Effects of Interventions on Cerebral Perfusion in the Alzheimer's Disease Spectrum

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Review

Effects of interventions on cerebral perfusion in the Alzheimer's disease spectrum: A systematic review☆

Sofia Marcolini [a,*,1], Ingeborg Frentz [a,b,1], Carlos A. Sanchez-Catasus [c,d], Jaime D. Mondragon [a], Paula Kopschina Feltes [d], Anouk van der Hoorn [e], Ronald J.H. Borra [e], M. Arfan Ikram [b], Rudi A.J.O. Dierckx [d], Peter Paul De Deyn [a,f]

[a] Department of Neurology and Alzheimer Center, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands
[b] Department of Epidemiology, Erasmus University Medical Center, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands
[c] Department of Neurology, Clínica Universidad de Navarra, 31008 Pamplona, Spain
[d] Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands
[e] Department of Radiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands
[f] Laboratory of Neurochemistry and Behavior, University of Antwerp, Wilrijk, Antwerp, Belgium

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ABSTRACT

Cerebral perfusion dysfunctions are seen in the early stages of Alzheimer's disease (AD). We systematically reviewed the literature to investigate the effect of pharmacological and non-pharmacological interventions on cerebral hemodynamics in randomized controlled trials involving AD patients or Mild Cognitive Impairment (MCI) due to AD. Studies involving other dementia types were excluded. Data was searched in April 2021 on MEDLINE, Embase, and Web of Science. Risk of bias was assessed using Cochrane Risk of Bias Tool. A meta-synthesis was performed separating results from MCI and AD studies. 31 studies were included and involved 310 MCI and 792 CE patients. The MCI studies (n = 8) included physical, cognitive, dietary, and pharmacological interventions. The AD studies (n = 23) included pharmacological, physical interventions, and phytotherapy. Cerebral perfusion was assessed with PET, ASL, Doppler, fNIRS, DSC-MRI, Xe-CT, and SPECT. Randomization and allocation concealment methods and subject characteristics such as AD-onset, education, and ethnicity were missing in several papers. Positive effects on hemodynamics were seen in 75 % of the MCI studies, and 52 % of the AD studies. Inserting cerebral perfusion outcome measures, together with established AD biomarkers, is fundamental to target all disease mechanisms and understand the role of cerebral perfusion in AD.

1. Introduction

Even though Alzheimer's disease (AD) is the leading cause of dementia and a major socioeconomic burden worldwide (Cantarero-Prieto et al., 2020; Maresova et al., 2015), currently, no curative treatment is available. AD is associated with the accumulation of amyloid-β and tau (Mattsson et al., 2014) and progressive brain atrophy. Several systematic reviews explored the effects of diverse interventions on AD, mainly based on the amyloid hypothesis of the disease (Glenner and Wong, 1984). Some of these reviews investigated diet (Yusufov et al., 2017), psychosocial and cognitive interventions (Carrion et al., 2018; Duan et al., 2018; Ruiz-Muelle and López-Rodríguez, 2019), physical exercise (Du et al., 2018; Jia et al., 2019), repetitive transcranial magnetic stimulation (Dong et al., 2018), and pharmacological treatments such as memantine (Matsunaga et al., 2015b), cholinesterase inhibitors (Dou et al., 2018; Tan et al., 2014), lithium (Matsunaga et al., 2015a), or insulin (Avgerinos et al., 2018). Most of these interventions seem to improve or slow down the development of AD symptoms, but the underlying mechanisms remain elusive. Recently, an important milestone has been reached as the Food and Drug Administration (FDA) has

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* Correspondence to: University of Groningen, University Medical Center Groningen, Department of Neurology, Hanzeplein 1, 9713 GZ Groningen, the Netherlands.
E-mail address: s.marcolini@umcg.nl (S. Marcolini).

[1] These authors contributed equally to this work

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provisionally approved aducanumab, a monoclonal antibody that was shown to slow down the deposition of Aβ (Sevigny et al., 2016), for patients with mild cognitive impairment (MCI) or mild dementia. However, scientists' opinions on its accelerated approval are not unanimously in favor, due to uncertainties on the efficacy of aducanumab in reducing cognitive impairment and the target that the drug works on (Alexander and Karlawish, 2021; Mullard, 2021). All in all, interventions designed to treat AD are many and diverse.

Early in the development of AD, brain function in specific regions is reduced which is reflected in regionally reduced cerebral blood flow (CBF) (Mattsson et al., 2014). The exact relationship of CBF alterations with the progression of early AD is still unknown, driving the interest in investigating the role of vascular dysfunctions and cerebral perfusion in the AD spectrum (Østergaard et al., 2013). Cerebral perfusion plays a primary role in the early cascade of events leading to disease progression (Iturria-Medina et al., 2016) as CBF decreases consistently throughout the progression of AD (Albrecht et al., 2020). Hypoperfusion co-occurs with other AD-related events like neuroinflammation (Tublin et al., 2019), making it difficult to define whether this phenomenon is a cause or consequence of the disease (Austin et al., 2011). Currently, vascular dysregulation and reduced cerebral perfusion are thought to precede the classical biomarkers associated with AD (Kisler et al., 2017). Several vascular pathways related to cerebral perfusion and cognitive impairment have been reviewed in de la Torre et al. (2016), and other recent work has described the fundamental role of brain vasculature in AD (Badji and Westman, 2020; Cortes-Canteli and Iadecola, 2020; Klohs, 2020; de la Torre, 2016; Love and Miners, 2016; Solis et al., 2020). Substantial research has pointed at a connection from ''head to heart'', focusing mainly on associations of cerebral hypoperfusion and neuronal degeneration (Tublin et al., 2019). Generally, there seems to be a "heart-brain continuum" which suggests the existence of a vicious cycle between dementia and cardiac dysfunction (Tublin et al., 2019; Yang et al., 2020). Additionally, the AT(N) biomarker scheme by the National Institute on Aging and Alzheimer's Association (NIA-AA) (Jack et al., 2018), reports that the scheme can be expanded to include a vascular (V) component once this is better defined. In response, Sweeney et al. (2019) claim that vascular imaging biomarkers such as arterial spin labeling, dynamic susceptibility-contrast or transcranial doppler should be adopted in research and epidemiological studies, as well as in interventional trials (Sweeney et al., 2019). An overview of randomized controlled trials (RCTs) including cerebral perfusion outcome measures in the AD spectrum is missing.

The purpose of this systematic review is to explore the effect of pharmacological and non-pharmacological interventions on perfusion parameters in the AD spectrum. A secondary aim is to obtain an understanding of the number of RCTs that included cerebral perfusion as outcome measure. Considering the increasing evidence pointing at CBF being abnormal at early stages of disease, we hypothesize that CBF and relevant measures such as cognition are influenced by interventions targeting hemodynamics in the early phases of the AD spectrum. Hence the research question is: what are the effects of pharmacological and non-pharmacological interventions on perfusion parameters in RCTs performed in patients with an AD spectrum diagnosis? This work may help to identify targets to prevent disease progression and stimulate development of therapeutics.

2. Methods

2.1. Eligibility criteria

Studies were considered eligible if they met the following inclusion criteria:

1) They were RCTs, to reduce heterogeneity in study methods and ensure internal validity of included studies;
2) Patients covering the AD spectrum were included if inclusion was performed following specified criteria for MCI and or AD, e.g., NIA-AA, Diagnostic Statistical Manual (DSM);
3) Subjects underwent a pharmacological or non-pharmacological treatment;
4) Cerebral perfusion was assessed. The exclusion criteria were: 1) they were not RCTs; 2) other types of dementia patients were involved (e.g., Lewy Body dementia, mixed dementia, vascular dementia); 3) efficacy of the treatment on cerebral perfusion was not evaluated;
5) The full text was not available in English, Italian, Dutch, German, Spanish, or Portuguese as these were the languages the authors speak and understand;
6) The article reported only the study protocol and no results.

Due to the diverse nature of the interventions and assessment methods of CBF we were unable to perform a meta-analysis. Thus, a meta-synthesis of results was conducted appraising the evidence found for the various treatments included, grouped on the patient population (AD and MCI due to AD).

2.2. Information sources and search strategy

A systematic review of the literature was performed on MEDLINE, Embase, and Web of Science in April 2021. The following concepts were used to define the search terms:

1) "Alzheimer Disease", "MCI", "cognitive dysfunction";
2) "Hemodynamics", "blood flow", "perfusion" :
3) "Treatment", "training", "therapeutics". A further string was added to select only RCTs and two other strings to exclude animal studies and review papers. The complete search strategy for the three databases can be found in the Supplementary Material (Tables A3, A4 and A5).

2.3. Study selection

Search results from the three databases (n = 541) were imported into EndNote (Camelot UK Bidco Limited (Clarivate), Philadelphia), the duplicates that were found in EndNote were removed (n = 56) (Identification stage). The resulting studies were uploaded into the software Rayyan (Ouzzani et al., 2016), which was used for the title-abstract screening phase. In Rayyan, another 35 duplicates were detected, leading to a total of 91 studies being removed. After the removal of duplicates, 450 articles were left to screen. The entire selection process was conducted by two reviewers (IF and SM). The title-abstract selection was performed in a blinded manner and was preceded by a pilot where 30 studies were screened by both reviewers. After the pilot screening, the authors came together to discuss eventual disagreements (n = 5), and a consensus about their inclusion was reached before proceeding with the screening procedure, a total of 387 articles were excluded based on title-abstract selection. To assess studies eligibility, full-text assessment was done on the remaining sixty-three studies. The full-text assessment was also performed independently by the two reviewers focusing on the inclusion and exclusion criteria, disagreements were solved by a consensus meeting. The investigators of three studies were contacted via e-mail due to doubts on the inclusion criteria (i.e., whether the studies were RCT's and the type of patients they included), two of these studies were then excluded as they did not meet the inclusion criteria. These steps are summarized in a PRISMA flow chart (Page et al., 2021) Fig. 1.

Seven papers closely met the inclusion criteria but were not included as they were study protocols and did not report any results. They are discussed in the "Future Directions" section.

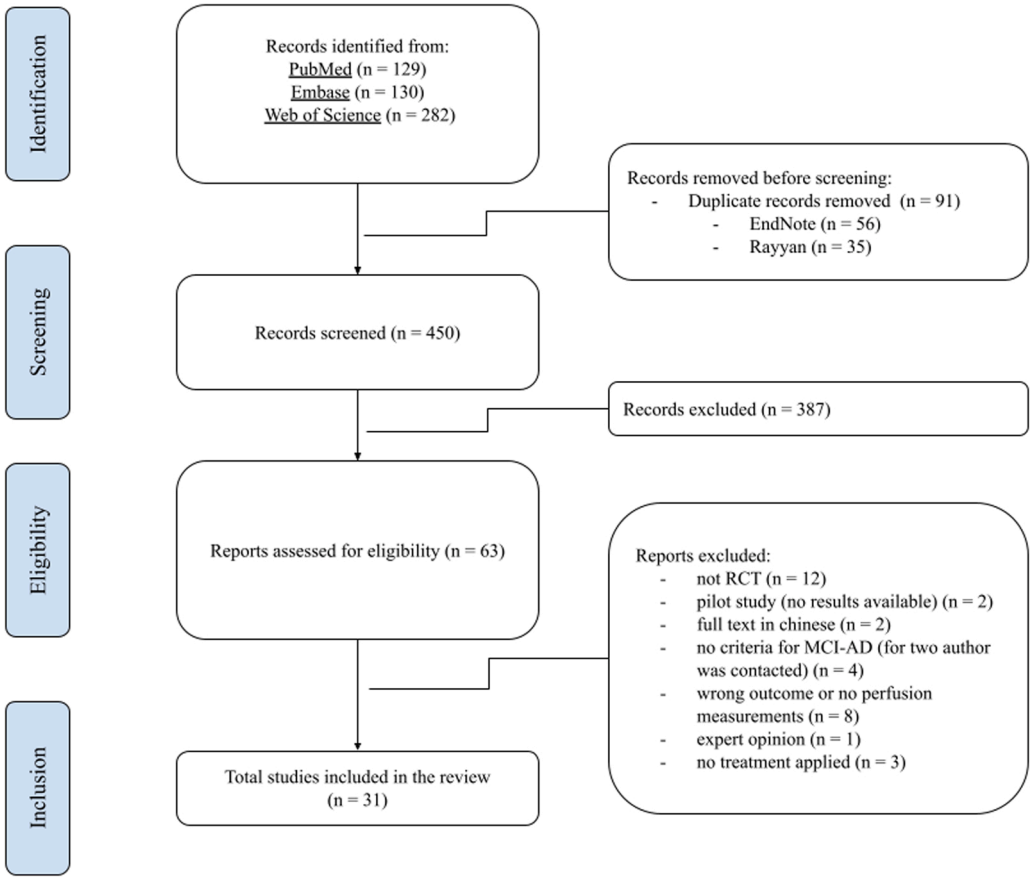

Fig. 1. PRISMA inclusion flow chart.

