



Review article

A systematic review of the association between dementia risk factors and cerebrovascular reactivity

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ABSTRACT

Cumulative evidence suggests that impaired cerebrovascular reactivity (CVR), a regulatory response critical for maintaining neuronal health, is amongst the earliest pathological changes in dementia. However, we know little about how CVR is affected by dementia risk, prior to disease onset. Understanding this relationship would improve our knowledge of disease pathways and help inform preventative interventions. This systematic review investigates 59 studies examining how CVR (measured by magnetic resonance imaging) is affected by modifiable, non-modifiable, and clinical risk factors for dementia. We report that non-modifiable risk (older age and apolipoprotein ε4), some modifiable factors (diabetes, traumatic brain injury, hypertension) and some clinical factors (stroke, carotid artery occlusion, stenosis) were consistently associated with reduced CVR. We also note a lack of conclusive evidence on how other behavioural factors such as physical inactivity, obesity, or depression, affect CVR. This review explores the biological mechanisms underpinning these brain-behaviour associations, highlights evident gaps in the literature, and identifies the risk factors that could be managed to preserve CVR in an effort to prevent dementia.

1. Introduction

Dementia is a condition in which a person's cognitive function progressively declines to the point where it interferes with their daily living (Chertkow et al., 2013). Global estimates indicate that the prevalence of dementia is either increasing or remaining stable in most countries (Stephan et al., 2018). Given that the population is ageing, the number of older adults living with dementia is predicted to increase drastically (Cao et al., 2020; Jia et al., 2020; Nichols et al., 2022; United Nations, 2019). This has notable healthcare, social, and economic consequences both for patients and carers (Cheng, 2017; Shon and Yoon, 2021). In the absence of disease modifying treatments, lowering the risk of dementia in older adults is a critical step for improving quality of life.

There are a number of modifiable or behavioural factors that can increase the risk of developing dementia, and in particular Alzheimer's or vascular dementia. These include low education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic

brain injury (TBI), and exposure to air pollution (Livingston et al., 2020; Mendez, 2017; Peters et al., 2019; Xu et al., 2017). Targeting these 12 risk factors may help prevent around 40% of dementia cases worldwide (Livingston et al., 2020). Additionally, genetic factors such as carrying at least one copy of the apolipoprotein ε4 (APOE ε4) allele can lead to a 3-fold (heterozygous ε4) to 15-fold (homozygous ε4) increase in the risk for Alzheimer's disease (Yin et al., 2018). Clinical risk factors, such as peripheral artery diseases (Newman et al., 2005; Tasci et al., 2018), or cerebrovascular lesions, such as strokes, infarcts, and white matter hyperintensities (WMH) can also increase the chances of developing Alzheimer's or vascular dementia (Scott et al., 2018). Recent research has focused on cerebrovascular reactivity (CVR) as a promising biomarker of these early pathological changes that precede the onset of dementia (Bokkers et al., 2011; Gupta et al., 2012; Ribigan et al., 2016; Suri et al., 2015; Wolters et al., 2016).

CVR is the ability of the brain's vessels to dilate in response to a vasoactive stimulus, such as carbon dioxide (i.e., CO₂-CVR) or acetazolamide (Liu et al., 2019). CVR can be reliably and non-invasively

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measured with magnetic resonance imaging (MRI) using either blood-oxygenation-level dependent (BOLD) MRI, arterial spin labelling (ASL) MRI, or quantitative flow phase-contrast MRI (Liu et al., 2019). Transcranial Doppler ultrasound (TCD) is also frequently used to measure CVR. However, unlike cerebral perfusion (e.g., ASL) which measures the blood flow per volume of tissue, TCD only measures blood velocity in arteries (Burley et al., 2021; McDonnell et al., 2013). Measurements of TCD are only taken in single major vessels, which may not always represent local changes in tissue blood supply (McDonnell et al., 2013). By contrast, MRI can map CVR in the brain's micro-vessels, allowing for greater spatial sensitivity (Sleight et al., 2021). Therefore, MRI-based measurements of CVR are more useful for describing the specific brain regions that are associated with dementia risk.

Several studies have shown that CVR is impaired in preclinical rodent models of Alzheimer's disease (Glodzik et al., 2013; Nicolakakis et al., 2008), as well as in patients with mild cognitive impairment (Shim et al., 2015), Alzheimer's disease and vascular dementia (Alwatban et al., 2019; Gao et al., 2013; Vicenzini et al., 2007), even after controlling for common vascular risk factors, such as atherosclerotic disease and hypercholesterolemia (Gongora-Rivera et al., 2018). Reduced CVR has also been shown to correlate with the degree of cognitive impairment (Kim et al., 2021; Silvestrini et al., 2006), and impairments in CVR might predict decline in processing speed and episodic memory (see Catchlove et al., 2018b for a review on the relationship between CVR and cognitive impairment; Peng et al., 2018).

Although there is considerable evidence that CVR is compromised in dementia, the underlying reasons for this remain unknown. Moreover, the relationship between CVR and well-known risk factors for dementia is poorly understood. Studying this association could help inform preventative interventions aimed at modifying CVR in order to reduce dementia risk (Murrell et al., 2013). This systematic review summarises observational and experimental studies investigating the associations between CVR (measured using MRI) and dementia risk factors in adults. Specifically, we summarise the associations between CVR and (a) non-modifiable risk factors (age and APOE $\epsilon 4$); (b) the 12 aforementioned modifiable/behavioural risk factors; and (c) clinical risk factors. We conclude by exploring the biological mechanisms underpinning these brain-behaviour relationships and highlighting avenues for future research.

2. Methods

The protocol for this systematic review was pre-registered with PROSPERO (International Prospective Register of Systematic Reviews; ID: CRD42021292793) in 2021, between the stages of our initial search and study screenings. We have followed the PRISMA reporting guidelines for systematic reviews throughout the current paper (Page et al., 2021).

2.1. Data sources and searching method

The electronic bibliographic databases including Ovid MEDLINE, Embase and PubMed were searched from inception (1946 for MEDLINE, 1974 for Embase, and 1966 for PubMed) to the 24th of November 2021. The search was limited to studies that were written in English and focused on humans rather than animals.

Three concepts guided the search terms: outcome (CVR) AND population of interest (healthy OR dementia/Alzheimer's disease/Mild Cognitive Impairment adults) AND dementia risk factors. Dementia risk factors were selected based on the literature (Breijyeh and Karaman, 2020; Livingston et al., 2020; Serrano-Pozo et al., 2021). Search terms included both generic expressions (e.g., "dementia risk factor" or "genetic risk factor") as well as specific risk factors (e.g., "diabetes mellitus" or "major depressive disorder"). The following risk factors were selected for this study:

- (1) **Non-modifiable risk factors** including age and APOE $\epsilon 4$ status;
- (2) **Modifiable/behavioural risk factors** were derived from the 12-risk factor model (Livingston et al., 2020) and included less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution;
- (3) **Clinical risk factors** including strokes, atrial fibrillation, atherosclerosis, peripheral artery disease, and arterial stiffness.

Details of the search terms are presented in [Supplementary Material 1](#).

2.2. Inclusion and exclusion criteria

We focussed on studies that measured CVR using MRI, but we did not restrict studies based on their choice of vasodilatory stimuli. Hence, we included studies that used pharmacological stimuli (e.g., acetazolamide) or respiratory challenges (e.g., breath holding, hyperventilation, and inhalation of hypercapnic normoxic gas).

Inclusion criteria:

- a) Correlational studies (e.g., observational studies).
- b) Experimental studies (e.g., randomized controlled trials and quasi-experiments).

Exclusion criteria:

- a) Qualitative studies and case reports.
- b) Reviews and meta-analyses, conference abstracts and editorial or opinion papers.
- c) Studies that involved participants with a non-relevant disease, such as a disease that is not an evidenced risk factor of dementia or cognitive decline.
- d) Studies that investigated Lewy body dementia, frontotemporal dementia or Parkinson's dementia.
- e) Studies that did not investigate CVR as a variable of interest.
- f) Studies that did not investigate risk factors for dementia as a variable of interest.
- g) Studies that were not conducted with humans.
- h) Studies that were not written in English.
- i) Studies that did not associate dementia risk factors with CVR.
- j) Non-MRI studies, i.e., studies assessing CVR using TCD, Xenon CT (computed tomography), PET (positron emission tomography), or SPECT (single-photon emission computed tomography) were excluded as we sought to avoid procedures that were either less spatially sensitive, more expensive, or involved ionising radiation.

2.3. Data selection and data synthesis

2.3.1. Study selection

Two reviewers (CW and GR) independently conducted literature searches on the same platform using the same search terms in order to agree on the number of articles to be included. The *eliminating duplicates* functions in Ovid and Endnote were used to remove duplicates. Then, based on the stated inclusion/exclusion criteria, both reviewers separately examined the titles and abstracts and selected the relevant studies for the review. The two reviewers compared and discussed the lists of included studies, and any disagreements about article inclusion were resolved by discussion with a third reviewer (SS).

2.3.2. Data extraction

In a data extraction table, details about the author, title, country, year of publication, study design, participant demographics, study objective, risk factors studied, method of assessing CVR, vasodilatory challenge, and main findings on the association between CVR and dementia risk factors were recorded. The data extraction table was completed by one reviewer (CW), and the extracted data was reviewed by the second reviewer (GR). Disagreements were resolved with the help

of a third reviewer (SS).

2.3.3. Data synthesis

The main findings were reported using a narrative synthesis technique. The table of data obtained from the studies was structured according to the types of dementia risk factors: non-modifiable, modifiable/behavioural, and clinical risk factors. A formal meta-analysis was not possible due to considerable methodological heterogeneity between studies.

2.3.4. Mini-meta-analysis

In order to investigate quantitative results of the association, we performed a mini-meta-analysis for the associations between age and CVR. The statistical parameters were extracted from the eligible studies. Effect size was analysed using a random-effects model to calculate the overall standard difference in means. Heterogeneity was assessed using the I^2 statistic, with a value greater than 50% indicating substantial heterogeneity (Cochran, 1954). Publication bias was evaluated using a funnel plot and Begg and Mazumdar rank correlation test (Begg and Mazumdar, 1994; Egger and Smith, 1995). The meta-analysis was performed using Comprehensive Meta-Analysis (version 3.7).

2.4. Quality assessment

Both reviewers (CW and GR) used the NIH Quality Assessment Tool (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>) to determine whether the eligible studies had a risk of bias. This test uses 14 questions to analyse numerous potential sources of bias in a study, including clear research questions, study population eligibility,

sample size justification, and the validity and reliability of the study measurements. Inter-rater discrepancies were resolved by conversations with a third reviewer (SS), and each study was given either a good, fair, or poor quality rating.

