Journal of Translational Medicine

REVIEW

Open Access

Mapping cerebral blood flow in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and orthostatic intolerance: insights from a systematic review

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Abstract

Background Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex and debilitating condition with a large proportion of patients that experience orthostatic intolerance (OI). This systematic review aimed to assess whether cerebral blood flow (CBF) is reduced in ME/CFS and OI, and whether the presence of both conditions leads to an additional decline in CBF.

Methods PubMed (from 1943), MEDLINE (from 1946), EMBASE (from 1947) and Cochrane were searched from inception to February 14th, 2025, using terms including "chronic fatigue syndrome", "myalgic encephalomyelitis", "orthostatic intolerance" and "cerebral blood flow". Article selection required the following criteria: published in English; CBF measured in participants with either ME/CFS or OI, or both ME/CFS and OI combined. Quality assessment and risk of bias was assessed using the Newcastle–Ottawa Scale and the systematic review was conducted in accordance with the PRISMA 2020 guidelines.

Results Of 14,928 articles, 118 were included, 26 (22.1%) of which studied CBF in ME/CFS alone, 81 (68.6%) in OI alone and 11 (9.3%) in both ME/CFS and OI. Overall, the articles included 9185 participants, with a mean age of 39.1 years (SD = 8.8), and 73.8% of participants were female. Studies found CBF was significantly reduced in 12 of the articles focused on ME/CFS and in 56 of those focused on OI; compared to controls. Additionally, in 4 out of 11 studies that examined both conditions, CBF was further reduced in participants suffering from both conditions compared to those with ME/CFS alone.

Conclusions CBF is reduced in ME/CFS and OI alone and having both conditions comorbidly amplifies CBF reductions. Therefore, observing CBF changes in ME/CFS with and without OI may be important in monitoring disease severity. Despite this, few studies focus on the combination of ME/CFS and OI, and OI may be a confounding factor in CBF in a large portion of ME/CFS studies.

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Keywords ME/CFS, Myalgic encephalomyelitis, Chronic fatigue syndrome, Orthostatic intolerance, Cerebral blood flow

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterised by persistent fatigue, post-exertional malaise (PEM), brain fog and unrefreshing sleep lasting at least 6 months [1]. Symptoms affect multiple body systems and are often accompanied by multiple heterogenous symptoms and comorbid conditions [2]. It is estimated that between 28 and 82% of adults and up to 96% of adolescents [1, 3, 4] with ME/CFS experience orthostatic intolerance (OI) symptoms, which refers to symptoms that include light-headedness, dizziness, blurred vision, tachycardia, nausea, disequilibrium and fainting that appear when upright and resolve when returning to a supine position [5]. OI symptoms are a key component of the diagnostic criteria for ME/CFS [1, 6–9] and are thought to be attributed to a decrease in cerebral blood flow (CBF). Reduction in CBF is linked to autonomic nervous system dysfunction, which leads to abnormal haemodynamic control of heart rate and blood pressure when postural changes occur [3]. The most common forms of OI in ME/CFS patients are postural orthostatic tachycardia syndrome (POTS) and orthostatic hypotension (OH) [3, 10], with OI in ME/CFS patients typically intensifying during PEM events [11].

Adequate and relatively constant CBF is critical to maintaining consciousness and functioning and reduced CBF may be a large contributing factor to the cognitive impairment seen in ME/CFS, commonly known as 'brain fog' [12]. Brain fog is common in both ME/CFS patients with and without OI in addition to the characteristic symptom of fatigue in ME/CFS and PEM events. Multiple techniques currently are available to measure CBF [13], with the most commonly utilised including magnetic resonance imaging (MRI), doppler ultrasound, near infrared spectroscopy (NIRS) and transcranial doppler ultrasound echography (TCD). However, assessment of CBF is not currently required to diagnose either ME/CFS or OI despite many patients reporting the experience of OI symptoms without presenting with the characteristic heart rate or blood pressure fluctuations associated with orthostasis in various OI conditions [3]. There are currently no known diagnostic biomarkers available for ME/CFS and this often results in diagnostic delays, which have been associated with reduced rates of recovery and symptom improvement [14]. In addition to ME/CFS, OI conditions can often be difficult to diagnose, with patients waiting an average of 4.9 years until diagnosis [15]. As CBF reductions are known to occur in both these conditions, utilising CBF measurement techniques as diagnostic tools may assist in reduced time to diagnosis and improved patient outcomes in both ME/CFS and OI. Importantly, decreased CBF has been observed in ME/CFS patients without OI, highlighting that measuring CBF could be a critical tool for monitoring disease severity and PEM events in these patients.