2.4. Data collection process and data items

To search for data, a PICO question has been formulated: What is the effect of pharmacological and non-pharmacological treatments (I) on brain perfusion outcomes (O) in AD and MCI (P)?

Data was extracted independently by the two reviewers (IF and SM) using an Excel (Microsoft Corporation, Redmond, Washington) form created for this purpose. The data items that were extracted are reported in Tables 1 and 2. The data extracted includes description of the sample (sample size, mean age, MCI or AD criteria used), intervention (description and duration), perfusion outcome measures (perfusion technique, analysis method, and perfusion outcome) and results (perfusion result, cognition results, and other results when applicable). Differences between IF and SM were handled by a consensus meeting.

2.5. Risk of bias in individual studies

Risk of bias assessment was performed by the two reviewers independently (IF and SM). A pilot extraction was performed on three studies to standardize the risk of bias assessment criteria. Disagreements in the pilot and other papers were resolved by consensus. The assessment was performed using the Cochrane Risk of Bias Tool (Supplementary Table **A7**). An inter-rater reliability score for the risk of bias assessment was calculated in SPSS (Version 27) using Cohen's kappa. The average Cohen's Kappa of the seven risk of bias items was 0.62, therefore indicating substantial agreement between the two raters according to the cut-off indicated in McHugh (2012) (McHugh, 2012). The two raters solved the disagreements about risk of bias evaluation to reach a consensus.

3. Results

3.1. Study selection and characteristics

The search in the three databases resulted in 450 studies to screen. After article selection, screening, and determination of eligibility, 31 studies were included. The selection procedure and reasons for exclusion are described in the flow diagram (Fig. 1). All included studies were RCTs and written in English.

3.1.1. MCI

Eight studies assessed the effect of different interventions on blood flow in MCI patients as summarized in Fig. 2. The mean age ranged from 62.58 to 79.3, mean education 8.7–18.4 years and the proportion of female participants ranged from 30 % to 80 %. Only one study investigated the effect of a pharmacological intervention, namely donepezil (Chen et al., 2006). One study tested the efficacy of a combined multi-domain cognitive training and physical exercise in a social setting (also involving music therapy and social stimulation) (Maffei, 2017). The effect of multitask movement music therapy was evaluated with controls following a single-task training (Shimizu et al., 2018). One study looked at the effect of Omega 3 (Schwarz et al., 2018). One study investigated whether an anodal-transcranial direct current stimulation (a-tDCS) + cognitive training significantly altered regional cerebral blood flow (rCBF) compared to sham tDCS (s-tDCS) + cognitive training (Das et al., 2019). Two studies from the same group assessed the effect of one-year aerobic exercise compared to stretching and toning (Thomas et al., 2020; Tomoto et al., 2021). The effect of cognitive training alone was investigated by L.C. Beishon et al., 2021 Supplementary Table **A1** offers a detailed description of the treatments applied in the included studies.

Table 1
Data Extraction Table - MCI Studies.

Study	Description of sample			Intervention		Perfusion outcome measure			Results		
	Included sample size	Mean age (years ± SD)	MCI criteria	Description	Duration (weeks)	Perfusion technique	Analysis method	Perfusion outcome	Perfusion results	Cognition results	Other results
Chen et al., 2006	11 MCI (4 intervention, 7 placebo)	Intervention: 74.8 ± 7.4 Placebo: 68.4 ± 4	Petersen *et al.*, 1999	Donepezil	32	[^{15}O] water PET imaging	ROI (left and right frontal, temporal, parietal, occipital tissue) and FOI	gCBF and rCBF (*activation*)	No group differences were found during either the verbal production (counting) task or the verbal recall memory task. The donepezil group showed no differences in rCBF after treatment (6 months) compared to baseline. The placebo group showed a reduction in CBF during the verbal recall task at 6 months compared to baseline.	At 6-month follow-up, performance on a list-learning test was similar for both groups.	Not Available
Maffei et al., 2017	113 MCI (55 intervention, 58 control)	Intervention: 74.0 ± 4.8 Placebo: 74.9 ± 4.4	Portet *et al.*, 2006	Multidomain training, including cognitive, physical exercise and music therapy	30	3D ASL MRI	ROI (hippocampal and parahippocampal regions)	CBF	CBF was increased in the hippocampal and parahippocampal regions of MCI-training subjects, but statistical significance was reached only for parahippocampal regions.	A significant beneficial effect of the combined training on the primary outcome (ADAS-Cog) was detected.	Not Available
Schwarz et al., 2017	13 MCI (8 intervention, 5 placebo)	Intervention: 67 ± 9 Placebo: 66 ± 9	Mayo clinic criteria	Omega-3 fatty acid supplementation	26	DSC-MRI	ROI (entorhinal gyrus, inferior temporal gyrus, inferior parietal gyrus, precuneus, isthmus cingulate gyrus, and superior parietal gyrus)	rCBF and rCBV	The intervention showed an effect on cerebral perfusion in the combined ROI, with medium effect sizes for rCBF and rCBV for the treatment group.	Not Available	Not Available
Shimizu et al., 2018	39 MCI (30 intervention, 9 control)	Intervention: 74.90 ± 4.29 Control: 73.33 ± 7.31	Petersen (2004) and Petersen *et al* (1999)	Movement Music Therapy with naruko clapper	12	fNIRS	7 channels in each temporal lobe and 15 in the prefrontal lobe.	CBF (*activation*)	CBF changes were positively correlated between many channels in the Movement Music Therapy intervention group. This indicates that the Movement Music Therapy intervention increased functional connectivity in prefrontal areas more than the Single Task Training intervention.	Frontal assessment battery increased significantly in the Movement Music Therapy group.	Post-intervention improvements in the four areas of flexibility, functional mobility, gait and muscle endurance were seen in the Movement Music Therapy group. Body balance was maintained in the Movement Music Therapy group.
Das et al., 2019	22 MCI (12 intervention, 10 sham)	Intervention: 62.58 ± 8.43	Petersen *et al.*, 2001	SMART training & a-tDCS	4	pCASL MRI	Voxel-based	rCBF	A significantly larger increase in rCBF was seen at the right MFC in	The s-tDCS + SMART group showed significant immediate	Not Available

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Table 1 (*continued*)

Study	Description of sample			Intervention		Perfusion outcome measure			Results		
	Included sample size	Mean age (years ± SD)	MCI criteria	Description	Duration (weeks)	Perfusion technique	Analysis method	Perfusion outcome	Perfusion results	Cognition results	Other results
		Sham: 63.30 ± 7.38	ADNI 2010						the a-tDCS + SMART compared to the s-tDCS + SMART (T1 to T2). There were no significant relationships between neurocognitive changes and rCBF changes.	cognitive gains (T2 to T1) in executive functions of inhibition (DKEFS-Color word interference) and innovation (TOSL), and episodic memory as measured by retrieval of facts from a lengthy text (TOSL). The a-tDCS + SMART training showed no such gains. The cognitive benefits did not last for over 3-months after training (T3 to T1).	
Thomas et al., 2020	30 MCI (15 intervention, 15 control)	Intervention: 66.4 ± 6.6 Control: 66.1 ± 7.2	Petersen criteria modified by ADNI	Aerobic exercise	52	pCASL MRI	Voxel-wise and ROIs (occipital, parietal, frontal lobe, ACC, PCC, hippocampus)	CBF	CBF changes significantly in ACC (aerobic exercise increase relative to stretch); PCC (aerobic exercise decrease relative to stretch); hippocampus (increase in aerobic exercise group); no significances in the other ROIs.	Logical memory scores in the aerobic exercise group improved significantly from pre-training levels, whereas the control group did not show a significant change.	The exercise group showed a significant increase in VO_2 max when comparing post-training to pre-training, while the stretch group did not show a difference.
Beishon et al., 2021	20 healthy 30 patients (MCI and AD) (22 intervention, 6 MCI, 6 AD; 25 control, 10 AD, 6 MCI)	Intervention: 63.0 ± 7.1 Control: 67.4 ± 9.3 Overall: 63 ± 7.1	Petersen, 2004 NIA/AA 2011	Multi-domain, online cognitive training *Feasibility study*	12	TD ultrasonography	Insonation of the middle cerebral arteries	CBFv (*activation*)	No differences in resting CBFv after treatment between groups. Also, there were no correlation between change in CBFv and in any of the clinical or cognitive measures.	No improvements in cognition on the Addenbrooke's Cognitive Examination III.	No improvements in mood (GDS) or function (Lawton IADL), and QoL in the cognitively impaired training group. QoL improved in the trained healthy controls, but not in the cognitively impaired.
Tomoto et al., 2021	52 MCI (22 intervention, 30 controls)	Intervention: 64.8 ± 6.4 Control: 66.1 ± 6.8	Petersen criteria modified by ADNI	Aerobic exercise	52	Duplex ultrasonography and TD	From the internal carotid and vertebral arteries	nCBF, CBFv.	CBF PI decreased and nCBF increased in the aerobic exercise compared with stretching-and-toning groups. ICA blood flow and CBFv increased after aerobic exercise training.	The aerobic exercise group showed a small but statistically significant improvement on letter fluency performance compared with the stretching-and-toning group, but no other cognitive differences	Aerobic exercise significantly improved VO_{2peak} at 6- and 12-month when compared with the stretching-and-toning group. Carotid beta-stiffness index decreased in aerobic exercise compared with

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Table 1 (*continued*)

Study	Description of sample			Intervention		Perfusion outcome measure			Results		
	Included sample size	Mean age (years ± SD)	MCI criteria	Description	Duration (weeks)	Perfusion technique	Analysis method	Perfusion outcome	Perfusion results	Cognition results	Other results
										were seen between groups over time.	stretching-and-toning. Systemic and carotid blood pressure, CVR, and cfPWV decreased in both groups, while there were no changes in CIMT.