3. Results

A total of 4197 studies were identified in the initial search, of which 119 articles met the inclusion criteria at the first screening stage. After reviewing the full texts for the 119 articles, a final sample of 59 studies were included in the review (sample selection in Fig. 1). The risk of bias evaluation found that no studies had a significant quality risk; only eight out of 59 were rated as “fair” quality, and no study fulfilled the threshold for “poor” quality (Supplementary Material 2). There was no noticeable difference in the results between the “fair” and “good” quality studies for each risk factor.

Overall, we found relevant studies investigating the associations between CVR and both non-modifiable factors (i.e., age and APOE $\epsilon 4$), six of the 12 established modifiable/behavioural risk factors (i.e., physical inactivity, obesity, hypertension, diabetes, depression, and TBI), and several known clinical risk factors (e.g., strokes, stroke-related cerebrovascular diseases, small vessel diseases, arterial occlusions or arterial stenosis, and aortic stiffness). Summaries of the studies are reported in Tables 1–3. The number of papers discussing negative or positive associations between each risk factor and CVR can be seen in Fig. 2.

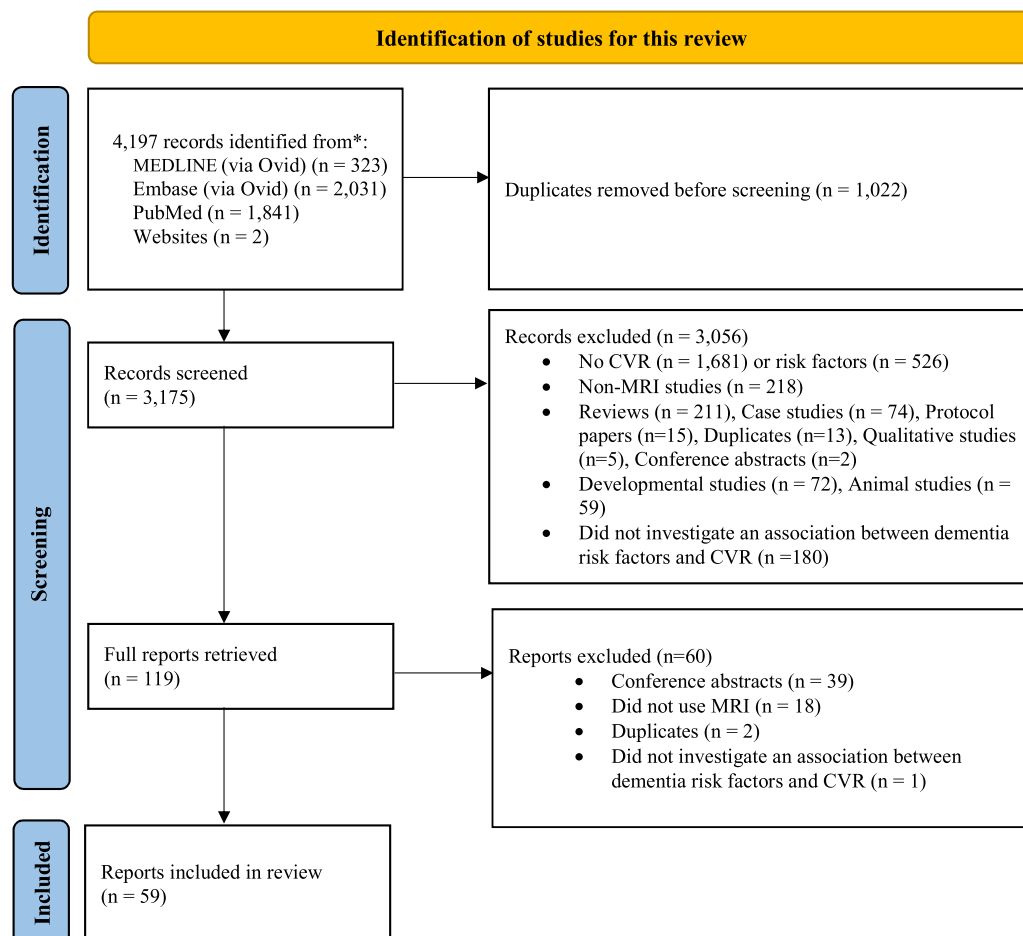


Fig. 1. Study identification and selection process. *Records shown here were duplicated by Ovid interface and reference manager.

3.1. Non-modifiable risk factors

3.1.1. Age

14 studies examined age-related changes in CVR. Overall, there were consistent findings of age-related decreases in CVR in 11 studies, while three studies did not find any relationships between age and CVR.

Compared with younger adults (22–30 years old across the 11 studies), older people (55–75 years old) had lower CVR either in the whole brain (Taneja et al., 2020; Tucker et al., 2020), grey matter (Catchlove et al., 2018a; Intzandt et al., 2020; Leoni et al., 2017; Thomas et al., 2013) or in specific regions, such as the temporal lobe (Catchlove et al., 2018a; Thomas et al., 2013), cingulum (Catchlove et al., 2018a), or occipital cortices (Hund-Georgiadis et al., 2003; Thomas et al., 2013). Some studies also found that older adults had slower hemodynamic responses to CO₂ compared to the younger group (Leoni et al., 2017; Rasmussen et al., 2019). However, Raut et al. (2016) reported that while there was no age-related difference in the amplitude of BOLD signal change to CO₂, the area of activation in the grey matter was larger for young people than older people.

Some studies found age-specific associations in CVR. For instance, one cross-sectional study found that CVR decreased with increasing age in older adults (55–75 years) but not in younger adults (21–45 years; Catchlove et al., 2018a). Moreover, a longitudinal study noted that participants' CVR generally declined over the four-year observation period (Peng et al., 2018), but that CVR declined faster in middle-aged participants (41–60 years) compared to older participants (61 years and above). This study also suggested that the quickest declines in CVR were observed in the temporal lobe, followed by the parietal and frontal lobes.

In contrast, two studies observed no age-related differences in CVR in global grey matter with a relatively small effect size of $\text{hedges' } g = 0.03$ for BOLD-CVR (Burley et al., 2021), or in the frontal cortex with a large

effect size of $R^2 = 0.152$ (Gauthier et al., 2015). In addition, one older study with only 10 participants used acetazolamide instead of a gas stimulus and found no significant correlations between age and vaso-reactivity (Mandai et al., 1994). McKetton et al. (2018) used two types of hypercapnia challenges: step CO₂, in which the P_{ET}CO₂ (end-tidal partial pressures of CO₂), was immediately increased to 10 mmHg above baseline, and ramp CO₂, where the P_{ET}CO₂ was gradually increased to hypercapnia status. When CO₂ was increased gradually, it was found that CVR was lower in the older group compared to the younger group in the frontal lobe's white matter. As for grey matter CVR, no age-related differences were found when CO₂ was administered gradually. When CO₂ was increased to hypercapnia status immediately without gradation, no age-related differences in CVR were found in either the grey or white matter.

After excluding one study which did not report necessary statistics (Thomas et al., 2013), a meta-analysis of the remaining 13 studies that assessed the associations between age and CVR showed an overall large mean effect size of -1.004 (95% confidence interval (CI) = -1.302 to -0.707 , $p < 0.001$; Fig. 3) suggesting that CVR may decrease with age. However, the studies were significantly heterogeneous ($Q = 25.6$, $p = 0.012$, $I^2 = 53.1$), indicating that the summary effect estimate may not be representative of the true effect. Begg and Mazumdar rank correlation was not significant with $\tau = -0.026$ (two-tailed $p = 0.903$) though the meta-analysis was biased towards underestimating the true effect. The funnel plot did not indicate significant publication bias (Fig. 3). Given the heterogeneity of studies in their choice of vasodilatory stimuli, brain regions of interest, and demographics, we did not perform meta-analysis for the other risk factors to avoid misinterpretations.

Table 1

Summary of studies investigating the associations between non-modifiable risk factors and CVR. Abbreviations: ASL= Arterial spin labelling, BOLD= Blood oxygenation level dependent, CVR= Cerebrovascular reactivity, ETCO₂= End tidal carbon dioxide (i.e., the amount of carbon dioxide (CO₂) in exhaled air), MRI= Magnetic resonance imaging.

Non-modifiable risk factors										
Author and year	Country	Study design	Total Sample size	Sample Size of sub-groups	Age mean (SD or range)/ years	Sex (% of male)	CVR		Findings *	
							MRI method	Vasodilatory stimuli		
Age										
Burley et al., 2021 [#]	UK	cross-sectional	N=30	young:18 old:12	young:25 ± 7 old:69 ± 4	young:61% old:58%	BOLD	inhalation of 5% CO ₂ or 7% CO ₂ in ambient room air	no significant difference between groups	
Catchlove et al., 2018a	Australia	cross-sectional	N=59	young:30 old:29	young:30±6.22 old:65±5.57	young:60% old:38%	BOLD	inhalation of 5% CO ₂ , 21% O ₂ , and 74% N ₂	young > old (cingulum, grey matter and temporal areas)	negative association between age and CVR for old but not for young
Gauthier et al., 2015 [#]	Canada	cross-sectional	N=85	young:31 old:54	young:24±3 old:63±5	young:68% old:31%	BOLD	40 mmHg (normocapnia) to 45 mmHg (hypercapnia) ETCO ₂ through gas delivery	no significant difference between groups (frontal cortices)	
Hund-Georgiadis et al., 2003 [#]	Germany	cross-sectional	N=12	young:6 old:6	young:24.8 (23-27) old:57 (51-63)	young:50% old:50%	BOLD	voluntary hyperventilation	young > old (occipital cortices)	
Intz et al., 2020 [#]	Canada	cross-sectional	N=76	young:26 old:50	young:23.7±2.9 old:63.4±4.9	young:73% old:34%	BOLD	40 mmHg (normocapnia) to 45 mmHg (hypercapnia) ETCO ₂ through face mask	young > old	
Mandai et al., 1994 [#]	Japan	cross-sectional	N=10	correlational	51 (28-76)	total:70%	3D time-of-flight MR angiography	17 mg/kg IV of acetazolamide	no relationship between age and CVR	
Leoni et al., 2017	Brazil	cross-sectional	N=17	young:10 old:7	young:30±7 old:64±8	N/A	ASL, BOLD	inhalation of 5% CO ₂ in medical air	young > old	
McKetton et al., 2018	Canada	cross-sectional	N=38	age 18–28 years:11 age 29–38 years:11 age 39–54:8 age 55–76:8	N/A	total:53%	BOLD	10 mmHg PETCO ₂ above baseline (using step CVR for immediate increase of CO ₂ and ramp CVR for steady increase of CO ₂)	young > oldest group (bilateral frontal white matter regions of the anterior and middle cerebral artery watershed area)	no significant difference between groups (ramp CVR in grey matter, step CVR and total mean CVR)
Peng et al., 2018 [#]	USA	longitudinal (4 years)	baseline N=205 follow-up N=116	within-subject design	age:20-88 at baseline	baseline:40% follow up:33%	BOLD	inhalation of 5% CO ₂ , 21% O ₂ and 74%N ₂	negative association between age and CVR (rate: temporal lobe > parietal and frontal lobe, the greatest decline occurred during middle age)	
Rasmussen et al., 2019 [#]	Denmark	RCT	N=41	age 30-40:8 age 40-50: 9 age 50-60:12 age 60+: 12	30-40: e3:35.7±2.7, e4:34.5±2.0 40-50: 40-50:	30-40:63% 40-50:33% 50-60:42% 60+:58%	BOLD	breath-holding	young > middle age for e4	