The aim of this systematic review is to determine if CBF is decreased in patients with ME/CFS and OI and to evaluate whether there are further decreases in CBF in patients with both ME/CFS and OI as comorbidities.

Methods

Search strategy

A systematic review of the literature was conducted using databases that included PubMed (from 1943), Ovid MEDLINE (from 1946), EMBASE classic and Embase (from 1947) and Cochrane Central Register of Controlled Trials (CENTRAL) which were searched from inception to February 14th, 2025. The review protocol was registered with PROSPERO International prospective register of systematic reviews (registration number: CRD42023376018) [16] and was formulated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The search terms used included "chronic fatigue syndrome", "myalgic encephalomyelitis", "ME/CFS", "orthostatic intolerance", "orthostatic hypotension", "neurocardiogenic syncope", "vasovagal syncope", "postural orthostatic tachycardia syndrome", "POTS", "cerebral blood flow", "brain blood flow" and "cerebral perfusion" (Supplementary Material 1).

Article selection

Identified articles were managed using the reference management software EndNote (Version 21 Clarivate Analytics, Philadelphia, USA). Duplicate articles were removed using EndNote and the articles that remained were exported to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) for screening. Two independent reviewers (EMC and DT or KH) each assessed the titles and abstracts and subsequently the full texts of articles not excluded at this stage were downloaded for further assessment against the exclusion criteria to obtain the final included articles. Disagreements that arose between reviewers regarding inclusion of articles were resolved by a third reviewer (CWA).

Eligibility criteria

Articles were included in this systematic review if they met the following inclusion criteria: (1) CBF was

measured in patients diagnosed with either ME/CFS or OI or in patients with both ME/CFS and OI. (2) ME/CFS diagnosis was made using any major diagnostic criteria [1, 6–9, 18] with other differential diagnoses having been ruled out (3) OI diagnosis included any type and definition of OI. (4) The article was published in English. Articles were excluded if: (1) OI or ME/CFS had been induced experimentally by the use of medication. (2) CBF was not measured or reported. (3) No control group or a control group without either ME/CFS or OI had been included. (4) Case reports of less than five participants, reviews, conference abstracts, editorials and letters to the editor.

Data extraction and synthesis

Two reviewers (EMC and DT or KH) extracted the following variables: first author, publication year, population studied, study setting, number of participants, percentage of females, mean or median age, ME/CFS definition, OI type and definition, type of postural change/exercise, type of blood pressure measurement (continuous or intermittent), type of device utilised to measure CBF, blood pressure, heart rate, CBF velocity, cerebrovascular resistance, cerebral oxygen saturation, MRI/SPECT scan findings as well as the changes in CBF.

Study quality and risk of bias assessment

The quality and risk of bias assessments of all articles included in the systematic review was performed separately by two authors using the nine-point Newcastle–Ottawa Scale (NOS) [19] for cross-sectional studies. Each article is assigned a score between 0 and 9 and articles that scored between 0 and 3 points were classified as low quality, scores between 4 and 6 points were classified as moderate quality and 7–9 points were classified as high quality (Supplementary Material 2).

Results

Study selection and search strategy

Figure 1 shows the PRISMA flowchart of our search. In total, 14,928 articles were identified through the data base searches. After exclusion of duplicates, 11,218 articles remained and were subsequently assessed against the exclusion criteria by title and abstract and finally full text (367 included). Of these, 118 articles were included in the systematic review, 26 of which looked at CBF in participants with ME/CFS only, 81 in participants with OI only and 11 looked at CBF in participants with both ME/CFS and OI combined.