Note. a-tDCS = anodal-transcranial Direct Current Stimulation; AD =Alzheimer's Disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; ACC = Anterior Cingulate Cortex; ADAS-Cog =Alzheimer's Disease Assessment Scale-Cognitive Subscale; ASL-MRI = Arterial Spin Labeling-Magnetic Resonance Imaging; CBFv = Cerebral Blood Flow velocities; CDR = Clinical Dementia Rating; CIMT = Carotid Intima-Media Thickness; cfPWW = Carotid-femoral Pulse Wave Velocity; CVR = Cerebrovascular Resistance; DSC-MRI= Dynamic Susceptibility Contrast-MRI; DSM = Diagnostic and Statistical Manual of Mental Disorders; DKEFS-Color word interference; fNIRS = functional near-infrared spectroscopy; FOI = Function of interest; FAB = Frontal Assessment Battery; GDS = Geriatric Depression Scale; IADL = Instrumental Activities of Daily Living; ICA = Internal Carotid Artery; MCI = Mild Cognitive Impairment; MFC = Middle Frontal Cortex; NIA-AA = National Institute on Aging-Alzheimer's Association; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; nCBF = normalized Cerebral Blood Flow; PET = Positron Emission Tomography; pCASL = pseudo-Continuous ASL; PI =Pulsatility Index; ROI = Regions of Interest; QoL = Quality of Life; rCBF = regional Cerebral Blood Flow; rCBV = regional Cerebral Blood Volume; SPECT = Single-Photon Emission Computerized Tomography; s-tDCS = sham transcranial Direct Current Stimulation; PCC = Posterior Cingulate Cortex; 15O = Oxygen-15 radioactive isotope; TD = Transcranial Doppler; TOSL = Test of Strategic Learning; VO2 = Volume of Oxygen.

3.1.2. AD

Twenty-three studies assessed the effect of different interventions on blood flow in AD patients, these are outlined in Fig. 3, while treatment descriptions are in Supplementary Table **A1**. The patients' mean age ranged from 62.6 to 91.1, mean education 5.9–16.7 years (education was only reported in seven of the included studies), and the proportion of female participants ranged from 40% to 100%. Only one study investigated the effect of moderate to high intensity aerobic exercise training on blood flow in AD (van der Kleij et al., 2018). The effect of phytotherapy was examined in three studies. These looked at the effects of anapsos (Álvarez et al., 2000), kihito (Higashi et al., 2007), and donepezil in combination with Kami-Untan-To (Maruyama et al., 2006). Six studies assessed the effects of acetylcholinesterase inhibitors (AChEI), among which two studies specifically studied oral tetrahydroaminoacridine (THA) and lecithin (COHEN et al., 1992), THA in combination with lecithin or without lecithin (Gustafson, 1993). In addition, tacrine administration (Prentice et al., 1996), donepezil (Nakano et al., 2001), and galantamine administration on rCBF (Keller et al., 2011), and finally, the combination of three types of AChEI (donepezil, rivastigmine, and galantamine) were studied (Shimizu et al., 2015). Two studies focused on drugs targeting acetylcholine differently, releasing it instead of inhibiting it. One study used linopirdine (Van Dyck et al., 1997) and the other citicoline (Álvarez et al., 1999). Eight studies assessed the effects of other pharmacological interventions that did not target acetylcholine. Some of these drugs were pyritinol treatment in two studies from the same group (Knezevic et al., 1989; Mubrin et al., 1989) and L-deprenyl (a selective MAO-B inhibitor) (Agnoli et al., 1992). The effect of memantine was tested in subjects that were already using donepezil for six months or longer, by including patients in the memantine combination donepezil group and then controls in the non-memantine combination donepezil group (Araki et al., 2014). The minimum safe and effective dose of methylthioninium, a tau aggregation inhibitor, required to prevent AD progression was analyzed in a sub-study (Wischik et al., 2015). One study assessed the effects of metformin, an insulin-sensitizing medication (Koenig et al., 2017). Another study investigated the effect of nilvadipine, an antihypertensive drug (De Jong et al., 2019). Finally, a trial examined whether lanabecestat slows the progression of AD compared to placebo, this sub-study was discontinued due to futility (Zimmer et al., 2021). Three studies looked at the effects of other types of interventions. These were estrogen therapy (Premarin) (Wang et al., 2000), sodium lactate infusion (Kálmán et al., 2005), and plasma exchange (Cuberas-Borrós et al., 2018).

3.2. Risk of bias within studies

The risk of bias for this review was evaluated based on seven criteria: random sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessment, incomplete outcome data addressed, and selective reporting. A summary of the assessment results has been reported in Supplementary Table **A2**.

None of the studies presented with high risk of bias in random sequence generation and allocation concealment, but several studies, especially the AD studies published before 2011, did not report how randomization was performed. Four studies had an elevated risk of bias in participant blinding. In three of these studies, participants could not be blinded due to the nature of the intervention (L.C. Beishon et al., 2021; Thomas et al., 2020; Tomoto et al., 2021). However, participants were instructed not to discuss their interventions with investigators or other included subjects. Lastly, in Shimizu et al. (2015) participant blinding was not performed since it was an open-label trial (Shimizu et al., 2015). Four studies could not perform personnel blinding. In LC. Beishon et al., 2021 personnel blinding was not possible due to the nature of the intervention (L.C. Beishon et al., 2021). In Shimizu et al. (2015) personnel blinding was not performed since it was an open-label trial (Shimizu et al., 2015) and van der Kleij et al. (2018) was a single-blind trial (van der Kleij et al., 2018). Three studies had a high

Table 2
Data Extraction Table - AD Studies.

Study	Description of sample			Intervention		Perfusion outcome measure			Results		
	Included sample size	Mean age (years ± SD)	AD criteria	Description	Duration (weeks)	Perfusion technique	Analysis method	Perfusion outcome	Perfusion results	Cognition results	Other results
Knezevic et al., 1989	26 AD	76.2 ± 8.0	DSM-III	Pyritinol *Crossover design*	20 (10 weeks per treatment)	Xenon inhalation cerebrography		rCBF (*also ctivation*)	Resting rCBF remained unchanged with both groups, while more changes for activation CBF were seen in the pyritinol group. Treatment led to a smaller number of more active regions so more focal activation (while untreated had an increase in almost all areas).	Treatment has a beneficial effect on psychiatric (SCAG, ADAS), neurological, and cognitive (CETM, short-term memory recall and recognition) operations in demented individuals.	Not Available
Mubrin et al., 1989	26 AD	76.2 ± 8.0	DSM-III	Pyritinol *Crossover design*	22 (10 weeks per treatment)	Xenon Inhalation cerebrography		rCBF (*also activation*)	Resting CBF remained unchanged with both groups. Activation CBF showed more pronounced changes after treatment (smaller number of activated regions in the treatment group than placebo – more focal).	Increase performance in the WPLR in the treatment group (associated with lower number of activated areas), vice versa for controls.	Not Available
Agnoli et al., 1992	10 AD (5 intervention, 5 placebo)	Overall: 68.6 ± 4.5 Per group n.s.	NINCDS/ ARDRDA criteria	L-deprenyl	8.5	SPECT imaging	4 pairs of bilateral regions (frontal, temporal, parietal, occipital)	rCBF	L-deprenyl patients showed no changes in rCBF before and after treatment. Placebo patients showed a significant further decrease of rCBF in parietal lobes.	Significant improvement in memory efficiency as well as in attention tasks was demonstrated at the end of treatment only for the patients treated with L-deprenyl. Additionally, improvements in GBS scale, verbal fluency and picture copy task	Not Available

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Table 2 (*continued*)

Study	Description of sample			Intervention		Perfusion outcome measure			Results		
	Included sample size	Mean age (years ± SD)	AD criteria	Description	Duration (weeks)	Perfusion technique	Analysis method	Perfusion outcome	Perfusion results	Cognition results	Other results
										were seen in treated patients.	
Cohen et al., 1992	6 AD	Range 63 to 80	NINCDS/ ADRDA criteria	Lecithin THA *Crossover design*	18 (1 week per treatment, then 15 weeks outpatient)	SPECT imaging	ROIs (areas of the cortex and basal ganglia)	Cerebral perfusion ratio	No significant change in cerebral perfusion was observed from initial treatment with THA and lecithin.	One patient demonstrated mild behavioral improvement under THA treatment.	EEG: spectral energy in the slow frequency (delta-theta) bands reduced in 4 patients.
Gustafson et al., 1993	17 AD	62.6 ± 6.8	DSM-III-R NINCDC-ADRDA	THA Lecithin *Crossover design*	26 (6 weeks per treatment)	Xenon inhalation		rCBF	THA treated patients showed a stable rCBF level and a central-parietal CBF increase compared to the progressive rCBF decrease in the control group.	No significant differences in psychometric results (language, memory, inductive thinking).	Not Available
Prentice et al., 1996	19 AD (10 intervention, 9 placebo)	68 ± 12 Per group n.s.	DSM-III NINCDS-ADRDA	Tacrine	12	SPET imaging	ROI (anterior cingulate, frontal cortex)	rCBF (*activation*)	There were acute tacrine effects in the frontal and anterior cingulate regions of the upper slice, as well as in the anterior temporal region of the lower slice. Furthermore, increase in the superior frontal and cingulate ROIs and a reduction in the anterior temporal ROI. Also, a greater reduction in cingulate perfusion at week 13.	There was no significant effect on cognitive function (CAMCOG; MMSE; Rivermead Behavioral Memory Test) over 12 weeks of chronic treatment.	Not Available
van Dyck et al., 1997	24 AD (15 intervention, 9 placebo) + 13 healthy controls	68.9 ± 8.2 Per group n.s.	NINCDS-ADRDA	Linopirdine	8	SPECT imaging	ROI (cerebellum, prefrontal cortex, premotor cortex, superior temporal cortex, sensorimotor cortex, inferior parietal cortex, medial parietal cortex, superior parietal cortex)	rCBF	Patients treated with LPD showed a significant increase in rCBF in the parietal association cortex which represented a reversal of approximately 15% of the baseline deficit.	Treatment was associated with a trend towards improvement in the CGIC and weaker trends toward improvement in the cognitive portion of the ADAS and the DBDS	Not Available

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Table 2 (*continued*)

Study	Description of sample			Intervention		Perfusion outcome measure			Results		
	Included sample size	Mean age (years ± SD)	AD criteria	Description	Duration (weeks)	Perfusion technique	Analysis method	Perfusion outcome	Perfusion results	Cognition results	Other results
Álvarez et al., 1999	30 AD (13 intervention, 17 placebo)	Intervention: 76 ± 9 Controls: 73 ± 45	ICD10 DSM-IV NICDS/ ADRDA criteria	Citicoline	12	TD ultrasonography	MCA	Blood flow in MCA	When data of the two MCA were analyzed together, citicoline induced a significant increase in mean, systolic and diastolic velocities as compared to placebo.	In comparison with placebo, citicoline improved ADAS-cog scores, but this improvement was not significant.	Brain bioelectrical activity of the alpha type showed a decrease from baseline in the placebo group and an increase after treatment.
Álvarez et al., 2000	23 AD (9 placebo, 6 360 mg/day, 8 720 mg/day)	73.8 ± 7.6 Per group n.s.	NICDS-ADRDA DSM-IV	Anapsos	4	TD ultrasonography	MCA	Blood flow in MCA	Mv in the MCA of AD decreased after treatment with placebo and increased in subjects receiving 360mg a day of anapsos. Trend of increased Mv also in left middle cerebral artery after 720 mg a day. Opposite effect in the right hemisphere. Similar effects for diastolic CBF velocities. No effect for pulsatility, resistance, effective pulsatility indices.	Improvement in cognitive performance (ADAS) in a dose dependent manner.	Changes were seen between placebo and anapsos in brain bioelectrical activity (accelerates EEG activity patterns).
Wang et al., 2000	47 AD (24 intervention, 23 placebo)	Intervention: 72.6 ± 9.1 Placebo: 71.0 ± 9.1	NINCDS-ADRDA	Conjugated estrogen (Premarin)	12	SPECT imaging	ROI (frontal, anterior temporoparietal, posterior temporoparietal, occipital). 4 ROIs in each hemisphere, set up symmetrically on each cerebral slice, making a total of 32 ROIs in the supratentorial area.	rCBF	The changes of CBF in the treated group were not significantly different from those in the placebo group.	No meaningful differences were found between the secondary outcome measures (CASI, CDR, CIBIC-plus, BEHAVE-AD, HARS, HDRS).	Elevated levels of estrone and estradiol, indicating good compliance to treatment.