(continued on next page)

Table 1 (continued)

										$\epsilon 3:46.1 \pm 1.4$, $\epsilon 4:46.4 \pm 3.0$ 50-60: $\epsilon 3:55.3 \pm 3.3$, $\epsilon 4:56.8 \pm 2.4$ 60+: $\epsilon 3:65.2 \pm 2.2$, $\epsilon 4:54.7 \pm 3.3$	
Raut et al., 2016 #	U S A	cross-section al	N=44	young:22 old:22	young:22 (18– 27) old:59 (50–74)	young:50% old:45%	BOLD	breath-holding	young > old (activation volume)	no difference between groups (activation magnitude)	
Taneja et al., 2020	U S A	cross-section al	N=49	young:32 old:17	young: sample1:23.6±0.6, sample2:20.9±0.6 old: sample1:59.6±1.6, sample2:66.0±3.0	young:50% old:35%	phase contrast MRI, ASL, BOLD	inhalation of 5%CO ₂ , 21% O ₂ , and 74% N ₂	young > old (using phase contrast)	no age-related difference using ASL or BOLD	
Thomas et al., 2013 #	U S A	cross-section al	N=19	young:9 old:10	young:27.0±3.6 old:75.4 ± 5.6	young:56% old:80%	BOLD	inhalation of 5% CO ₂ , 21% O ₂ , and 74% N ₂	young > old (frontal, temporal, parietal and occipital lobes, subcortical grey matter, insula, cerebellum, and the entire cerebrum)		
Tucker et al., 2020 #	U S A	non-rando mised trial	N=17	young:7 middle:10	young:24 ± 5 middle:48 ± 6	young:71% middle:20%	BOLD	inhalation of 5% CO ₂ , 21% O ₂ and 74% N ₂	young > middle age		
APOE $\epsilon 4$											
Jefferson et al., 2018 #	U S A	cross-section al	N=192	normal cognition:113/ 155 had CVR (29% of 155 participants carried APOE $\epsilon 4$) mild cognitive impairment:79/ 115 had CVR (41% of 115 participants carried APOE $\epsilon 4$)	normal cognition:72±7 mild cognitive impairment:73±7	normal cognition:59 % mild cognitive impairment:5 7%	ASL	inhalation of 5% CO ₂ and 95% medical-grade room air (hypercapnic normoxia)	APOE did not moderate the association between aortic stiffness and CVR in cognitively healthy or MCI		
Rasmussen et al., 2019 #	De n mark	RCT	N=81	$\epsilon 4$ carriers:41 non-carriers:40	30-40: $\epsilon 3:35.7 \pm 2.7$, $\epsilon 4:34.5 \pm 2.0$ 40-50: $\epsilon 3:46.1 \pm 1.4$, $\epsilon 4:46.4 \pm 3.0$ 50-60: $\epsilon 3:55.3 \pm 3.3$, $\epsilon 4:56.8 \pm 2.4$ 60+: $\epsilon 3:65.2 \pm 2.2$, $\epsilon 4:54.7 \pm 3.3$	$\epsilon 4$ carriers:49% non- carriers:50%	BOLD	breath-holding	$\epsilon 3$ -carriers > $\epsilon 4$ -carriers		
Suri et al., 2015	U K	cross-section al	N=53	$\epsilon 2$ carriers:18 $\epsilon 3$ homozygotes:1 7 $\epsilon 4$ carriers:18	$\epsilon 2$ - carriers:24.11±5.3 1 $\epsilon 3$ - homozygotes:24.1 1±4.96 $\epsilon 4$ - carriers:23.88±4.7 5	$\epsilon 2$ - carriers:39% $\epsilon 3$ - homozygotes: 47% $\epsilon 4$ - carriers:44%	ASL	inhalation of 4% CO ₂ , 21% O ₂ , balanced with N ₂	$\epsilon 2$ -carriers and $\epsilon 3$ -homozygotes > $\epsilon 4$ -carriers.		

*Findings show the main results of the associations between risk factors and CVR.

#Studies have been reported multiple times in Tables 1–3 as they examined more than one risk factor in the same study, and hence have overlapping samples.

	Negative associations between the risk factor and CVR, i.e., CVR decreases as the risk factor increases or verse versa
	No associations between the risk factor and CVR
	Positive associations between the risk factor and CVR, i.e., CVR increases as the risk factor increases or verse versa

3.1.2. APOE $\epsilon 4$

Three studies have investigated APOE $\epsilon 4$ and two of them reported that carrying the APOE $\epsilon 4$ allele increased the likelihood of having impaired CO₂-CVR regardless of age. In young adults, there was evidence that compared with carriers of the APOE $\epsilon 2$ or $\epsilon 3$ alleles, $\epsilon 4$ -carriers had the lowest measures of CVR in widespread brain regions, including the hippocampus (Suri et al., 2015). Similar findings were also demonstrated in middle-aged people (50–60 years). Using a breath-holding task, Rasmussen et al. (2019) found that APOE $\epsilon 4$ carriers had slower peak BOLD responses to hypercapnia relative to $\epsilon 3$ carriers. The third study investigated the interaction between aortic stiffness and APOE on CVR (Jefferson et al., 2018). Although this did not directly compare main effects of APOE on CVR, the authors found that APOE $\epsilon 4$ did not influence the association between temporal lobe CVR and aortic stiffness, both in cognitively healthy adults and in people with mild cognitive impairment.

3.2. Modifiable/behavioural risk factors

3.2.1. Obesity

Only two studies investigated the association between obesity and CVR. Frosch et al. (2017) found that obese and overweight adults (defined as BMI >25 kg/m²) had lower CO₂-CVR compared to healthy

weighted controls, and this group difference reached a large effect size of $\eta^2_p = 0.174$. They also found that higher BMI was linked to lower CVR, but this link was no longer significant after controlling for insulin resistance. In contrast, a small surgical intervention study (N = 6 bariatric surgery candidates) found no differences in CVR between obese pre-bariatric surgery patients (BMI >35 kg/m²) and age-matched controls prior to surgery (Tucker et al., 2020). Interestingly, in this study global CVR did not change following bariatric surgery despite patients losing weight, BMI, and body circumference.

3.2.2. Physical inactivity

Due to the lack of studies assessing physical inactivity, we reviewed studies evaluating the associations between exercise or cardiorespiratory fitness and CVR. Foster et al. (2020) found that grey matter CO₂-CVR was positively correlated to aerobic fitness (measured as participants' maximum oxygen consumption; VO₂max). However, Burley et al. (2021) observed no significant differences in either global grey matter CVR (Hedges' $g = 0.38$) or sub-cortical CVR (Hedges' $g = 0.53$ – 0.61) with BOLD MRI between a younger fit group (indicated by VO₂max) and an older unfit group (assessed by physical activity questionnaires). Gauthier et al. (2015) reported a negative association between VO₂max and CVR in frontal regions with a relatively large effect size ($R^2 = 0.11$), but positive correlations in periventricular watershed

regions and within the postcentral gyrus.

MRI studies have also reported no immediately beneficial effects of exercise interventions on CVR. For instance, CVR did not change after a 3-month physical exercise training programme, and there was no significant difference in CVR between groups who completed physical exercise training and those who completed cognitive training (Chapman et al., 2016). However, there was also no change in VO_2max after the physical training intervention, which might either be due to participant's prior sedentary lifestyle or the fact that the intervention was too short. Similarly, Steventon et al. (2020) performed MRI scans at baseline and 25 min post-exercise and observed no changes in CVR before and after 20 min of cycling.

Two studies have also reported negative associations between lifelong physical activity and CVR in older adults. Master athletes (who were ranked in regional or national running competitions) showed lower whole-brain CVR than sedentary age-matched individuals, and there was a negative association between global CVR and fitness (VO_2max ; Thomas et al., 2013). Additionally, Intzandt et al. (2020) showed that there were negative relationships between cardiovascular fitness and BOLD-CVR in grey matter throughout the cortex for elderly

subjects, whereas there was no link for younger adults.

3.2.3. Depression

Depression was the only psychiatric risk factor for dementia included in this review, and there were consistent results of no relationships between depression and CVR. [Abi Zeid Daou et al. \(2012\)](#) reported no differences in CVR between people with and without depression and there was also no significant association between depression severity and CVR. Similarly, [Moreton et al. \(2018\)](#) used another depression scale and found that though CADASIL patients with depressive symptoms had lower CVR relative to those without depression, this was not statistically significant. Furthermore, an interventional study in individuals with depression found that there was no correlation between baseline depression severity and CVR in any fronto-cingulate regions ([Abi Zeid Daou et al., 2017](#)). However, higher CVR in the caudal medial frontal gyrus was related to less effective response to antidepressants.

3.2.4. Type 2 diabetes

People with type 2 diabetes had lower CVR than healthy controls, according to three out of the four selected studies. [Last et al. \(2007\)](#)

Table 2

Summary of studies investigating the associations between modifiable/behavioural risk factors and CVR. Abbreviations: ASL= Arterial spin labelling, BOLD=Blood oxygenation level dependent, BMI= Body mass index CVR= Cerebrovascular reactivity, ETCO_2 = End tidal carbon dioxide (i.e., the amount of carbon dioxide (CO_2) in exhaled air), fNIR= functional near-infrared spectroscopy, HIT-6= Headache Impact Test-6, higher score means higher headache severity and burden, IR= insulin resistance, MADRS= Montgomery- Asberg Depression Rating Scale, higher score means more severe depression, MCA= Middle cerebral artery, MRI= Magnetic resonance imaging, PCA= Phase contrast angiography, RCT=Randomised controlled trial, T2DM= Type 2 diabetes mellitus, TBI= Traumatic brain injury, VO_2 = Amount of oxygen the body can use during exercise.

