reported; p/y, per year; WML, white matter lesions; ε4, apolipoprotein E epsilon 4 allele.

*Change per year.

APPENDIX E

Funnel plots on gCBF and MMSE

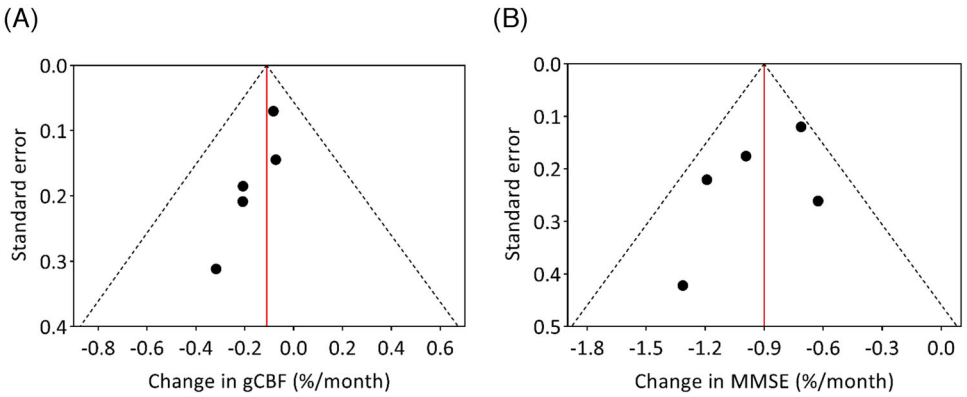

FIGURE E.1 Funnel plots on gCBF (A) and MMSE (B) for studies included in the quantitative meta-analyses. gCBF, global cerebral blood flow; MMSE, Mini-Mental State Examination