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Table 2 (*continued*)

Study	Description of sample			Intervention		Perfusion outcome measure			Results		
	Included sample size	Mean age (years ± SD)	AD criteria	Description	Duration (weeks)	Perfusion technique	Analysis method	Perfusion outcome	Perfusion results	Cognition results	Other results
Nakano et al., 2001	35 AD (15 intervention, 20 placebo)	Intervention: 69.3 ± 6.9 Placebo: 71.2 ± 5.6	DSM-IV NINCDS-ADRDA	Donepezil	52	SPECT imaging	Voxel-based and ROI (aorta, brain hemispheres)	rCBF	Preservation of adjusted rCBF in the anterior cingulate gyrus and right prefrontal cortex of treated patients (suggesting preservation of functional brain activity). No differences in absolute rCBF.	Placebo compared to treated patients performed worse on forward and reverse digit span test, on 30-min delayed recall Ray-Osterrieth complex figure test, on Stroop test at follow-up. Placebo group decreased in the MMSE, forward digit span and Stroop.	Not Available
Kálmán et al., 2005	20 AD	73.5 ± 4.2 Per group n.s.	NINCDS-ADRDA ICD-10	Sodium lactate infusion *Crossover design*	2 days (1 day per treatment)	SPECT imaging	Voxel-based	rCBF	No significant rise in rCBF. In 7 out of 20 patients SL further decreased rCBF. Hypoperfusion in some of the brain regions preferentially affected in AD might be exacerbated by lactate.	Not Available	Not Available
Maruyama et al., 2006	38 AD (18 combination, 20 control)	Donepezil + Kami-Untan-To (combination): 73.7 ± 5.6 Donepezil (control): 74.6 ± 3.9	NINCDS-ADRDA	Donepezil Kami-Untan-To	12	SPECT imaging	ROI (frontal regions)	rCBF	The rCBF in frontal regions significantly increased in the combination group.	Posttreatment MMSE scores significantly improved only in the combination group, ADAS-cog scores also improved significantly in the combination group.	Not Available
Higashi et al., 2007	10 AD (4 intervention, 6 control)	Kihito (intervention): 86.1 ± 5.0 GJG (control): 84.2 ± 6.4	DSM-IV	Kihito extract GJG	13	SPECT imaging	ROI (Anterior cingulated, posterior cingulated, frontal, parietal, temporal, occipital and hippocampus segments)	rCBF	Kihito administration was not related to an increase in CBF. There was an increased area of CBF in both GJG and kihito groups and this was mainly in frontal and cingulate (no statistics run between the groups due to small sample).	MMSE scores showed significant improvement at 3 months after treatment in the kihito group, but not in the non-treatment or GJG groups.	Basal levels of Activities of Daily Living did not differ among the three groups, and Activities of Daily Living was unchanged at 3 months after treatment in all groups.

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Table 2 (*continued*)

Study	Description of sample			Intervention		Perfusion outcome measure			Results		
	Included sample size	Mean age (years ± SD)	AD criteria	Description	Duration (weeks)	Perfusion technique	Analysis method	Perfusion outcome	Perfusion results	Cognition results	Other results
Keller et al., 2011	18 AD (12 intervention, 6 placebo)	Intervention: 70.9 ± 2.7 Placebo: 65.8 ± 3.7	NINCDS-ADRDA	Galantamine	13	[^{15}O] water PET imaging	ROI (frontal cortex; frontal, anterior cingulate and frontal association cortex, parietal cortex, parietotemporal cortex and temporal cortex; temporal and medial temporal lobe)	rCBF	The treated patients showed a slight increase of rCBF at 3 weeks followed by a strong increase after 3 months treatment.	There were no statistically significant changes observed after long term galantamine treatment compared with the baseline. However, positive trends in each cognitive test except for the Clock Recognition Test were observed.	Not Available
Araki et al., 2014	37 AD (19 combination, 18 control)	Donepezil + Memantine (combination): 77.9 ± 9.8 Donepezil (control): 79.8 ± 4.6	DSM-IV ICD-10	Memantine + Donepezil	24	NIRS	22-channel probe on the frontal region	Local CBF (*activation*)	Significant difference between the combination group and the control group was observed at the 24th week in CH5 (right middle frontal gyrus), CH7, and CH8 (left middle frontal gyrus).	There was significant difference between the combination group and the control group in MMSE and in Clock Drawing Test.	A significant difference between the combination group and the control group was observed in delusion, agitation, depression and dysphoria, anxiety, inaction and apathy, irritability and instability, and abnormal behavior.
Shimizu et al., 2015	55 AD (19 donepezil, 17 rivastigmine, 19 galantamine)	Donepezil: 78.4 ± 6.5 Galantamine: 77.4 ± 6.0 Rivastigmine: 77.2 ± 5.4	NINCDS-ADRDA	Donepezil Galantamine Rivastigmine	52	SPECT imaging	3-dimensional stereotactic surface projection	rCBF	All groups showed a significant increase in rCBF, mainly in the frontal lobe. Significant rCBF reduction was observed in the temporal lobe and cingulate gyrus in all 3 groups.	All AChEIs prevented the progression of cognitive impairment after 12 months of treatment, as shown by no significant decreases compared with baseline in MMSE and ADAS-cog total scores.	Not Available
Wischik et al., 2015	135 AD Per group n.s.	69 mg: 73.4 ± 8.7 138 mg: 73.8 ± 9.9 228 mg: 73.8 ± 9.0 Placebo: 74.6 ± 8.6 (from the overall study with n = 321)	DSM-IV NINCDS-ADRDA	Methylthioninium in 3 dosages	24	SPECT imaging	ROI (average across ROIs was analyzed)	rCBF	Mild subjects receiving placebo had significant rCBF decline in all regions. At the 138 mg/day dose, all regions other than the left frontal lobe were significantly	In subject with moderate disease, the 138mg Methylthioninium /day dose was effective in preventing decline in the ADAS-cog after 24 weeks. Similar effects were seen for the MMSE from baseline	Not Available

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Table 2 (*continued*)

Study	Description of sample			Intervention		Perfusion outcome measure			Results		
	Included sample size	Mean age (years ± SD)	AD criteria	Description	Duration (weeks)	Perfusion technique	Analysis method	Perfusion outcome	Perfusion results	Cognition results	Other results
									different from placebo.	in subjects with moderate disease.	
Koenig et al., 2017	20 AD	70.1 ± 6.89	CDR-Global 1.0	Metformin *Crossover design*	16 (8 weeks per treatment)	pCASL-MRI	ROIs (temporal, parietal, and frontal cortices)	rCBF	No statistically significant treatment effects were observed in any of the pre-defined regions of interest using an intent-to-treat sample.	A statistically significant treatment effect was observed on one measure of executive functioning, and statistical trends on a measure of learning and memory and a measure of attention.	No significant change within individuals in CSF glucose or protein levels, or in CSF Aβ42, total tau, or phosphorylated tau levels across groups.
Cuberas-Borrós et al., 2018	37 AD (18 intervention, 19 control)	Intervention: 65 [Q1, Q3: 60.0-76.0] Control (sham PE): 65.5 [Q1, Q3: 58.0-78.0]	NINCDS-ADRDA criteria	Plasma exchange	21	SPECT imaging	Voxel-based and VOI analysis (Brodmann areas: BA 7, BA 9, BA 10, BA 21, BA 22, BA 23-24, BA 37, BA 38, BA 39, BA 40, and BA 46)	Brain perfusion	The control group showed a progressive decrease in perfusion during the study. The treatment group showed a stabilization or absence of progression of perfusion decrease.	Not Available	Not Available
van der Kleij et al., 2018	51 AD (27 intervention, 24 placebo) + 22 healthy	Intervention: 68 ± 7 Placebo: 69 ± 7	Clinical diagnosis of probable AD	Aerobic exercise	16	Pulsed ASL-MRI	ROIs (whole brain, frontal regions, ACC, PCC, SPG, precuneus)	gCBF and rCBF	The change in both gCBF and rCBF over the study period did not differ between the groups.	Not Available	No difference in the VO2 peak at baseline between the exercise and control arm, whereas the VO2 peak was increased after 16 weeks in the exercise group, but stable in the control group.
de Jong et al., 2019	32 AD (18 intervention, 14 placebo)	Overall: 72.8 ± 6.2 Intervention: 72.6 ± 6.9 Placebo: 19.7 ± 3.1	NIA-AA 2011 NIA-AA 2018	Nilvadipine	26	Time-pulsed ASL-MRI	ROIs (global, hippocampal, PCC, precuneus)	CBF	CBF increase in the hippocampus, whereas other regions showed stable or small nonsignificant increases.	Not Available	Nilvadipine induced a significant reduction in blood pressure recorded at the 6-month follow-up visit,

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Table 2 (*continued*)

Study	Description of sample			Intervention		Perfusion outcome measure			Results		
	Included sample size	Mean age (years ± SD)	AD criteria	Description	Duration (weeks)	Perfusion technique	Analysis method	Perfusion outcome	Perfusion results	Cognition results	Other results
											compared with placebo.
Zimmer et al., 2021	76 AD (66 "50 mg", 65 "20 mg", 82 placebo)	50 mg: 72.8 ± 6.3 20 mg: 72.1 ± 6.6 Placebo: 71.7 ± 6.5	NIA-AA	Lanabecestat	78	Florbetapir perfusion PET imaging	ROIs (bilateral parietal angular gyrus, posterior cingulate, and temporal lobes), pons plus vermis as a reference	Cerebral perfusion	No significant differences in cerebral metabolism and perfusion between the groups.	No evidence of lanabecestat slowing pathophysiologic progression of AD.	Not Available

Note. Aβ42 = Amyloid β-42; ACC = Anterior Cingulate Cortex; AChEIs = Acetylcholinesterase Inhibitors; AD =Alzheimer's Disease; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADNI = Alzheimer's Disease Neuroimaging Initiative; ASL-MRI = Arterial Spin Labeling-Magnetic Resonance Imaging; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease; CAMCOG = Cambridge Cognitive Schedule; CASI = Cognitive Assessment Screening Instrument; CBF = Cerebral Blood Flow; CDR = Clinical Dementia Rating; CETM = Contextual Effects upon Text Memory; CGIC = Clinical Global Impression of Change; CIBIC-plus = Clinician Interview-Based Impression of Change; CSF = Cerebrospinal Fluid; DBDS = Dementia Behavior Disturbance Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; EEG = Electroencephalogram; GJG = Goshajinkigan, HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; ICD = International Statistical Classification of Diseases and Related Health Problems; LPD = linopirdine; MCA = Middle Cerebral Artery; MMSE = Mini-Mental State Examination score; Mv = Mean velocity; NIA-AA = National Institute on Aging-Alzheimer's Association; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NIRS = near-infrared spectroscopy; ^{15}O = Oxygen-15 radioactive isotope; PCC = Posterior Cingulate Cortex; PET = Positron Emission Tomography; rCBF = regional Cerebral Blood Flow; ROI = Regions of Interest; SCAG = Scale of Clinical Assessment for Geriatrics; SL = Sodium Lactate; SPECT = Single-Photon Emission Computerized Tomography; SPG = Superior Parietal Gyrus; TD = Transcranial Doppler; THA = Tetrahydroaminoacridine; WPLR = Word Pair Learning and Recall; VO^2 = Volume of Oxygen; VOI = Volume of Interest.

risk of bias regarding the blinding of outcome assessment. Higashi et al. (2007) had a high risk of bias in outcome assessment since the clinical evaluations (cognitive and behavioral tests) were performed with a single-blind method (Higashi et al., 2007). Shimizu et al. (2015) was an open-label trial (Shimizu et al., 2015). In most AD studies, the risk of bias in reporting incomplete outcome data and in selective reporting was unclear, while low risk was seen in all MCI studies (apart from one that had unclear selective reporting). One study had low risk for all criteria, six studies had a low risk of bias for six out of seven criteria, another three had low risk for five out of seven criteria.