Modifiable/Behavioural risk factors									
Author and year	Country	Study design	Total Sample size	Sample Size of sub-groups	Age mean (SD or range)/ years	Sex (% of male)	CVR		Findings *
							MRI method	Vasodilatory stimuli	
Obesity									
Frosch et al., 2017	USA	cross-sectional	N=60	normal weight controls:20 obese/overweight with insulin resistance:24 obese/overweight without insulin resistance:16	control=53.27±4.27 obese, IR=51.83±4.87 obese, non-IR=50.69±3.15	controls:30% obese/overweight with insulin resistance:63% obese/overweight without insulin resistance:50%	ASL	change in 5–7 mm Hg ETCO_2 from room air through snorkel like mouthpiece	control > obese/overweight no association between BMI and CVR when controlling for insulin resistance
Tucker et al., 2020 [#]	USA	non-randomised trial	N=16	normal weight controls:10 bariatric surgery candidates:6	controls:48 ± 6 obese:52 ± 10	normal weight controls:20% bariatric surgery candidates:17%	BOLD	inhalation of 5% CO_2 , 21% O_2 and 74% N_2	no difference between groups before and after surgery
Physical inactivity									
Burley et al., 2021 [#]	UK	cross-sectional	N=15	young fit:9 (78%) old unfit:6 (33%)	young fit:28 ± 8 old unfit:70 ± 5	young fit:78% old unfit:33%	BOLD	inhalation of 5% CO_2 or 7% CO_2 in ambient room air	no difference between younger fit and older unfit
			N=18	young fit:10 (70%) old unfit:8 (75%)	young fit:22 ± 2 old unfit: ±72 ± 4	young fit:70% old unfit:75%	BOLD/PCA	inhalation of 5% CO_2 in ambient room air	non-significant trend for young > old (cingulate and motor regions) for BOLD
Chapman et al., 2016	USA	RCT	N=36	physical training:18 cognitive training:18	physical training:64.0 ± 4.3 cognitive training:61.8 ± 3.3	physical training:28% cognitive training:44%	BOLD	inhalation of 5% CO_2 in room air	no change in CVR during the 3-month physical training no difference in CVR between groups
Gauthier et al., 2015 [#]	Canada	cross-sectional	N=54	correlational	total: 63±5	total:31%	BOLD	40 mmHg (normocapnia) to 45 mmHg (hypercapnia) ETCO_2 through gas delivery	positive association between VO_2max and CVR (periventricular watershed regions and within the postcentral gyrus) negative association between VO_2max and CVR (frontal regions)
Foster et al., 2020	UK	cross-sectional	N=20	correlational	total:25 ± 4.6	total:45%	ASL	inhalation of 5% CO_2 in medical air	positive association between CVR and aerobic fitness/ VO_2peak
Intz et al., 2020 [#]	Canada	cross-sectional	N=76	young:26 old:50	young:23.7±2.9 old:63.4±4.9	young:73% old:34%	ASL, BOLD	40 mmHg (normocapnia) to 45 mmHg (hypercapnia) ETCO_2 through face mask	old: negative association between VO_2peak and CVR (grey matter) young: no association between VO_2peak and CVR
Steventon et al., 2019	UK	self-controlled	N=16	within-subject design	total:26.2±3.4	total:44%	ASL	inhalation of 5% CO_2 in medical air	no significant change in CVR after exercise
Thomas et al., 2013 [#]	USA	cross-sectional	N=18	master athletes:10 (2 did not have CVR) sedentary:10	master athletes: 74.5±5.8 sedentary:75.4±5.6	master athletes:70% sedentary:80%	BOLD	inhalation of 5% CO_2 , 21% O_2 and 74% N_2	sedentary > athletes negative association between VO_2max and CVR

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Table 2 (continued)

Depression									
Abi Zeid Daou et al., 2012	USA	cross-sectional	N=35	nondepressed:16 depressed:19	no depressed:68.00±5.82 depressed:68.10±7.29	nondepressed:45% depressed:39%	ASL	inhalation of 5% CO ₂ , 21% O ₂ and 74% N ₂	no significant difference between groups
Abi Zeid Daou et al., 2017	USA	non-randomised trial	N=18	remitters:8 non-remitters:10	remitters:69.1±7.7 non-remitters:67.1±6.9	remitters:36% non-remitters:40%	ASL	inhalation of 5% CO ₂ , 21% O ₂ and 74% N ₂	no association between baseline MADRS depression score and CVR (fronto-cingulate) positive association between CVR and depression alleviation after 12-week antidepressant treatments (caudal medial frontal gyrus)
Moreton et al., 2018 [#]	UK	cross-sectional	N=13 out of 22 had CVR	correlational	total:49.6±11.2	total:50%	ASL	inhalation of 6% CO ₂ in air	no association between depressive symptoms and CVR
Type 2 Diabetes									
Chung et al., 2015	USA	longitudinal (2 years)	N=65	baseline: control:30 T2DM:35 follow-up: control:21 T2DM:19	baseline: control:67.1±10.4, diabetes:65.1±8.2 follow-up: control:69.4±9.6 diabetes:69.7±8.1	baseline: control:53% T2DM:46% follow-up: control:48% T2DM:37%	ASL	linear regression of perfusion and CO ₂ values (mL/100 g/min/ mm Hg) across normal breathing and CO ₂ rebreathing	no significant difference at baseline control > patients after 2-year follow-up (global, frontal, temporal, occipital and insula cortices)
Jor'dan et al., 2014	USA	cross-sectional	N=128	contro:67 diabets:61	control:67±9 diabetic:65±8	contro:41% diabets:51%	ASL	inhalation of 5% CO ₂ and 95% air to increase CO ₂ of 45 mmHg	no significant difference between groups negative association between gait speed and CVR in patients
Last et al., 2007 [#]	USA	cross-sectional	N=51	contro:25 diabets:26	control:60.4±8.6 diabetes:61.6±6.6	contro:52% diabets:50%	ASL	inhalation of 5% CO ₂ and 95% air	control > patients (frontal, temporal, parieto-occipital, and cortical regions)
Tchistiakova et al., 2014	Canada	cross-sectional	N=34	hypertension:22 hypertension with diabetes:12	hypertension:73.4±6.2 hypertension with diabetes:71.8±5.6	hypertension:45% hypertension with diabetes:56%	BOLD	breath holding	hypertension > hypertension with diabetes (bilateral-lingual gyrus, cuneus and superior parietal areas; right-lateral occipital, inferior parietal and precuneal regions; and left pericalcarine cortex)
Hypertension									
Blair et al., 2020 [#]	UK	cross-sectional	N=53	correlational	total:68.0±8.8	total:74%	BOLD	inhalation of 6% CO ₂ in air	negative association between systolic blood pressure and CVR in patients
Hajjar et al., 2010	USA	cross-sectional	N=62	control:22 hypertension:40	total:66.7±1.0	total:45%	ASL	inhalation of 5% CO ₂ and 95% air	control > patients
Peng et al., 2018 [#]	USA	longitudinal (4 years)	N=93(cross-sectional)	control:58 current hypertension:21 past hypertension:14	control:69.3±8.9 current hypertension:68.1±13.5 past hypertension:62.2±19.1	total:67%	BOLD	inhalation of 5% CO ₂ , 21% O ₂ and 74% N ₂	past hypertension and control > current hypertension
Traumatic brain injury (TBI)									
Amyot et al., 2018	USA	cross-sectional	N=42	control:15 TBI:27	control:38.1±7.4 TBI:37.6±15	control:79% TBI:70%	BOLD	inhalation of 5% CO ₂ in room air	controls > patients (grey matter and white matter); patients > controls (volume of abnormal CVR)
Amyot et al., 2020	USA	cross-sectional	N=42	control:15 TBI:27	control:38.1±10.9 TBI:38.2±7.4	control:73% TBI:74%	BOLD, fNIRS	inhalation of 5% CO ₂ in room air	control > patients
Amyot et al., 2021	USA	retrospective cohort	N=37	control:15 TBI:22	control:38±8 TBI:38±11	control:80% TBI:80%	BOLD	inhalation of 5% CO ₂ in room air	control > patients negative association between HIT-6 score and CVR
Champagne et al., 2019	Canada	cross-sectional	N=63	control:31 TBI:32	athletes without TBI:19±2 athletes with TBI:19±3	control:100% TBI:100%	BOLD, ASL	10 mmHg ETCO ₂ above normoxia	repetitive sub-concussive > no TBI (the right visual cortex, the left superior and inferior parietal lobules, the left premotor motor cortex, the right supplementary cortex, and the right parietal operculum)
Haber et al., 2018	USA	cross-sectional	N=41	control:14 TBI:27	control:38.9±6.8 TBI:37.6±11.1	control:78% TBI:71%	BOLD	inhalation of 5% CO ₂ , 21% O ₂ and 74% N ₂	control > patients

*Findings show the main results of the associations between risk factors and CVR. For physical inactivity, the red colour represents the association between risk factor (physical inactivity and CVR), which is the reverse of the association between physical fitness index (e.g., reported VO₂max) and CVR.

Studies have been reported multiple times in Tables 1–3 as they examined more than one risk factor in the same study, and hence have overlapping samples.

	Negative associations between the risk factor and CVR, i.e., CVR decreases as the risk factor increases or vice versa
	No associations between the risk factor and CVR
	Positive associations between the risk factor and CVR, i.e., CVR increases as the risk factor increases or vice versa

observed reduced CVR in the frontal, temporal, parieto-occipital, and cortical regions in patients with diabetes. People with diabetes also had accelerated impairments in CVR than non-diabetic controls after a two-year follow-up (Chung et al., 2015), and this effect had a large effect size with $r_{adj}^2 = 0.16–0.53$ for various brain regions. Furthermore, in those with pre-existing hypertension, people who with co-morbid diabetes had decreased CVR in the bilateral lingual gyrus, cuneus and precuneus, parietal areas, and right lateral occipital regions (Tchistiakova et al., 2014). However, Jor'dan et al. (2014) found no differences in CVR between type 2 diabetes and non-diabetic groups. Nevertheless, they found that those with a slow gait speed had a lower CVR in the

diabetes group ($r_{adj}^2 = 0.13$), but not in the healthy controls.

3.2.5. Hypertension

Three studies assessed the association between hypertension and CVR. There were consistent results that hypertension was associated with lower CVR (Blair et al., 2020; Hajjar et al., 2010; Peng et al., 2018), predominantly in the frontal and parietal areas with large effect sizes of $\eta^2 > 0.3$ (Hajjar et al., 2010). Interestingly, Peng et al. (2018) noted that while cross-sectional hypertension was linked to worse CVR outcomes, the longitudinal changes in CVR over four years were unrelated to hypertensive status (Peng et al., 2018). For people with stroke, CVR was

Table 3

Summary of studies investigating the associations between clinical risk factors and CVR. Abbreviations: ASL= Arterial spin labelling, BOLD=Blood oxygenation level dependent, CADASIL= Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CVR= Cerebrovascular reactivity, CM= Cerebral microangiopathy, ETCO_2 = End tidal carbon dioxide (i.e., the amount of carbon dioxide (CO_2) in exhaled air), ICA= Internal carotid artery, MCA= middle cerebral artery, MRI= Magnetic resonance imaging, mSS= Suzuki Score, ranging from 0 to IV with higher grades representing more severe disease of Moyamoya, PWV= pulse wave velocity is a measure of arterial stiffness, and higher PWV indicates increased arterial stiffness, PVS= Perivascular spaces, WMH= White matter hyperintensities.