Participant characteristics and health outcomes

Table 1 provides a summary of the study and participant characteristics of the included articles. In total, 9,185 participants (73.8% females) with a mean age of 39.1 (SD 8.8) years were studied amongst the included articles. In the group of articles focused on ME/CFS or OI alone, 1942 participants (75.3% females) with a mean age of 38.8 (SD 9.5) and 5,524 participants (57.5% females) with a mean age of 44.6 (SD 8.2) were studied respectively. In articles focused on ME/CFS and OI combined, 1719 participants were studied (88.5% females) with a mean age of 33.9 (SD 8.6). Among ME/CFS only studies, the Fukuda 1994 [6] criteria was most commonly used (by 14 articles) to diagnose ME/CFS [20–33], followed by three articles which utilised the Holmes 1988 [7] definition [34–36], two which utilised both the Oxford 1991 [18] and Holmes 1988 definitions [37, 38], two which utilised both the Fukuda and the International Consensus Criteria (ICC) 2011 [8, 39, 40] and two which used both the Fukuda and the Canadian Consensus Criteria (CCC) [9, 41, 42] definitions (Table 2). One article used the Institute of Medicine (IOM) 2015 [1], CCC 2003 and the ICC definitions [43]; as well as one article which used the Fukuda and a modified Holmes criteria [44]. One article used unspecified criteria from the Centres for Disease Control and Prevention (CDC) [45]. In articles studying ME/CFS and OI combined, four used the Fukuda definition alone [46–49], five used both the Fukuda and the ICC definitions [3, 10, 50–52] and two articles used both the ICC and IOM criteria [53, 54] (Table 2). Overall, 11 subtypes of OI were studied with POTS and OH being the most reported (in 66.6% and 90.9% of articles focused on OI alone and in ME/CFS + OI combined respectively). Of the articles focusing on OI only, 32 studied OH [55–86], 16 studied POTS [87–102], 15 studied vasovagal syncope (VVS) [103–115], and 17 focused on other OI conditions or a combination of multiple OI conditions [116–135] (Table 1). In the articles that researched ME/CFS and OI combined, six looked at POTS [46, 47, 49, 50, 52, 54], four studied POTS and delayed OH [3, 10, 51], one studied POTS, VVS, delayed and initial OH [48] and one studied participants with psychogenic pseudo syncope [53].

Cerebral blood flow measurement techniques

Various magnetic resonance imaging (MRI) techniques (n = 11) [21–28, 41–43] and single-photon emission computed tomography (n = 9) [29–31, 34–38, 44] were the most commonly used techniques to measure CBF in articles that studied participants with ME/CFS alone (Table 2). Other less commonly used techniques included TCD [20, 45] and extracranial doppler echography (ECD) [39, 40] that were used in two articles each, in addition to near infrared spectroscopy (NIRS) [32] and xenon computed tomography [33] utilised in one article each. However, in articles that studied participants with OI only, 53 used TCD [56, 57, 60–71, 87–98, 101–112, 116–120, 122–126, 130, 131, 133–135], nine used NIRS [75–77, 99, 113, 114, 128, 129, 132], six used SPECT [78–82, 115],