3.3. Perfusion techniques and outcomes

The scientific articles included in this review used different techniques to assess CBF, here we provide an overview. Some of the CBF assessment techniques included in this review cannot cross the intact blood-brain barrier (BBB) allowing for assessment only of the arteries that supply blood to the brain (e.g., Dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI), dynamic perfusion computed tomography (PCT), and transcranial doppler (TD)).

DSC-MRI (Quarles et al., 2019) and PCT (Keedy et al., 2012) are widely used methods. DSC-MRI was used in one of the included studies (Schwarz et al., 2018). Both these techniques use tracers that are not diffusible through the BBB. TD ultrasonography (Robba et al., 2019), for which no tracer is needed, can also only measure CBF in the arteries that supply blood to the brain. These techniques use mathematical models to estimate CBF and related measures such as cerebral blood volume (CBV) and mean transit time (MTT) of blood to brain tissue. Other measures that can be obtained with TD are average mean (Mv), systolic (Sv) and diastolic (Dv) flow velocities, pulsatility index (PI = [Sv-Dv]/Mv), resistance index (RI = [Sv-Dv]/Sv), and the effective pulsatility range (EPR = Mv-[Sv-Dv]). TD was used in several of the included studies (Álvarez et al., 2000, 1999; L.C. Beishon et al., 2021; Tomoto et al., 2021).

Unlike DSC-MRI, PCT, and TD, positron emission tomography (PET) (Zhang et al., 2014), single-photon emission computed tomography (SPECT) (Ferrando and Damian, 2021), and xenon-enhanced computed tomography (XeCT) (Yonas et al., 1996) use tracers capable of crossing the BBB, thus also allowing the study of CBF at the level of brain tissue (microcirculation). More recently, arterial spin labeling (ASL) MRI (Soldozy et al., 2019) and functional near-infrared spectroscopy (fNIRS) (Pham et al., 2019) were introduced, these techniques measure cerebral hemodynamics (including microcirculation) from endogenous signals from the brain. All these methods were used in the rest of the papers included. The study of cerebral microcirculation alterations is relevant in the investigation of normal aging and the AD spectrum since it might be at this stage that specific changes occur beyond the alterations of the cerebral macro-vasculature (Beishon et al., 2021; Toth et al., 2017). Each of these techniques has advantages and disadvantages when compared to each other, but all are reproducible in the study of CBF in humans. More details on these techniques can be found elsewhere (Ferrando and Damian, 2021; Keedy et al., 2012; Pham et al., 2019; Quarles et al., 2019; Robba et al., 2019; Soldozy et al., 2019; Yonas et al., 1996; Zhang et al., 2014).

Most of the studies addressing CBF in the AD spectrum have used univariate analysis methods, either based on regions or volumes of interest (ROI or VOI) or voxel-based. Multivariate analyses are also used by research groups, allowing connectivity analysis of CBF networks (Jann et al., 2015; Sánchez-Catasús et al., 2018, 2017) and to study how network changes are related to normal or pathological aging.

3.4. Results of individual studies

3.4.1. Perfusion results in MCI

The current systematic review has included eight studies involving MCI subjects. A summary of the extracted data is presented in Table 1

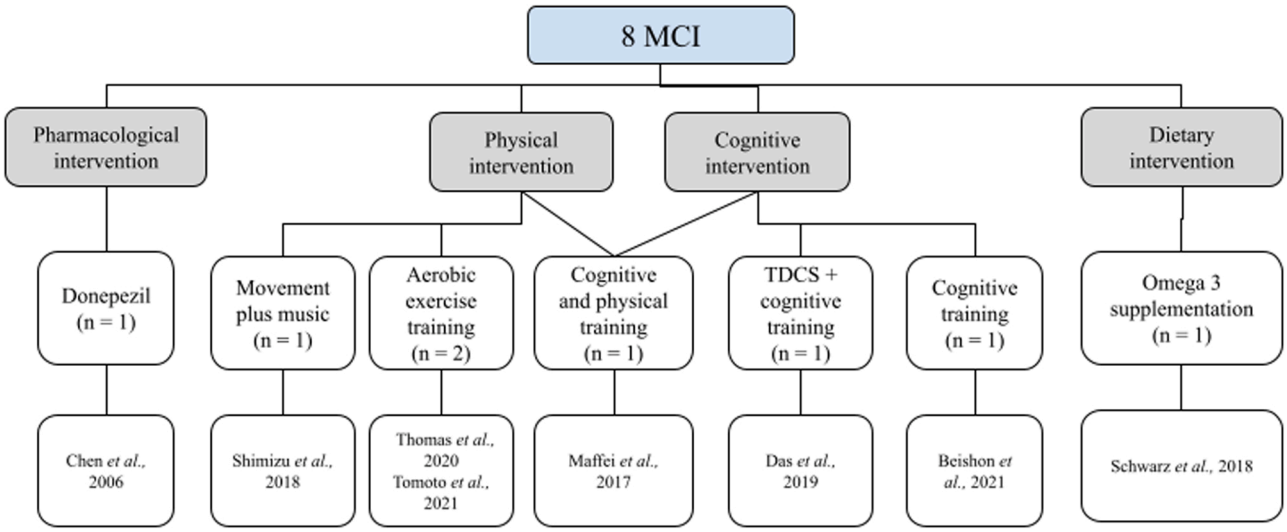

Fig. 2. Studies included for the MCI patients divided based on treatment type.

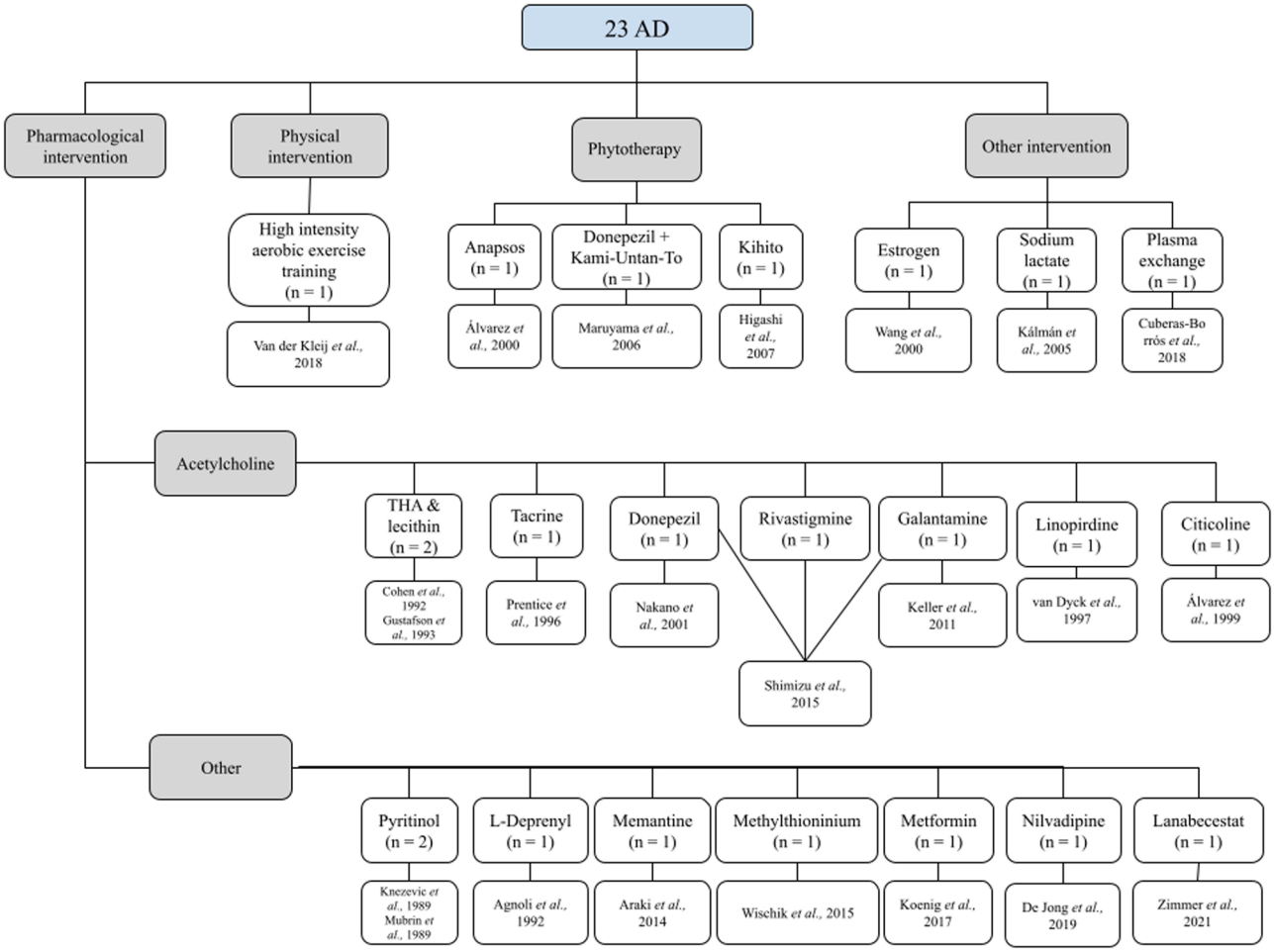

Fig. 3. Studies included for the AD patients divided based on treatment type.

(description of sample, intervention, perfusion measure and relative method, perfusion results and other results when applicable); study results have also been summarized below.

3.4.1.1. Pharmacological intervention. Thirty-two weeks donepezil administration did not lead to changes in rCBF, assessed during a verbal memory task with [^{15}O] water PET imaging, from intake to six months later. Nonetheless, rCBF in the placebo group was reduced after six months in the left frontal and temporal lobes. According to the authors, results should be cautiously interpreted since probability was uncorrected, and the sample size was very small (n = 11) (Chen et al., 2006).

3.4.1.2. Physical interventions. After twelve-week movement music therapy, similar changes in CBF measures were recorded in several brain

areas (bilateral temporal lobe, dorsolateral prefrontal cortex - DLPFC, prefrontal cortex - PFC) with fNIRS. Some of these regions seemed to act like a hub in the intervention group, while the correlation was lower in the single-task-training control group (Shimizu et al., 2018). One-year aerobic exercise compared to stretching and toning led to anterior cingulate cortex CBF increase measured with pseudo-Continuous ASL MRI (pCASL-MRI), which was related to enhanced logical memory (Thomas et al., 2020). Contrarily, posterior regions, specifically the posterior cingulate cortex, revealed a decrease in CBF after aerobic exercise compared to controls (posterior-to-anterior redistribution of brain perfusion). The same group applied this identical intervention in another study and measured CBF with duplex ultrasonography and TD. They found a decrease in carotid arterial stiffness and CBF pulsatility index, and an increase in global normalized CBF in the aerobic exercise group compared to controls (Tomoto et al., 2021). Additionally, a relationship between improvement in cardiorespiratory fitness and arterial stiffness and CBF was found. This positive association was mediated by a reduction in carotid stiffness and CBF pulsatility.