Clinical risk factors									
Author and year	Country	Study design	Total Sample size	Sample Size of sub-groups	Age mean (SD or range)/ years	Sex (% of male)	CVR		Findings *
							MRI method	Vasodilatory stimuli	
Stroke and related cerebrovascular disease									
Akouda et al., 2016	Netherlands	prospective cohort study	N=50	control:15 lobar microbleeds:35	control:63.9±4.3 microbleeds: 64.0±5.4	control:53% lobar microbleeds:43 %	BOLD	functional task: visual stimulus with 16 flashing consecutive blocks	no difference between CVR in controls and patients with lobar microbleeds, regardless of whether they were symptomatic or how many microbleeds they had
Atwi et al., 2019	Canada	perspective cohort study with one year follow up	N=60	control:18 moderate WMH:20 severe WMH:12 CADASIL:10	control:30±12 moderate WMH:74±9 severe WMH:75±8 CADASIL:56±7	control:56% moderate WMH:60% severe WMH:50% CADASIL:40%	BOLD	maximum change in ETCO ₂ of 10 mm Hg	control > severe WMH and CADASIL groups (white matter) no difference in CVR between control and patients with severe WMH and CADASIL
Blair et al., 2020 *	UK	cross-sectional	N=53	correlational	total:68.0 ± 8.8	total:74%	BOLD	inhalation of 6% CO ₂ in air	negative association between WMH volume, Fazekas scores, small vessel disease score, PVS, presence of lacunes, deep atrophy and CVR
Conijn et al., 2011	Netherlands	cross-sectional	N=40	control:31 lacunar infarcts:9 microbleeds:18	total:58.9±10.0	total:76%	BOLD	breath-holding	control > patients no difference between controls and patients with white matter lesions/ lacunar infarcts
Donahue et al., 2013	USA	cross-sectional	N=12	correlational	total:45.7±11.6	total:17%	BOLD	inhalation of 5% CO ₂ , 95% O ₂	negative association between mSS hemispheres and CVR higher CVR in regions with less advanced stages of Moyamoya disease
Donahue et al., 2014	USA	cross-sectional	N=70	patient:60 (31 atherosclerotic, 29 Moyamoya)	control:33.1±8.5 atherosclerotic:59.8±13.2 moyamoya:41.8±12.7	control:50% atherosclerotic:48 % Moyamoya:24%	BOLD	inhalation of 5% CO ₂ , 95% O ₂	control > atherosclerotic patients (in several cortical areas in the hemisphere of the stenotic vessel) less severe Moyamoya > more severe Moyamoya (specialized to one hemisphere)
Gerammayeh et al., 2015	UK	longitudinal (100 days)	N=72	control:26 stroke:46	control:56.5 (37-78) stroke:61.2 (26-79)	control:35% stroke:65%	BOLD	breath-holding	control > peri-infarct > lesion regions for lateralized cerebral infarction decreased CVR in the peri-infarct and lesioned regions was not recovered over time
Goode et al., 2016	UK	longitudinal (20 months)	N=23	single symptomatic event:15 recurrent symptomatic event:8	total:67.5±9	total:91%	BOLD	inhalation of 10% CO ₂ , ETCO ₂ between 7 and 8mmHg	single stroke > recurrent stroke (grey matter middle cerebral artery territory in ipsilateral but not contralateral side)
Hund-Georgia et al., 2003 *	Germany	cross-sectional	N=11	control:6 cerebral microangiopathy (CM):5	control:57 (51-63) CM:61.8 (54-67)	control:50% CM:60%	BOLD	voluntary hyperventilation	control > patients (frontal and parietal cortices) no difference in temporal and cerebellar cortices between groups
Heyn et al., 2010	Canada	retrospective cohort	N=11	correlational	total:34 (10-48)	total:36%	BOLD	40 mm Hg (normocapnia) to a PETCO ₂ of 50 mm Hg (hypercapnia)	negative association between mSS for Moyamoya diseases and CVR (middle cerebral artery and anterior cerebral artery territories)
Juttukonda et al., 2021	USA	longitudinal (1.5 years) with cross-sectional component	N=69	non-atherosclerotic (Moyamoya) disease:43 atherosclerotic:26	Moyamoya: (stroke=49.6±10.4, no stroke=41.6±13.6) atherosclerosis: (stroke=71.5±8.8, no stroke=60.7±12.7)	Moyamoya: (stroke=20%, no stroke=18%) atherosclerosis: (stroke=25%, no stroke=55%)	BOLD	inhalation of 5% CO ₂ and 95% O ₂	non-stenosed hemispheres > stenosed hemispheres for atherosclerosis and Moyamoya disease
Krainik et al., 2005	Germany	cross-sectional	N=16	control:8 recovery from stroke:8	controls:57.8±5.1 recovery from stroke:52.5±12.4	control:50% recovery from stroke:63%	BOLD	controlled hyperventilation at 1 Hz, ETCO ₂ change of 25 mm Hg	control > patients (ipsilesional primary sensorimotor cortex and supplementary motor area)
Ladner et al., 2012	Australia	cross-sectional	N=36	control:11 Moyamoya:25	controls:46±12 Moyamoya:42±13.5	Moyamoya: 20%	BOLD	inhalation of 5% CO ₂ and 95% O ₂	control > patients
Last et al., 2007 *	USA	cross-sectional	N=51	control:25 diabetes:26	control:60.4±8.6 diabetes:61.6±6.6	control:52% diabetes:50%	ASL	inhalation of 5% CO ₂ and 95% air	control:negative association between WMH and CVR patients:WMH associated with regional CVR difference
Lee et al., 2021	Taiwan	cross-sectional	N=31	control:10 hypertensive intracerebral haemorrhage:21	control:66.1 ± 6.0 patient:62.5±11.3	control:30% patient:76.2%	ASL	intravenous diprydamole injection (0.57 mg/kg)	control > patients (basal ganglia, frontal lobe and temporal lobe)
Mandai et al., 1994 *	Japan	cross-sectional	N=16	control:10 ischemic cerebrovascular disease:6	healthy:51 (28-76) ischemic cerebrovascular disease:59 (50-74)	control:70% ischemic cerebrovascular disease:100%	3D time-of-flight MR angiography	17 mg/kg IV of acetazolamide	control > patients
Moreton et al., 2018 *	UK	cross-sectional	N=13 out of 22 had CVR	correlational	total:49.6±11.2	total:50%	ASL	inhalation of 6% CO ₂ in air	negative association between number of lacunes (>=5) and CVR
Papassi et al., 2021	France	longitudinal (3.3 years)	N=20	single stroke:12 recurrent stroke:8	single stroke:56.3±11.4 recurrent stroke:68.4±9.0	single stroke:67% recurrent stroke:63%	BOLD	inhalation of 8% CO ₂ , 21% O ₂ , and 71% N ₂	negative association between number of recurrent strokes and CVR single stroke < recurrent stroke patients (for asymmetric CVR impairments)
Raut et al., 2016 *	USA	cross-sectional	N=44	control:22 acute stroke:22	control:59 (20-74) acute stroke:59 (44-75)	control:45% acute stroke:64%	BOLD	breath-holding	no difference between patients and controls no difference between ipsilesional and contralesional hemispheres
Sam et al., 2015	Canada	retrospective cohort	N=47	control:27 Moyamoya:13 steno-occlusive disease:7	control:(19-71) Moyamoya:(18-52) steno-occlusive disease:(18-78)	control:59% Moyamoya:23% steno-occlusive disease:86%	BOLD	40 mm Hg (normocapnia) to a PETCO ₂ of 50 mm Hg (hypercapnia)	unilateral revascularisation improved regional cortical CVR
Thrippleton et al., 2018	UK	cross-sectional	N=27	control:(13 had CVR) minor stroke:15 (14 had CVR)	control:33.8±9.5 minor stroke:66.4±8.1	control:73% minor stroke:80%	BOLD	inhalation of 6% CO ₂ in medical air	control > patients
Zhao et al., 2009	USA	cross-sectional	N=87	control:48 cerebral artery territory infarcts:39	control:67.8±7.0 infarcts:64.5±8.8	control:48% cerebral artery territory infarcts:49%	ASL	inhalation of 5% CO ₂ and 95% air	control > patients in stroke side non-stroke side > stroke side

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Table 3 (continued)

Peripheral artery disease										
Bokkers et al., 2011	Ne the rla nds	cross-sectional	N=32	control:16 ICA occlusion:16	control:56.5±5.7 ICA occlusion: 56.3 ys±13.8	control:31% ICA occlusion: 75%	ASL	14 mg/kg acetazolamide with a maximum dose of 1200 mg	ICA occlusion side fed by the unaffected contralateral ICA had the most impaired CVR	Non-occluded side > occluded side
Campos Herrera et al., 2016	Br azi l	cross-sectional	N=22	control:7 patient:15	control:64.5(51–85) patient:68(52–90)	control:71% patient:73%	BOLD	breath-holding	patients > control (proportion of people with impaired CVR)	
De Vis et al., 2015	Ne the rla nds	cross-sectional	N=25	control:14 ICA occlusion:11	control:66±4 ICA occlusion: 66±7	control: 91% ICA occlusion: 86%	ASL, BOLD	change in ET/CO ₂ of 10mmHg	BOLD: control > patients; among patients, contralateral > ipsilateral MCA territory	ASL: no difference between control and patients, or contralateral and ipsilateral MCA territory
Hartika mp et al., 2012	Ne the rla nds	cross-sectional	N=39	control:18 ICA stenosis:21	control:68.4±5.9 stenosis:68.8±7.9	control:67% stenosis:67%	phase-contrast MRI	14 mg/kg acetazolamide with a maximum dose of 1200 mg	control/contralateral ICAs > stenosed ICAs	
Hartika mp et al., 2018	Ne the rla nds	cross-sectional	N=117	control:29 asymptomatic ICA occlusion:9 symptomatic ICA occlusion:29	control:62±8.2 asymptomatic ICA occlusion:62±11 symptomatic ICA occlusion:56 ±14	control:45% asymptomatic ICA occlusion:67% symptomatic ICA occlusion:72%	ASL	14 mg/kg acetazolamide with a maximum dose of 1200 mg	control > patients	
				asymptomatic ICA stenosis:27 symptomatic ICA stenosis:23	asymptomatic ICA stenosis:66±7.3 symptomatic ICA stenosis:69±7.2	asymptomatic ICA stenosis:70% symptomatic ICA stenosis:74%			control > symptomatic patients (ipsilateral hemisphere)	no significant difference between controls and asymptomatic patients
Jefferson et al., 2018 ^a	US A	cross-sectional	N=192	normal cognition:113/155 had CVR (29% of 155 participants carried APOE ε4) mild cognitive impairment:79/115 had CVR (41% of 115 participants carried APOE ε4)	normal cognition:72±7 mild cognitive impairment:73±7	normal cognition:59% mild cognitive impairment:57%	ASL	inhalation of 5% CO ₂ and 95% medical-grade room air	normal cognition: positive association between aortic stiffness and CVR (in the temporal lobes in APOE ε4 carriers only)	MCI: no association
Kaczmarz et al., 2021	Ger man y	cross-sectional	N=59	control:30 patient:29	control:70.2±4.8 patients:70.4±7	controls:43% patients:66%	BOLD	breath-holding	control > patients (contralateral hemisphere)	no difference between groups (white matter)
Sabra et al., 2021	Ca na da	cross-sectional	N=48	correlational	total:63.55±4.86	total:35%	ASL	40 mmHg (normocapnia) to 45 mmHg of ET/CO ₂ (hypercapnia)	males: positive association between aortic stiffness and CVR	females: negative association between aortic stiffness and CVR
Sam et al., 2014	Ca na da	retrospective cohort	N=59	control:41 ICA steno-occlusive disease patient:27 (left) 21(right)	control:(50-87) ICA steno-occlusive disease patient:24-83 (left) 25-91 (right)	control:54% ICA steno-occlusive disease patient:52% (left) 81%(right)	BOLD	40 mm Hg (normocapnia) to a PETCO ₂ of 50 mm Hg (hypercapnia)	contralateral side > ipsilateral side in patients > control	
Sobczyk et al., 2020	Ca na da	prospective cohort	N=101	control:46 carotid artery stenosis:55	control:65 (no SD) carotid artery stenosis:61±17	control:65% carotid artery stenosis:75%	BOLD	40 mm Hg (normocapnia) to a PETCO ₂ of 50 mm Hg (hypercapnia)	negative association between stenosis severity and CVR	

* Findings show the main results of the associations between risk factors and CVR.
Studies have been reported multiple times in Tables 1–3 as they examined more than one risk factor in the same study, and hence have overlapping samples.