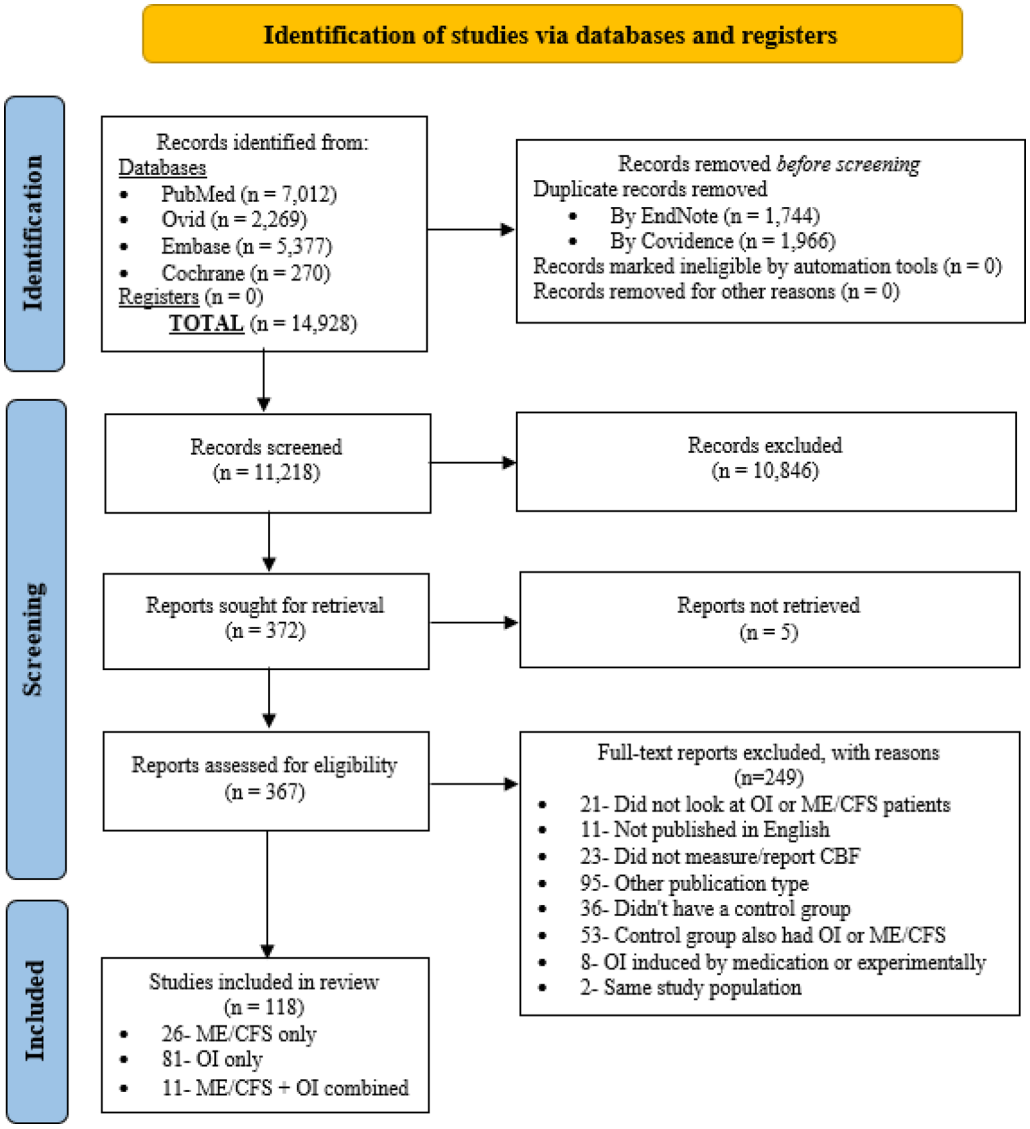

Fig. 1 Flow diagram of the selected studies for the systematic review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA). CBF: cerebral blood flow. ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome. OI: orthostatic intolerance. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71

five used TCD and NIRS simultaneously [55, 58, 59, 86, 121], four used various MRI techniques [83–85, 100], two used extracranial doppler echography (ECD) [74, 127], and one article each utilised rheoencephalography [72] and positron emission tomography (PET) [73]. In the articles focusing on both ME/CFS and OI combined, seven used ECD [3, 10, 50–54], three used TCD [46, 47, 49] and one used NIRS [48]. The majority of CBF measurements were taken at rest in ME/CFS only articles (n = 19, 73.1%), and during a tilt table/active stand test in both OI only articles (n = 73, 90.1%) and ME/CFS + OI articles (n = 11, 100%) (Table 2).

Cerebral blood flow in ME/CFS and orthostatic intolerance

A slightly larger proportion of articles that studied ME/CFS alone revealed a significant decrease in CBF (n = 12) than those who showed no change in CBF (n = 10) when compared to healthy controls (Fig. 2A) (Supplementary Material 3). In the remaining four articles, a significant increase in CBF in ME/CFS alone was observed (Table 3). A majority of articles that focused on OI alone, showed a significant decrease in CBF in participants with OI in comparison to healthy controls (n = 57, 70.37%) (Fig. 2A). Just over a quarter of the OI alone articles found no change in CBF (n = 22), while two articles reported an increase in CBF compared to healthy controls. In the group of articles studying ME/CFS and OI combined

Table 1 Study and participant characteristics

	Overall (n = 118)	ME/CFS Only (n = 26)	OI Only (n = 81)	ME/CFS + OI (n = 11)
Number of participants (n)	9185	1942	5524	1719
Females (%)	73.8%	75.3%	57.5%	88.5%
Age, mean (SD)	39.1 (8.8)	38.8 (9.5)	44.6 (8.2)	33.9 (8.6)
Type of OI studied (n)				
POTS	23	–	17	6
Orthostatic hypotension	32	–	32	0
Vasovagal syncope	15	–	15	0
POTS and orthostatic hypotension	9	–	5	4
Other*	13	–	12	1
Type of intervention/treatment (n)				
At rest/supine	19	19	0	0
Tilt table/active stand test	87	3	73	11
During exercise	2	2	0	0
Cognitive test	4	2	2	0
Other#	6	0	6	0
CBF measurement technique (n)				
ASL or DSC MRI	16	11	5	0
Single photon emission computed tomography	15	9	6	0
Transcranial or extracranial Doppler ultrasound	73	4	59	10
Near infra-red spectroscopy	11	1	9	1
Xenon computed tomography	1	1	0	0
PET Scan	2	0	2	0