Summary: A movement and music intervention led to prefrontal area activation and improvement in executive functioning (Shimizu et al., 2018); aerobic exercise led to CBF increase in the anterior cingulate cortex, decrease in posterior cingulate cortex, and improvement in logical memory (Thomas et al., 2020); in a sub-study, the same aerobic exercise intervention led to reduction of carotid arterial stiffness and CBF pulsatility, increase in global CBF, and improved cardiorespiratory fitness (Tomoto et al., 2021).

3.4.1.3. Cognitive interventions. A thirty-week combined cognitive, social, musical, and physical training led to CBF increase (measured by 3D ASL MRI) in the hippocampal and parahippocampal regions, but statistical significance was only reached for the parahippocampal regions. For the non-training groups, no significant changes were detected (Maffei, 2017). A four-week cognitive training (gist-reasoning) was combined with a-tDCS and their effect on cerebral perfusion was measured with pCASL MRI. The intervention led to an increase in resting rCBF in subjects receiving a-tDCS (on the left and right inferior frontal gyrus) compared to the sham group. Despite a-tDCS having modulated neural plasticity, this happened unexpectedly since the sham group demonstrated immediate gain in selected cognitive measures while the anodal group did not. Although enhanced rCBF was seen in the contralateral PFC as compared to the stimulated one, the same was not observed in the region beneath the stimulated left inferior frontal gyrus (Das et al., 2019). The effect of cognitive training alone, applied for twelve weeks, on perfusion was measured with TD and it was examined in a feasibility study (L.C. Beishon et al., 2021). Results found no differences in resting cerebral and physiological parameters at baseline or follow-up between control and training groups in the healthy or cognitively impaired (MCI and AD) cohorts. Healthy controls instead showed lower resting CBF velocities both in the dominant and non-dominant hemisphere at follow up.

Summary: a multidomain intervention (cognitive, social, musical, and physical) led to cognitive status improvement and parahippocampal CBF increase (Maffei, 2017); a-tDCS increased CBF but stopped the benefits of cognitive intervention (Das et al., 2019); investigating the effects of a cognitive training on cerebral hemodynamics was considered feasible to implement in the MCI (and AD) population and, despite the small sample size, positive effects have been detected (L.C. Beishon et al., 2021).

3.4.1.4. Dietary intervention. Twenty-six weeks of omega-3 fatty acid supplementation influenced cerebral perfusion measured with pCASL-MRI (medium effects for rCBF and regional cerebral blood volume, rCBV). Increases in rCBF and rCBV were seen in the omega group in the combined ROIs (entorhinal gyrus, inferior temporal gyrus, inferior parietal gyrus, precuneus, isthmus cingulate gyrus, and superior parietal gyrus) (Schwarz et al., 2018).

3.4.2. Perfusion results in AD

The current systematic review has included twenty-three studies involving AD subjects. The extracted data is presented in Table 2 and study results have been summarized below.

3.4.2.1. Physical intervention. AD patients following physical exercise for sixteen weeks did not show a change in CBF measured with Pulsed ASL (PASL-MRI) when compared to controls (van der Kleij et al., 2018). Exercise had an impact on cardiorespiratory fitness (Volume of Oxygen, VO_2 peak), but this did not translate to CBF.

3.4.2.2. Phytotherapy interventions. The effect of anapsos for four weeks on blood flow hemodynamics was investigated in one study using TD in the middle cerebral artery (MCA) (Álvarez et al., 2000). Mv in MCA of AD patients decreased after treatment with placebo, while Mv increased in subjects receiving 360 mg/day of anapsos. The 360 mg/day dose induced similar changes in systolic and diastolic cerebral blood flow velocities in AD, with no effect on pulsatility, resistance and effective pulsatility range indices.

Kami-Untan-To administered for twelve weeks was studied in combination with donepezil and its effects on perfusion were measured using $^{I\text{-}123}$iodoamphetamine-autoradiography ($^{I\text{-}123}$IMP-ARG) SPECT imaging (Maruyama et al., 2006). Results showed a significant increase in frontal regions rCBF only in the combination group (Kami-Untan-To + donepezil).

Kihito, administered for thirteen weeks, did not promote a global increase in CBF, measured with SPECT imaging using a $^{99\,m}$Technesium-ethylcysteinate dimer (99mTc-ECD). Instead, there was a regional increase in CBF mainly in the frontal and cingulate brain areas in both the Kihito and Goshajinkigan groups (Higashi et al., 2007). Group comparison analysis to further investigate if this increase was significant was not performed since the number of subjects who underwent a SPECT scan was too small for statistical analysis.

Summary: anapsos treatment improved cerebral perfusion in patients with dementia in a dose-dependent manner, with the strongest effect in patients treated with 360 mg/day (Álvarez et al., 2000); combination treatment of donepezil and Kami-Untan-To increased frontal rCBF (Maruyama et al., 2006); kihito treatment was not associated with globally increased CBF (Higashi et al., 2007).

3.4.2.3. Pharmacological Interventions

3.4.2.3.1. AChE Inhibition. The effects of THA, THA + lecithin, and placebo were tested over twenty-six weeks using ^{133}-Xenon inhalation (Gustafson, 1993). No significant differences in hemispheric blood flow levels or regional distribution between any of the treatment periods were found. The responders, however, showed the highest rCBF hemispheric mean values at the end of each treatment period compared to the other patient groups. There was also a difference in rCBF distribution values (% of total mean) with higher right prefrontal and frontotemporal values in responders compared to non-responders. Moreover, an increase in rCBF was found in responders in the left but not in the right temporal region during THA treatment. THA was investigated in another study for eighteen weeks (COHEN et al., 1992), using $^{I\text{-}123}$IMP SPECT imaging, and no significant changes in cerebral perfusion were observed under treatment with THA and lecithin.

Acute regional effects of tacrine administered for twelve weeks were investigated by Prentice et al. (1996) using $^{99\,m}$Tc-Exametazime SPET imaging (Prentice et al., 1996). Tacrine effects led to an rCBF increase in the frontal and anterior cingulate regions (16% increase) and to a decrease in the anterior temporal regions (11% decrease). In the frontal regions, tacrine effects existed only at the beginning or at the end of the trial (change of the pattern of response in these ROIs during the treatment, not during placebo). The tacrine treated group exhibited a further

reduction in cingulate perfusion after acute single dose tacrine at week thirteen, perhaps explained by a habituation effect in this region.

The use of donepezil alone, administered for fifty-two weeks, did not promote changes on global CBF, measured with SPECT imaging using $^{99\,m}$Tc-ECD (Nakano et al., 2001). Nonetheless, compared with the donepezil-treated patients, the placebo-treated patients showed a significant rCBF decline in the right and left anterior cingulate gyri, right prefrontal cortex, right inferior parietal lobules, and right middle temporal gyrus. No significant time-course changes in absolute rCBF were seen between donepezil-treated and placebo-treated AD patients.

Examining the effect of galantamine administered for thirty-three weeks, Keller et al. (2011) found that rCBF measured with [^{15}O] water PET imaging did not show any time and group interaction in any of the studied brain areas (frontal, parietal, parietotemporal, temporal cortex). Despite this, in the placebo group, rCBF increased by 10% at four weeks, decreasing to 2% at three months (Keller et al., 2011). In the galantamine group, it increased 5% at three weeks and further increased to 11% at three months. RCBF correlated with inhibition of AChE activity, number of nicotinic receptors, and cognitive change.

The effect of different AChEI (donepezil, rivastigmine, galantamine, administered for fifty-two weeks) on rCBF was compared using N-isopropyl-p $^{I\text{-}123}$IMP SPECT imaging in a study conducted by Shimizu et al. (2015). In all treatment groups, a significant increase in rCBF was seen in the frontal lobe. Specifically, the donepezil group showed an rCBF increase in the frontal pole and orbital surface. The rivastigmine group presented an rCBF increase in the lateral and medial frontal lobe as well as the cingulate and occipital lobe, whereas the galantamine group had increased rCBF in the frontal lobe and occipital lobe. Particularly, the rivastigmine and galantamine groups had an extensive and intense rCBF increase in the frontal lobe and the occipital lobes. Significant decreases in rCBF in the three groups were observed in the temporal lobe and the cingulate gyrus with a tendency for rCBF reduction in the medial temporal lobe in the donepezil group and in the cingulate in the galantamine group. Changes were also seen in the cerebellum, showing both an increase and a decrease in rCBF.

Summary: THA treatment did not significantly impact CBF (COHEN et al., 1992; Gustafson, 1993); acute tacrine treatment led to an rCBF increase in superior frontal cortex and a decrease in anterior temporal cortex, the medial frontal cingulate cortex was also associated with a reduction in rCBF (Prentice et al., 1996); treatment with donepezil for one year appeared to reduce the decline in rCBF, suggesting preservation of functional brain activity in donepezil-treated patients (Nakano et al., 2001); no effects of galantamine treatment on rCBF were found (Keller et al., 2011); comparing three AChEI (galantamine, rivastigmine, and donepezil) an overall greater relative rCBF increase was seen in all treatment groups in the frontal lobe (Shimizu et al., 2015).

3.4.3. Other Pharmacological Interventions

The effect of ten weeks pyritinol treatment was tested by Knezevic et al. (1989) using ^{133}Xenon inhalation cerebrography (Knezevic et al., 1989). Their study showed treatment-related changes (rCBF increase) during mental activation. Patients receiving placebo showed a higher number of activated regions (12 right, 11 left), compared to pyritinol (9 right, 8 left). Although, when comparing the results after treatment with those before treatment, more pronounced activation related changes were seen after treatment with pyritinol (+7% right +11% left) than after placebo (+7% right and +6% left). Mean hemispheric flow was slightly higher in the left hemisphere than in the right in the pyritinol group.

Mubrin et al. (1989) found that after placebo treatment, the mean hemispheric blood flow at rest (measured using ^{133}Xenon inhalation cerebrography) remained unchanged as compared to the pre-treatment, and the amplitude of the increase during activation diminished slightly (Mubrin et al., 1989). Furthermore, the placebo group had a smaller number of activated areas. After treatment with pyritinol, the resting CBF was unchanged. However, during mental activation more pronounced changes were seen in the pyritinol group compared to placebo. The size of the area of significantly higher blood flow during activation diminished again. Therefore, the treatment group had a significantly smaller number of activated regions which was accompanied by a significantly better performance in the Word Pair Learning and Recall test.

L-deprenyl administration for eight and a half weeks led to no differences in parietal lobes CBF measured by SPECT imaging using the perfusion tracer ^{99}Tc hexamethylropyleneamineoxime (HMPAO), but the placebo group showed a further decrease of CBF in these regions (Agnoli et al., 1992). No extensive conclusions could be made due to the small sample size and no correlations were found between CBF and modification in cognitive performance.

Linopirdine administered for eight weeks significantly increased rCBF (measured with SPECT imaging using $^{99\,m}$Tc-ECD) in medial and parietal cortices, and occipital association cortices, with a trend towards an increase in the superior parietal cortex, while placebo showed a decrease in rCBF (Van Dyck et al., 1997). They found that the pattern of cortical activation produced by linopirdine treatment had considerable overlap with the pattern of cortical hypoperfusion of AD patients.

The effect of twelve-week citicoline on hemodynamic changes in the middle cerebral artery was studied using TD ultrasonography (Álvarez et al., 1999). Their results showed a decrease in cerebral blood flow velocities and in the effective pulsatility range in right and left middle cerebral arteries from patients of the placebo group, as well as an increase of these values in patients treated with citicoline, especially in the left MCA. Citicoline did not induce any significant changes from baseline in hemodynamic parameters. When data of the two MCA were analyzed together, citicoline induced a significant increase in mean, systolic and diastolic velocities with respect to placebo.