	Negative associations between the risk factor and CVR, i.e., CVR decreases as the risk factor increases or verse versa
	No associations between the risk factor and CVR
	Positive associations between the risk factor and CVR, i.e., CVR increases as the risk factor increases or verse versa

lower in the white and grey matter if their systolic blood pressure was high (Blair et al., 2020).

3.2.6. Traumatic brain injury (TBI)

Four studies observed associations between TBI and impaired CVR, but one study found the opposite. Amyot et al. (2018) suggested that TBI patients had a lower amplitude of CVR in the whole grey and white matter, as well as higher volume of abnormal CVR, as compared with healthy controls. Cohen’s d > 0.7 suggested large effect sizes in all cortical regions (Amyot et al., 2018). Later, with both BOLD MRI and functional near-infrared spectroscopy, the same team verified this association with a relatively older cohort (Amyot et al., 2020). According to a recent study by this team, individuals with persistent TBI had lower whole-brain CVR, and the more severe the headache, the lower the CVR (Amyot et al., 2021). Furthermore, Haber et al. (2018) demonstrated that chronic TBI had a long-term negative influence on both whole-brain CVR and CVR in normal-appearing tissue. However, Champagne et al. (2019) reported that compared to football players without concussions, those with concussions had significantly higher BOLD-CVR and ASL-CVR in regions of the right visual cortex, left superior and inferior parietal lobules, left premotor motor cortex, right supplementary cortex, and right parietal operculum. The authors suggested that the football players’ improved CVR could have arisen from pre-existing differences in the resting metabolic factors (e.g., oxygen extraction and vessel morphology) between the two groups.

Of the 12 examined modifiable/behavioural risk factors, we found no MRI studies examining associations between CVR and levels of education, smoking, air pollution, hearing impairment, social isolation or alcohol consumption. We note that there are transcranial Doppler

studies that have examined effects of smoking and exercise on CVR (Burley et al., 2021; Silvestrini et al., 1996), but these were outside the scope of this review.

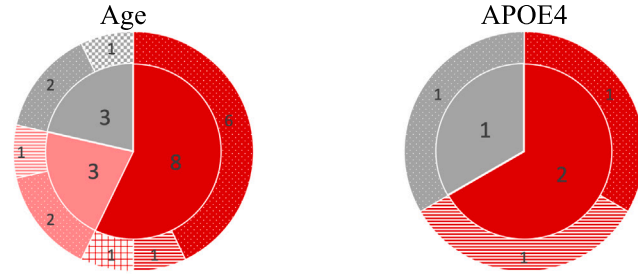
3.3. Clinical risk factors

3.3.1. Stroke and related cerebrovascular diseases

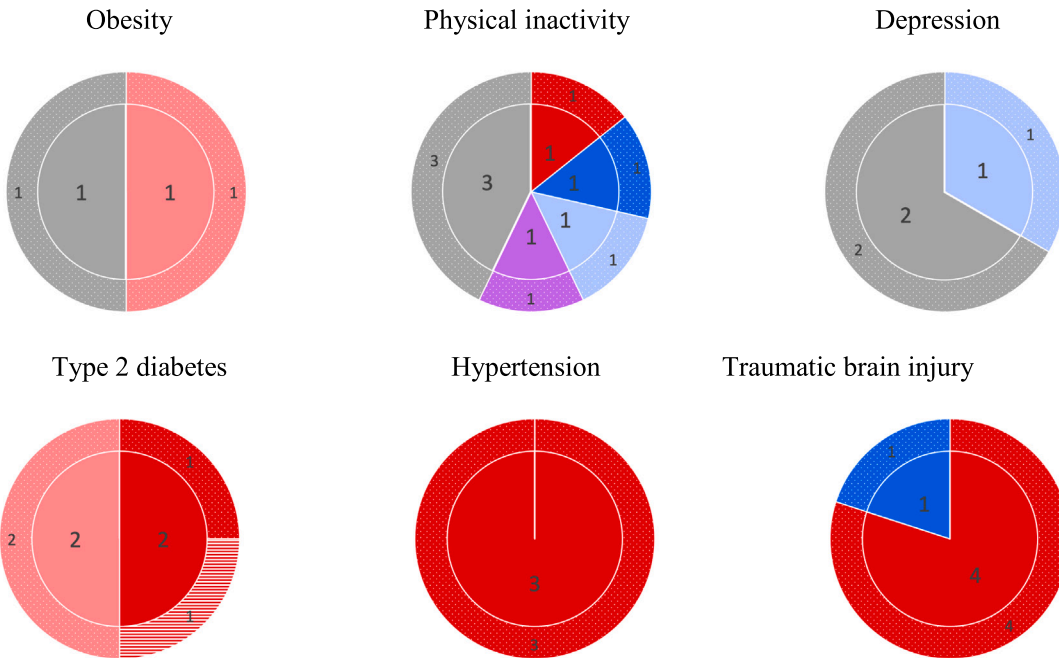
We reviewed five studies investigating CVR in stroke patients. Thrippleton et al. (2018) observed lower CVR in the grey matter of stroke patients compared to healthy controls. Krainik et al. (2005) noted that impaired CVR in stroke patients was largely observed in the lesioned hemisphere. Moreover, compared with single stroke patients, people with recurrent stroke episodes had lower CVR in the stroke-affected hemisphere, but not in the contralateral hemisphere (Goode et al., 2016; Papassin et al., 2021). In contrast, Raut et al. (2016) used a breath-holding vasodilatory stimulus and found that patients with acute stroke had similar CVR to age-matched controls.

Our literature search also resulted in seventeen studies which investigated stroke-related cerebrovascular disease, such as infarcts, perivascular spaces (PVS), microbleeds, white matter hyperintensities (WMH) and Moyamoya disease. In patients with a hereditary stroke disorder (CADASIL), a higher number of lacunes or lower brain volume was associated with impaired CVR (Moreton et al., 2018). Two studies found reduced CVR in the arterial territories (Zhao et al., 2009) and lesioned areas (Geranmayeh et al., 2015) of individuals with cerebral infarcts. However, Conijn et al. (2012) found no significant differences in global CVR between people with and without lacunar infarcts. Five MRI studies also examined CVR in Moyamoya patients. In general, CVR was lower in Moyamoya patients compared to healthy controls

A: Non-modifiable risk factors



B: Modifiable/behavioural risk factors



C: Clinical risk factors

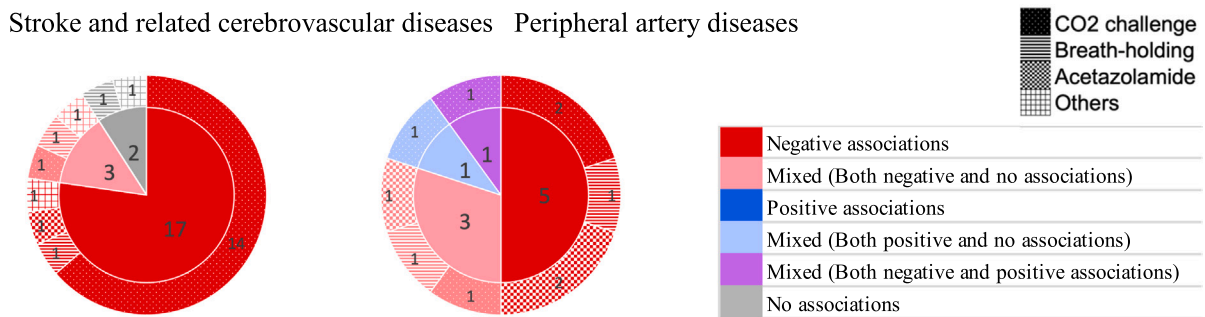


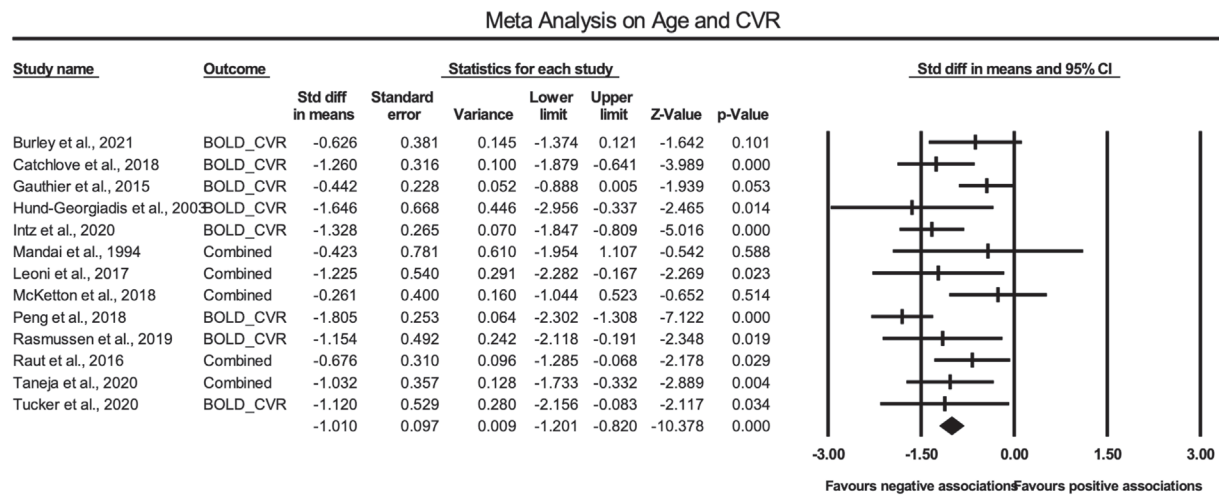
Fig. 2. Association of dementia risk factors with CVR, showing the number of studies and their choice of vasodilatory stimuli. More details on mixed studies and the vasodilatory stimuli are presented in [Tables 1–3](#). *Note: The figures do not account for the sample size or the effect size of the individual studies. 14 studies are represented multiple times as they have looked at multiple risk factors in the same study and hence have overlapping samples. These studies are marked with # in [Tables 1–3](#).*

(Donahue et al., 2014, 2013; Ladner et al., 2012). Higher Moyamoya scores (i.e., more severe Moyamoya) were associated with reduced CVR (Heyn et al., 2010), and regions with less advanced stages of Moyamoya disease had higher CVR (Donahue et al., 2014, 2013). Studies have therefore suggested that interventions, such as unilateral revascularisation, could improve CVR in both affected and non-affected hemispheres (Sam et al., 2015). For people with intracranial stenosis, impairments in CVR have been observed in both the stenosed and contralateral hemispheres (Mandai et al., 1994). Two studies with patients who had

atherosclerosis and Moyamoya disease showed that CVR was lower in the stenosed hemispheres compared to the non-stenosed hemispheres (Donahue et al., 2014; Juttukonda et al., 2021).