The effect of combined memantine and donepezil treatment administered for twenty-four weeks on local CBF was compared with treatment with donepezil alone using NIRS (Araki et al., 2014). The authors found a significant difference between the memantine administered group and the control group at the twenty-fourth week in the right and left middle frontal gyrus.

In the study conducted by Wischik et al. (2015), methylthioninium effect on rCBF (administered for twenty-four weeks) was investigated using $^{99\,m}$Tc-HMPAO SPECT imaging (Wischik et al., 2015). Results showed that mild AD subjects receiving placebo showed a decline in rCBF, while a smaller decline was observed in the rCBF of patients administered with methylthioninium treatment (with doses of 138 mg/day and 228 mg/day). In the analysis of rCBF changes in individual ROIs, mild AD subjects receiving placebo had significant rCBF decline in all regions. Differences from placebo were present for the 69 mg/day dose only in the right temporal lobe, for the 138 mg/day dose in all lobes except the left frontal lobe, and the 228 mg/day dose in right and left temporal lobes and in left occipital lobe. In moderate subjects, known to have more advanced perfusion deficits, the decline observed in the placebo group was non-significant, and no evidence of treatment benefit was present.

Metformin administered for eight weeks showed no statistically significant treatment effects in any of the pre-defined resting ROIs (temporal, parietal, and frontal cortices) using an intent-to-treat sample and recording rCBF using pCASL-MRI (Koenig et al., 2017). However, pooled post-hoc analyses demonstrated a significant increase in superior and middle orbitofrontal CBF over 8 weeks of treatment with metformin, but not placebo.

Reducing blood pressure through twenty-six weeks nilvadipine administration led to an increase in CBF in the hippocampus measured with time-pulsed 3D ASL-MRI (De Jong et al., 2019). No differences were found in global CBF, regional CBF in posterior cingulate cortex, or CBF in the other two ROIs namely precuneus and occipital lobe. This was also confirmed by CBF in sitting and standing positions. Global CBF did not change after blood pressure lowering meaning that cerebral autoregulation worked well to counteract the reduction in perfusion pressure.

Hippocampal CBF increase might have occurred through nilvadipine action in reversing hippocampal microvascular pathology and through nilvadipine influence on amyloid-beta.

Lanabecestat administration (in two different dosages, 20 mg or 50 mg) for seventy-eight weeks led to no differences in cerebral metabolism and cerebral perfusion measured with ^{18}F-florbetapir PET imaging compared to placebo administration (Zimmer et al., 2021). Despite this, a greater decrease in whole brain volume was seen in groups administered with 50 mg of lanabecestat compared to placebo, while no differences were observed in hippocampal volume.

Summary: pyritinol led to a more focal activation of brain regions which is considered a normalization (larger blood flow activation would mean greater effort expended by the participants during the test) (Knezevic et al., 1989; Mubrin et al., 1989); patients treated with L-deprenyl showed a stabilization of parietal CBF measures (Agnoli et al., 1992); linopirdine treatment reduced 15% of the parietal perfusion deficits seen in AD (Van Dyck et al., 1997); citicoline improved perfusion deficits observed in AD patients (Álvarez et al., 1999); memantine inhibited the reduction of cerebral blood flow in the prefrontal area (Araki et al., 2014); treatment with different doses of methylthioninium led to rCBF changes in patients with mild AD, while no perfusion changes were observed in the moderate patients (Wischik et al., 2015); metformin might lead to increases in orbitofrontal metabolism suggesting a potential mechanism of action related to effects on frontal-executive pathways, although the effects seen were in ventral brain regions which are sensitive to motion and artifacts (Koenig et al., 2017); nilvadipine led to hippocampal CBF increase (De Jong et al., 2019); lanabecestat led to no changes in cerebral perfusion (Zimmer et al., 2021).

3.4.4. Other pharmacological interventions

Investigating the effects of twelve weeks of estrogen therapy on rCBF measured with $^{99\,m}$Tc HMPAO SPECT imaging, the corticocerebellar ratio did not show a group difference between estrogen administered patients and placebo in the 32 ROIs selected. Grouping the 32 ROIs in four cortical regions (frontal, anterior temporoparietal, posterior temporoparietal and occipital) also showed no group differences (Wang et al., 2000).

Lactate infusion showed no rise in temporal-parietal rCBF of AD patients measured with $^{99\,m}$Tc-HMPAO SPECT imaging (Kálmán et al., 2005), indicating a defective vasodilatory response in AD and that lactate infusion can be used to provoke hypoperfusion.

AD patients treated with plasma exchange showed two to three lobes with perfusion improvements (measured with SPECT imaging using MBq of $^{99\,m}$Tc-ECD) while placebo-treated patients displayed two to three lobes with perfusion impairment (impairment was defined if subjects differed from a reference group of 22 healthy individuals). Differences between treated and controls were detected in hippocampal blood flow and Brodmann areas (BA 38-R, BA 38-L and BA 46-R). Despite these results, there was a poor correlation between SPECT and MRI. The percentage of patients showing lobe perfusion impairment was higher in the control group, while in the treatment group patients showed improvements (especially in parietal and temporal lobes) (Cuberas-Borrós et al., 2018).

Summary: estrogen therapy did not lead to different CBF changes compared to placebo (Wang et al., 2000); lactate infusion might exacerbate hypoperfusion in brain areas particularly affected in AD (Kálmán et al., 2005); plasma exchange treatment favored the stabilization of perfusion decline (Cuberas-Borrós et al., 2018).

4. Discussion

This systematic review provides an overview of the effects of different treatments on cerebral perfusion in MCI and AD patients. Since the brain is a highly vascularized and perfused organ, it might be particularly vulnerable to impairments in blood flow (Wolters et al., 2018). Decreases in CBF that are already present in normal aging processes (Lu et al., 2011; Tarumi and Zhang, 2018), can affect cognitive functions and trigger neurodegenerative processes (de la Torre, 2016). Considering there is a vascular contribution to AD (Janota et al., 2016), we summarized RCTs including cerebral perfusion as an outcome measure and provided a discussion for further research.

4.1. Intervention efficacy

Due to the diverse nature of interventions and perfusion techniques included in this review, no comprehensive and definite answer can be provided regarding their efficacy on cerebral hemodynamics. Nonetheless, a general summary and interpretation of results are hereby presented.

1) Almost all MCI studies applied non-pharmacological interventions. In six studies the treatment led to an increase in CBF, which often correlated with an increase in cognitive performance, mostly memory (Das et al., 2019; Maffei, 2017; Schwarz et al., 2018; Thomas et al., 2020; Tomoto et al., 2021). One study showed CBF differences (decrease) in the placebo group only and no differences in the treatment group (Chen et al., 2006), and one study showed no effects whatsoever on CBF (L.C. Beishon et al., 2021). Overall, the effects were seen in the frontal areas (DLPFC, middle frontal cortex, anterior cingulate cortex), in the bilateral temporal lobes and middle temporal lobes, especially the hippocampus and parahippocampal area. The implementation of physical, cognitive, dietary, and social interventions might have benefits in the MCI population.
2) Most AD studies used pharmacological interventions. The effects on CBF and cognition were diverse, often finding only small effects or trends. Many of the studies specified the frontal brain regions as the main regions involved. Six studies found treatment-related changes in CBF (parietal association cortex, middle cerebral artery, frontal regions, frontal gyrus) and influence of the treatment on cognition parameters (Álvarez et al., 2000; Araki et al., 2014; Van Dyck et al., 1997; Maruyama et al., 2006; Shimizu et al., 2015; Wischik et al., 2015). Three studies found a change in CBF (middle cerebral artery, frontal, anterior temporoparietal, posterior temporoparietal, occipital), but no treatment effect on cognition parameters (Álvarez et al., 1999; Keller et al., 2011; Prentice et al., 1996). Two studies found a more focal activation pattern of CBF and a beneficial effect of treatment on cognition (Knezevic et al., 1989; Mubrin et al., 1989). Two other studies found stabilization of CBF (anterior cingulate gyrus, prefrontal cortex), but no effects of treatment on cognition (Agnoli et al., 1992; Gustafson, 1993). Three studies found no changes in CBF but did find changes in cognition parameters (Higashi et al., 2007; Koenig et al., 2017; Nakano et al., 2001). Three studies found no changes in CBF and no effects of treatment on cognition (COHEN et al., 1992; Wang et al., 2000; Zimmer et al., 2021). One study found no effects of CBF and had no cognition parameters included (van der Kleij et al., 2018). Finally, the last three studies found either stabilization of CBF or a decrease in CBF and did not include any cognition parameters (Cuberas-Borrós et al., 2018; De Jong et al., 2019; Kálmán et al., 2005).

Overall, the treatments seem to have more effects on hemodynamics during the early stages of AD. However, the lack of positive results at later stages of AD might be due to the symptomatic nature of the interventions (i.e., pharmacological target mismatch with the CBF outcome).

4.2. Discussing the studies with low efficacy

Several elements have been reported by studies when discussing the negative or null findings on CBF, one of these was treatment duration. Cohen et al. (1992) stated that long-term THA exposure might have been

needed to produce measurable perfusion changes. This was in line with Gustafson's et al. (1993) finding that a six-week trial with THA had no effects on CBF, but after a twelve-months open trial, THA treated patients had a stable CBF, whereas the control group showed a progressive decrease in CBF. Treatment duration was also mentioned as a possible reason for the null results in Wang et al. (2000) where the authors stated that treatment may have been too short for estrogen to have an effect.

The type of method used to measure CBF might also have had an impact on results. In Nakano et al. (2001) there were differences in results between regional CBF, where effects were found, and global CBF, where no effects were seen. Thomas et al. (2020) also reported that the use of relative CBF values, each voxel normalized against whole-brain value, is more sensitive in detecting regional differences when whole-brain CBF does not show a difference. Additionally, Higashi et al. (2007) reported that the evaluation system used to analyze brain images (statistical parametric mapping program) might not have been sensitive enough to detect changes. Whether CBF is measured at rest or during a task might also have had an influence (Higashi et al., 2007). For instance, the study by Knezevic et al. (1989) found no differences in resting CBF, but different activation patterns were instead noted and could help explain why the cognitive scores improved, as they found cognitive improvement coupled with an increase in CBF in fewer areas. Similar patterns were seen in the study by Mubrin et al. (1989).

The type of control intervention might also play a role. In Higashi et al. (2007) Goshajinkigan might have been an inappropriate control since Goshajinkigan already increases peripheral vascular flow.

The stage of AD might be of paramount importance. The authors Van der Kleij et al. (2018) claimed that their negative results might have been due to the mild to moderate AD diagnosis of the participants, making the disease too advanced to induce any CBF increase. This implies that CBF should be targeted preferentially in healthy elderly or MCI patients to postpone or prevent AD pathology. Lastly, L.C. Beishon et al., 2021 combined MCI and AD participants due to a lack of statistical power in the analyses. As AD and MCI might have different hemodynamic profiles, this could have also influenced their results.

4.3. Limitations of the included evidence

Several limitations were present in the included literature. Regarding the interventions employed, there was a lack of non-pharmacological therapeutic interventions in the AD population. This was probably due to the impracticalities in testing the definite effect of these interventions (e.g., exercise, cognitive training) in AD as it would be considered relatively unethical to randomize part of the AD population to a 'not moving' arm, and a large trial would be required.