Two studies have reported that CVR was reduced in the presence of microbleeds (Conijn et al., 2012; Hund-Georgiadis et al., 2003), whereas one study found no differences in CVR between patients with microbleeds and healthy controls (Akoudad et al., 2016). Moreover, three studies found that reduced CVR was associated with WMH (Atwi et al., 2019; Blair et al., 2020; Last et al., 2007). Blair et al. (2020) also noted

a)



b)

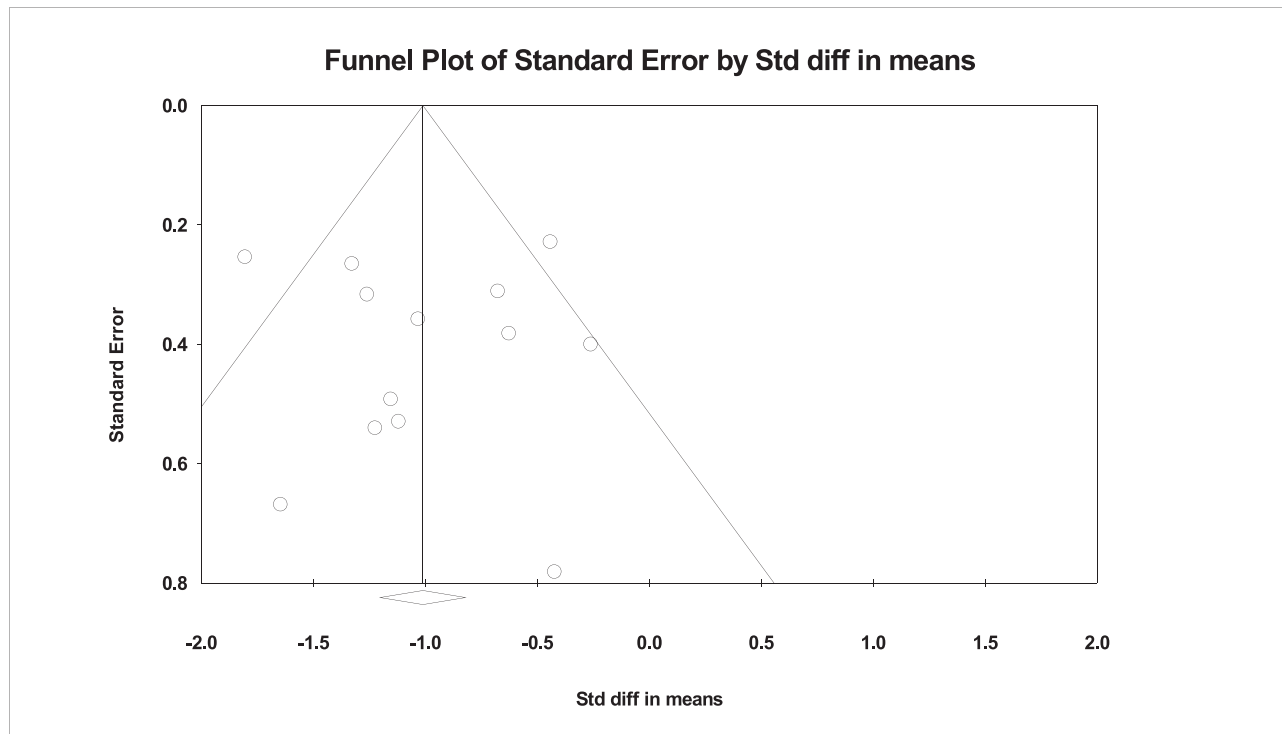


Fig. 3. a) Statistical summary and forest plot and b) funnel plot of effect size of the meta-analysis on the association between age and CVR. Most studies used BOLD CVR as the outcome, however some used “Combined” as the results combined CVR for different brain regions, or different measurements (e.g., activation volume/magnitude or ramp CVR/step CVR/mean CVR) or different MRI methods (e.g., BOLD-CVR, ASL-CVR).

lower levels of CVR with total small vessel disease (SVD) burden and more PVS. Similarly, [Atwi et al. \(2019\)](#) found that people with moderate and severe WMH, as well as those diagnosed with CADASIL, had lower white-matter CVR but not grey-matter CVR when compared to healthy controls. In contrast, [Conijn et al. \(2012\)](#) observed no associations between CVR and white matter lesions. One study showed that patients with hypertensive intracerebral haemorrhages had lower CVR than healthy controls ([Lee et al., 2021](#)).

3.3.2. Peripheral artery diseases

We reviewed ten studies examining peripheral artery phenotypes, such as stiffening (hardening), stenosis (narrowing), and occlusions (blockage) of the aorta and the carotid arteries, all of which have been shown to increase the risk of developing dementia ([Iulita et al., 2018](#); [Kang et al., 2020](#); [Lee et al., 2017](#); [Pase et al., 2012](#); [Sun et al., 2022](#)).

Two MRI studies examined associations between aortic stiffness and CVR. Surprisingly, [Jefferson et al. \(2018\)](#) reported a relatively preserved CVR despite increasing levels of aortic stiffness (measured as pulse wave velocity) in cognitively healthy adults (however they found no

association between CVR and aortic stiffness in participants with mild cognitive impairment). One explanation for this could be underlying sex differences in this association. Although the authors did not report any interactions with sex, another study noted that sex modulated the correlations between CVR and aortic stiffness, with females having lower CVR and males having higher CVR with increasing aortic stiffness (Sabra et al., 2021).

There were also consistent results showing that patients with carotid artery stenosis had impaired CVR (Campos Herrera et al., 2016; Hartkamp et al., 2012). In fact, Sobczyk et al. (2020) showed that CVR reduced as the severity of stenosis increased. However, (Hartkamp et al., 2018) only noted impairments in CVR in symptomatic but not asymptomatic patients with internal carotid artery (ICA) stenosis, suggesting that CVR might be preserved for asymptomatic stenosed patients. Most studies have consistently found CVR reductions mainly in the hemisphere of the stenosed or occluded vessels (Bokkers et al., 2011; de Vis et al., 2015; Hartkamp et al., 2018; Kaczmarz et al., 2021; Sam et al., 2014). However, Kaczmarz et al. (2021) reported that CVR of stenosed patients was also lower in the grey matter of the contralateral hemisphere but was comparable to healthy controls in the white matter. Hartkamp et al. (2018) found that CVR was compromised in both hemispheres of patients with ICA occlusion. De Vis et al. (2015) showed that CVR was lower in ICA occlusive patients compared to healthy controls, and CVR was lower in the ipsilateral than in the contralateral MCA territory. However, this difference was only observed using BOLD CVR but not with ASL CVR.

3.4. Vasodilatory stimulus

Most studies used CO₂ challenge as the vasodilator, with acetazolamide and breath-holding being relatively less common approaches (Fig. 2). For most risk factors, contradictory studies used a lesser common vasodilatory stimulus. For example, for studies on stroke and related cerebrovascular diseases, 77% of studies (17/22) consistently reported a negative association with CVR of which 82% (14/17) used CO₂. Conversely, 80% (4/5) of the studies that found no association or mixed results used breath-holding and other less common vasoactive stimuli (Fig. 2C). However, inconsistencies also existed between studies using CO₂ alone as in the case of the TBI where both negative (4/5 studies) and positive associations (1/5 studies) were observed using CO₂.

4. Discussion

4.1. Summary of the results

In this review, we summarised 59 MRI studies investigating the associations between CVR and non-modifiable, modifiable/behavioural, and clinical risk factors for dementia. Overall, we found reasonably strong and consistent evidence that CVR decreases as people get older. APOE ε4 carriers also had lower CVR than those without the ε4 risk allele. Nevertheless, we note that the number of MRI studies on CVR and APOE was limited (i.e., only 3 studies). Surprisingly, most studies found that physical activity was not associated or even inversely associated with CVR in older adults. Thomas et al. (2013) suggested that lifelong exposure to high level aerobic exercise may desensitise the cerebrovascular system and suppress the vaso-regulatory response to carbon dioxide, resulting in lower CVR in athletic individuals. However, the physical activity studies were largely inconsistent both in terms of the directionality of the associations and the affected brain regions. We also note that the studies included in this review mainly focused on CVR in physically active people, such as athletes, or people with physical training, and we identified almost no studies examining the associations between physical inactivity and MRI-based CVR. Thus, it is difficult to draw a clear conclusion about the associations between physical inactivity and CVR. Most studies examining other modifiable/behavioural

risk factors, such as type 2 diabetes, hypertension and TBI consistently found associations with impaired CVR, but the affected brain regions varied between studies. We noted that one study found a higher CVR in football players with history of sport-related concussions compared to those without concussions (Champagne et al., 2019), however in a subsequent follow-up the authors also found lower resting cerebral blood flow (CBF) in the concussion group compared to the controls (Champagne et al., 2021). The authors therefore suggested that the higher CVR in the concussed group was likely due to their preserved dilatory capacity of the cerebrovasculature, as their lower baseline CBF suggested greater tone, resulting in a greater shift in blood flow and higher CVR. Results on obesity were variable and limited. The reviewed literature also showed no associations between depression and CVR except one intervention study which found that patients with higher CVR exhibited less change in depression severity with sertraline treatment (Abi Zeid Daou et al., 2017).

As for clinical risk factors, there was consistent evidence that people with stroke, Moyamoya syndrome, peripheral artery occlusions or stenosis had lower CVR. In general, impairments in CVR were seen in widespread brain regions for patients with ICA occlusion and cerebral infarctions. However, people with carotid artery stenosis had greater reductions in CVR in the area ipsilateral to the stenosis than that in the contralateral area. There was mixed evidence for the associations between microbleeds, WMHs and CVR.

4.2. Mechanisms underlying the associations between dementia risk and CVR

While the exact mechanisms by which dementia risk factors may affect CVR are unclear, there are some possible biological explanations. The first would be endothelial dysfunction. For example, there is an increase in the production or release of vasoconstrictive proteins like endothelin-1 in older individuals, as well as a reduction in the release of vasodilatory substances like nitric oxide (NO; Kalaria, 1996). This change can result in a diminished ability for vasodilatation or possibly hyper-constriction of the vessels, eventually leading to insufficient responses to higher metabolic demands (Catchlove et al., 2018a). Lower endothelial NO production has been observed in hypertensive patients and is believed to reduce the cerebral response to CO₂ (Hajjar et al., 2010). Moreover, hyperglycaemia and insulin resistance in diabetes can cause inflammation, which can contribute to endothelial dysfunction (Chung et al., 2015). The association between TBI and impaired CVR might also arise from endothelial damage resulting from the brain injury (Amyot et al., 2018). Increased capillary thickness, microangiopathy, and altered endothelial permeability may all have a deleterious impact on CVR (Chung et al., 2015).

The second explanation may be attributed to abnormalities in the blood vessels, such as arterial stenosis (narrowing), arterial occlusion (blockage), and arteriosclerosis (stiffening of the artery walls). These structural abnormalities are often attributed to risk factors such as ageing, high blood pressure, obesity, or smoking (Barton et al., 2012; Livingston et al., 2020, 2017; Rahman and Laher, 2007; Rubio-Ruiz et al., 2014): all of which are also risk factors for dementia (Livingston et al., 2020, 2017). These arterial abnormalities can reduce the capacity of the brain-feeding arteries to supply blood to neurons, thereby affecting the vasodilatory response (Hartkamp et al., 2018). For instance, the decline in CVR for elderly people could, at least in part, be due to the increase in rigidity and decrease in elasticity of the body's vessels, which is commonly observed in ageing (Catchlove et al., 2018a). Eventually, impairments in CVR can result in a chronic inability to regulate blood supply to meet the brain's high metabolic demands. This persistent hypoperfusion can potentially lead to the neurological and cognitive decline typically seen in dementia (de La Torre, 2012).

The impaired CVR observed in most of the risk groups could also be attributed to dysfunctions of vascular smooth muscle cells (VSMCs) in the arteries (Hayes et al., 2022). Extracellular pH drops in the presence

of CO₂, causing VSMC membrane hyperpolarization and Ca²⁺ channel inactivation. These events may trigger a decrease in intracellular Ca²⁺ levels, relaxing smooth muscle tone (Duffin et al., 2018; Fisher and Mikulis, 2021). As a result, VSMC relaxation leads to vasodilation, which increases blood flow. It is possible that the dementia-risk groups (e.g., APOE ε4, Moyamoya diseases, CADASIL) with lower CVR may have impairments in this cellular mechanism, therefore reducing the ability of the arterial walls to vasodilate (Lin et al., 2012; Pfefferkorn et al., 2001).

4.3. Methodological heterogeneity across studies

While most of the risk factors had consistent associations with CVR, there were few studies which reported contradictory results. This variation could, in part, be due to the between-study differences in CVR measurements. For example, unlike the majority of studies that used CO₂ as the vasodilatory stimulus, one study used intravenous acetazolamide (a carbonic anhydrase inhibitor that causes acidosis) and found no correlation between age and CVR (Mandai et al., 1994). It has been suggested that acetazolamide might not be as suitable a vasodilatory stimulus as CO₂ due to considerable individual variability in the response to and tolerability of acetazolamide (Fierstra et al., 2013). This could affect the reproducibility of stimulus–response relationships in acetazolamide studies. Furthermore, while most of the stroke-related research found a link between the occurrence of stroke and lower CO₂-CVR, two studies that used breath-holding to assess CVR did not find such a relationship (Conijn et al., 2012; Raut et al., 2016). In contrast to the CO₂ delivery method, it is difficult to precisely monitor the CO₂ within arteries using breath-holding due to the variability of respiratory responses between individuals (Catchlove et al., 2018a). Moreover, participants may also show considerable variability in head motion during breath-holding, which could affect the quality of the imaging data (Raut et al., 2016). However, contradictory results can be found even with CO₂ inhalation, and the inconsistency of results cannot be attributed entirely to the heterogeneity of the vasodilators. Other possible explanations include variations in CO₂ inhalation paradigm, gas delivery apparatus, measurement of CO₂ time course, or CO₂ concentration (Liu et al., 2019). Additionally, while BOLD and ASL measures of CVR are complementary techniques (Zhou et al., 2015), there are assumptions depending on the sequence used (e.g., inversion efficiency, arrival time) that may contribute to some of the methodological heterogeneity (Aslan et al., 2010; Sanvito et al., 2021).

4.4. Implications of the findings

This review has raised several considerations for future research. 1) The majority of studies in this review were cross-sectional, so it is still unclear whether impairments in CVR worsen dementia risk factors or whether the cerebral vasodilatory capability is worsened in the presence of the risk factor itself (Conijn et al., 2012; Intzandt et al., 2020). Therefore, longitudinal studies are needed to address the causal relationship. 2) Some reviewed studies had relatively small sample sizes (e.g., fewer than 10 participants in all subgroups; Hund-Georgiadis et al., 2003; Krainik et al., 2005; Tucker et al., 2020), highlighting the need for larger studies with greater statistical power (Button et al., 2013). 3) Future studies should carefully consider the choice of confounding or moderating variables. For instance, Sam et al. (2014) noted that diabetes mellitus and depression might potentially confound the association between arterial stenosis and CVR. Consumption of caffeine might also introduce bias to the vasodilatory results (Peng et al., 2018). Moreover, as CVR is correlated with cognitive decline (Kim et al., 2021), the relationships between dementia risk factors and impaired CVR could vary according to cognitive status (Jefferson et al., 2018). It is therefore important to investigate whether impairments in CVR in the higher-risk groups can result in accelerated cognitive decline over time (for a review of the literature see (Catchlove et al., 2018b)). While previous studies have reported sex differences in CVR, with males having a higher

BOLD-CVR than females (Conijn et al., 2012; Kassner et al., 2010), only a few studies directly compared the effects of sex on the relationships between CVR and dementia risk factors. One study reported a moderating effect of sex on the association between aortic stiffness and CVR (Sabra et al., 2021). Some have reported no sex differences in age-related CVR decline (Catchlove et al., 2018a; Gauthier et al., 2015; McKetton et al., 2018) or in the associations between CVR and stroke related clinical factors (Blair et al., 2020; Conijn et al., 2012; Lee et al., 2021). However, given the fact that women have high incidence of dementia than men (Beam et al., 2018; Plassman et al., 2007), future research should examine the potential moderating role of sex in the CVR-dementia risk factors relationships. 4) Studies should investigate if managing dementia risk factors can preserve or reverse CVR decline. For instance, it has been suggested that CVR deficits can be reversed by restoring the blood supply of stroke patients through surgery (Mandell et al., 2011). Surgical revascularisation could increase total brain blood supply and restore perfusion in haemodynamically compromised brain tissue, therefore improving CVR (McKetton et al., 2019). Treatments of Moyamoya disease have been linked to improvements or recovery of CVR (Sam et al., 2015). One study also found that treated hypertensive patients had significantly higher CVR than those with poorly controlled blood pressure (Peng et al., 2018). Moreover, even though acute physical training (i.e., 20-min aerobic cycling) may not improve CVR (Stevenson et al., 2020), lifelong aerobic exercise has been known to have a positive effect on cerebral blood flow (Bailey et al., 2013; Thomas et al., 2013). Nonetheless, the evidence for interventions is still limited. 5) Given the lack of CVR studies investigating education, smoking, air pollution, hearing impairment, social isolation, and alcohol consumption, future MRI studies should focus on these important dementia risk factors.

4.5. Strengths and limitations of the review

To our knowledge, this is the first systematic review to investigate the relationships between dementia risk factors and CVR. The study included as wide a range as possible of the commonly established risk factors for dementia or mild cognitive impairment. However, there are several limitations of the review. In order to prioritise methodological consistency across studies, and to describe specific brain regions affected by dementia risk, we only included studies that utilised MRI to assess CVR. However, TCD is also a commonly used technique to measure CVR. Previous studies have noted agreements in the CVR values measured by TCD and MRI within the same participants (Burley et al., 2021; Campos Herrera et al., 2016; Moreton et al., 2018). However, the TCD and MRI studies do not always find the same directionality of correlations between CVR and various dementia risk factors (Campos Herrera et al., 2016; Intzandt et al., 2020). Especially for physical activity, most TCD studies suggested a positive association between aerobic exercise and CVR (Bailey et al., 2013; Foster et al., 2020; Murrell et al., 2013). However, this was not the case for the MRI studies reported here (Chapman et al., 2016; Gauthier et al., 2015; Intzandt et al., 2020; Stevenson et al., 2020; Thomas et al., 2013). TCD measures variations in blood velocity in the arteries, whereas BOLD MRI predominantly measures changes in deoxy-haemoglobin concentration in the venules and veins, resulting in possible discrepancies between CVR evaluated by the two methods (Burley et al., 2021). Therefore, evidence merely in terms of MRI data might not be sufficient to draw strong conclusions for our research questions. Finally, we note that grey literature (e.g., conference publications or publications outside traditional academic databases) was not included in this review, and hence we may have missed studies that failed to find statistically significant results (Egger et al., 2003).

5. Conclusion

We reviewed studies investigating the associations between a range of well-established risk factors for dementia and CVR measured by MRI.

There were consistent reports that older adults have lower CVR than younger adults. Clinical factors, such as stroke and artery stenosis-occlusive diseases, were also strongly associated with decreased CVR. The evidence also suggested that carrying APOE $\epsilon 4$ allele, being diagnosed with hypertension, diabetes or TBI were all related to impaired CVR. However, the associations between CVR and obesity, aortic stiffness, microbleeds, white matter hyperintensities and physical exercise were mixed. While limited in number, the evidence suggested that CVR was not affected in people with depression. We also found no MRI studies examining associations between CVR and education, smoking, air pollution, hearing impairment, social isolation, or alcohol consumption. Mixed results could be attributed to variability in choice of vasodilatory stimulus, study design, and sample size. Overall, this review offers valuable insights into how CVR is affected by modifiable/behavioural and clinical risk for dementia. It is possible that timely intervention and management of such risk factors may have beneficial effects on cerebrovascular health, and in turn potentially help delay or prevent dementia.

Contributions

CW and GR performed the literature search, literature screening, data extraction and study quality assessment. CW conducted the registration of the systematic review and wrote the initial draft of the manuscript. SS supervised the work and edited/reviewed the manuscript. All authors reviewed and edited the manuscript.

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Declaration of Competing Interest

The authors declare no competing financial interests.

Data Availability

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neubiorev.2023.105140](https://doi.org/10.1016/j.neubiorev.2023.105140).

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