Another point was the inclusion of patients and the description of the sample. Almost no study explicitly mentioned the type of dementia onset (early or late). Additionally, the sample size of many of the studies was too small to make extensive conclusions and often authors mentioned sample size as a possible reason for negative or null results. Several of the studies included do not report the ethnicity of participants, which is important as it appears to affect age of onset, APOE genotypes, comorbidities, and deterioration rate of cognition in AD (Chen and Panegyres, 2016). In the few studies reporting ethnicity, most subjects were Caucasian. Future efforts are needed to include more diverse populations and possibly include information on additional demographic variables (e.g., disadvantage metrics, see (Kind and Buckingham, 2018)). APOE status should be reported as well since studies show CBF reductions in APOE4 carriers before Aβ accumulation and brain atrophy (Sheline et al., 2010). Recent research has also linked APOE4 status with accelerated cardiovascular changes both in the presence and absence of Aβ (Montagne et al., 2021).

The type of outcome measures recorded by the different studies was also diverse and might have influenced results. Not all included studies had a cognitive or functional outcome measure, despite their important role in characterizing the treatment effects. To approve new drugs for AD the FDA has recommended the presence of a 3-point difference in the 11-item Alzheimer's Disease-Cognitive Subscale (ADAS-Cog11) or an improvement in general core cognitive and functional measures (Liu et al., 2021). Although, no gold standard has been defined in RCTs to detect a minimum clinical importance difference (Liu et al., 2021). Other important measures are blood pressure and blood pressure variability since their relationship with perfusion is frequently discussed and only one of the included studies looked at blood pressure.

Lastly, the methods used to measure perfusion were diverse (e.g., TD versus ASL-MRI). The protocols employed also differed, for instance, a small number of the included studies used an activation task with CBF measurement. This limited our ability to quantitatively summarize the results but, on the other hand, it highlighted the importance of deciding whether to perform resting or activation scans. Chen et al. (2006), reported that decrements in performance might become evident only under an activation task and are therefore relevant for milder syndromes like MCI (Chen et al., 2006). Additionally, ten of the included studies have been published over twenty years ago. The available equipment and software are likely to have changed, and this may have contributed to the differential results.

4.4. Limitations Performing the Review

The lack of a quantitative summary of results (meta-analysis) limits generalizability and thus does not allow us to carry out a reliable estimation of treatment efficacy. Additionally, three of the included studies had a "high risk of bias" in more than one of the domains assessed (L.C. Beishon et al., 2021; Higashi et al., 2007; Shimizu et al., 2015), reducing the quality of the presented evidence (L.C. Beishon et al., 2021; Higashi et al., 2007; Shimizu et al., 2015). Lastly, the current review only searched for RCTs including cerebral perfusion outcomes and did not focus on other measures of cerebrovascular functioning (e.g., microinfarcts, calcification, vascular inflammation) which should also be looked at. A plethora of examinations needed to measure cerebrovascular factors should be included in future interventional trials (such as calcification, CBF, middle cerebral artery velocity, cerebrovascular reactivity and resistance). Despite these limitations, the present review has been conducted systematically and was able to highlight important points for future research.

4.5. Implications and future directions

4.5.1. Current AD treatments

Currently, cholinesterase inhibitors (galantamine, rivastigmine, and donepezil) are prescribed to treat symptoms and delay the speed of disease progression in mild to moderate Alzheimer's disease. For patients suffering from moderate to severe AD, the N-methyl D-aspartate (NMDA) antagonist (memantine) has been approved as symptomatic treatment. The effects of these medications mainly target disease symptom reduction and do not have disease-modifying effects.

Many clinical trials of prospective therapies have failed to affect the progression of disease symptoms (Cummings et al., 2019). Anti-Aβ clinical trials, which are treatments based on the amyloid hypothesis of AD, have mainly proven to be ineffective (Zhou and Fukushima, 2020). Although, in June 2021, aducanumab, an amyloid-β directed antibody, is the first early-stage Alzheimer's disease treatment approved by the FDA in over 17 years (Dhillon, 2021). Approval of aducanumab was 'accelerated' based on the reduction of amyloid plaques in patients treated with the drug (Cummings and Salloway, 2021). Treatment with aducanumab should be started in patients with MCI or mild dementia, which was the population included in the clinical trials (Dhillon, 2021).

The approval of aducanumab by the FDA might lead to a decrease of research interest into other mechanisms which contribute to the pathology of AD, such as the vascular system. According to the two-hit vascular hypothesis of AD, a first vascular dysfunction hit (e.g., leading to BBB dysregulation, decrease in CBF, neuronal dysfunction) can

initiate a second hit which is characterized by the defective clearance of Aβ thereby promoting the aggregation of cerebrovascular Aβ (Zlokovic, 2011). Cerebrovascular Aβ seems to be more resistant to antibody-mediated destruction of plaque deposits and the action of antibody therapy has an additional negative effect by trafficking amyloid plaques into perivascular spaces (Greenberg et al., 2020). Cerebral Amyloid Angiopathy (CAA) is a cerebrovascular disorder characterized by Aβ deposition in cerebral blood vessels and meninges (Apátiga-Pérez et al., 2021). Leaders of the International CAA Association advise not to use aducanumab for CAA, due to the doubts and concerns of its safety in this population (Greenberg et al., 2021). Keeping in mind the vascular contribution to AD, intervention and prevention trials should not miss out on targeting mechanisms that are initiated even before Aβ deposition, such as preventing CBF decrease.

4.5.2. Future directions and insights from hypoperfusion measures

When considering aducanumab, only individuals with proven Aβ plaque deposition and in a mild stage of disease can benefit from it. Currently, only a few symptomatic treatments are available for AD, for this reason, further research is needed to develop curative treatments. Perfusion dysfunction, together with other events happening in the neurovascular unit, might precede the accumulation of Aβ plaques (Apátiga-Pérez et al., 2021), therefore, their role should not be neglected.

Considering the current review's results, adding cerebral perfusion markers as an outcome measure in RCTs can add essential information on treatment effects. In one of the included studies (Das et al., 2019), the intervention did not lead to any gain in cognitive measures as hypothesized by the authors, but led to CBF modifications (Das et al., 2019). The perfusion results allowed the authors to better rationalize why their first hypothesis was not supported. Thus generally, the interpretation of perfusion measurements is more informative if recorded together with cognitive and functioning measures.

As vascular dysfunction is an important component of AD, it is useful to apply noninvasive imaging techniques to determine the direction of the connection between AD underlying pathologies. This review found that improvements in CBF were seen in the early stages of disease and seem to correlate with cognitive functioning. This could stimulate a different approach for future RCTs. Studies of potentially disease-modifying therapies have generally been undertaken in patients with advanced clinically detectable and established disease. Pharmacological therapies may be more beneficial if they target mechanisms that become abnormal at the very beginning of the disease process when no symptoms are yet present. Although, this would only be possible when biomarkers that can detect these early changes are discovered.

If a study inserts a perfusion outcome measure, it would be wise to move towards the adoption of multivariate analysis and connectivity studies. Using fNIRS for instance would allow both the identification of changes in CBF in a particular area and whether this led to enhanced functional connectivity. Clinically used anatomical T1 and T2 weighted MRI images have low sensibility for the detection of injuries at the microstructural level at an early stage (Frantellizzi et al., 2020). Perfusion techniques are more likely to depict early functional changes. Of the different perfusion techniques available MRI might be most promising as it uses no irradiation and has a higher spatial resolution compared to PET. Advanced state-of-the-art perfusion techniques like DSC vessel architecture imaging have been shown to be very sensitive in detecting early changes in other populations (Digernes et al., 2017; Kim et al., 2021; Schmidt et al., 2020) and we suggest looking into this in future studies. This could be even further strengthened by combining state-of-the-art MRI techniques with functional PET imaging using MRI-PET.

Combining treatments can have beneficial effects. Higashi et al. (2007) and Maruyama et al. (2006) reported positive effects on cognition when using Kihito and Kami-Untan-To as 'add-on' to donepezil treatment (Higashi et al., 2007; Maruyama et al., 2006). Kami-Untan-To could be used complementary to improve the treatment success of cholinergic therapies for AD. In general, complementary interventions targeting different aspects of AD might be beneficial considering the multifaceted and multi-causal nature of the disorder.

Our results suggest that increases and or stabilization of perfusion measures are seen in MCI groups with some interventions (physical and cognitive training). This amelioration together with improvement in cognitive functioning is important to reflect the desired delay of AD symptom onset. Thus, further longitudinal studies should follow up these individuals to assess whether an early improvement in cerebral perfusion can lead to delayed disease onset. The positive effects of different interventions in increasing CBF have also been seen in mouse models (Bracko et al., 2020; Tarantini et al., 2021) and in healthy individuals (Chapman et al., 2013; Kleinloog et al., 2021; Li et al., 2021; Maass et al., 2015).

4.5.3. Ongoing trials considering cerebral perfusion

In addition to the literature discussed above, seven protocols of ongoing studies assessing the effect of interventions on hemodynamics were found during the selection process. These included liraglutide in AD patients (Egefjord et al., 2012) (targeting the formation of Aβ plaques, no studies published on its effect on CBF yet), a combination of long-chain n-3 polyunsaturated fatty acids and cocoa flavan-3-ols in MCI (Irvine et al., 2018), losartan in AD (Kehoe et al., 2017), Kami Guibi-tang (Shin et al., 2019) and Sailuotong in MCI (Steiner et al., 2018), executive function and memory training in MCI (Zhang et al., 2018), and a traditional Chinese Qigong exercise (Baduanjin) in MCI (Zheng et al., 2016).

Additionally, ongoing clinical trials including cerebral perfusion as outcome measure have been registered in ClinicalTrials.gov. One compares the effect of a diet high in saturated fat, glycemic index, and salt (Na^+) and a diet low in these nutritional parameters. Another RCT is investigating the effect of MitoQ, a mitochondria-targeting antioxidant, on blood flow. Finally, in post-menopausal females, the effect of leuprolide acetate (Eligard), a luteinizing hormone, is being tested on cerebral perfusion.

5. Conclusion

Different types of intervention had positive effects on cerebral perfusion in six out of eight studies involving MCI patients and in twelve out of twenty-three studies involving AD patients. In some of the remaining studies, especially for AD, at least a stabilization was noticed in the treatment groups. Specifically, no further decrease in the studied outcome measures was seen, while a decrease was detected in the non-treatment groups. Comparing the perfusion results with other neuroimaging or clinical outcomes was useful to better understand the effects of the intervention. A more global inclusion of biomarkers, from the most established (Aβ, tau) to CBF, and a better characterization of AD profile such as late or early-onset, hemodynamic baseline status, would render trials more informative. We also observe an increase in the evaluation of non-traditional medicines in clinical trials.

Other information

Registration and protocol

A review protocol has been registered in PROSPERO (protocol number CRD42021254344). The protocol can be accessed at the following link https://www.crd.york.ac.uk/prospero/display_record.php?RecordID= 254344.

The only amendment introduced in the registered protocol regards language restrictions, these have been adapted based on the languages known by the researchers involved.

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CRediT authorship contribution statement

Sofia Marcolini: Conceptualization, Methodology, Software, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project Administration. **Ingeborg Frentz:** Software, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Carlos A. Sanchez-Catasus**, **Paula Kopschina Feltes, Anouk van der Hoorn**: Writing – review & editing. **M. Jaime D. Mondragon**: Writing – review & editing, Supervision. **Ronald J. H. Borra, M. Arfan Ikram, Rudi A.J.O. Dierckx**: Funding Acquisition, Writing – review & editing, Supervision. **Peter Paul De Deyn**: Conceptualization, Funding Acquisition, Writing – review & editing, Supervision, Project administration.

Competing Interests

We declare that there are no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101661.

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