ASL, arterial spin labelling; DSC, dynamic susceptibility contrast; MRI, magnetic resonance imaging; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; OI, orthostatic intolerance; SD, standard deviation

*Other types of OI include: orthostatic hypertension, orthostatic cerebral hypoperfusion syndrome, hypocapnic cerebral hypoperfusion syndrome, inappropriate sinus tachycardia and psychogenic pseudo-syncope

#Other interventions/treatments included a head down maneuver, breath holding, CO_2 rebreathing and lower-body negative pressure

(n = 11), most found a significant decrease in CBF (n = 7, 63.64%), which was closely followed by no change in CBF when compared to healthy controls (n = 4, 36.36%), (Fig. 2A). However, when comparing participants with both ME/CFS and OI combined to participants with ME/CFS without OI, despite the small number of articles, the majority (n = 4, 57.14%) displayed a significantly larger decrease in CBF in participants with both ME/CFS and OI compared to having ME/CFS alone (Fig. 2B). Three of the eleven articles showed no change in CBF (42.86%) and the remaining four did not compare ME/CFS participants with and without OI (Table 3).

Quality assessment

Of the articles which studied ME/CFS alone, nineteen were of high quality [20, 22–24, 26–32, 34, 37, 39–43, 45] and seven articles were of moderate quality [21, 25, 33, 35, 36, 38, 44]. Eighty of the articles which focused on OI alone were high quality [55–65, 67–135] and the remaining one was of moderate quality [66]. All articles that focused on ME/CFS and OI combined were of high quality [3, 10, 46–54] (Supplementary Material 4).

Discussion

Both ME/CFS and OI alone were associated with significant decreases in CBF compared to healthy controls. Moreover, ME/CFS patients with OI as a comorbidity showed significantly greater reductions in CBF in comparison to ME/CFS patients without OI.

Cerebral blood flow in ME/CFS and OI alone

As previously described, ME/CFS patients often experience OI symptoms even in the absence of formal diagnostic criteria, which may contribute to inconsistencies in CBF findings [1, 136]. Conversely, some ME/CFS patients may not be formally diagnosed with OI and the articles that studied ME/CFS alone did not assess each participant for an OI condition prior to measuring CBF. Therefore, there is a possibility that the true values of CBF in ME/CFS alone were not represented in these articles due to undiagnosed OI conditions. Additionally, different exercises [137] or tilt table test angles [138] may also influence CBF. Another important aspect is that a large proportion of articles focused on ME/CFS alone used techniques such as MRI or SPECT, which are performed while the participant is supine and at rest. These conditions may not accurately reflect CBF changes that occur during postural shifts or physical activity, potentially overlooking the impact of OI symptoms on blood flow. Interestingly, articles that studied ME/CFS alone (Fig. 2A) showed the biggest proportion to have a significant increase in CBF compared to healthy controls when comparing with the studies which investigated OI alone or both ME/CFS and OI. An explanation for this may be that the ME/CFS alone articles included a large amount of the CBF measurements performed while the participants were supine. Additionally, activation of certain brain regions during tasks such as the Stroop task [26] and paced auditory serial addition testing [31, 42] resulted in an increase in CBF. The large proportion of studies showing a decrease in CBF in articles looking at OI alone was to be expected as it is widely accepted that low blood pressure or high heart rates while upright suggest low blood flow to the brain that elicits OI symptoms [5]. Typically, increased severity and number of OI symptoms were experienced by patients who have larger declines in blood pressure upon standing, which is reflected by larger reductions in CBF [3]. However, the CBF in participants with OI alone were likely to also be

Table 2 Study characteristics of included articles, stratified by type of cerebral blood flow measurement

First author	Population	Setting	N participants, female %, age (mean (SD))	Protocol
ME/CFS only				
Transcranial doppler ultrasound (TCD)				
Malfliet [45]	ME/CFS (unspecified)	NG	ME/CFS: 20, 100%, 41.1 (8.9) Controls: 20, 100%, 39.9 (14.2)	Cycling & Emotional stress test
Razumovsky [20]	ME/CFS (Fukuda 1994)	OC	ME/CFS: 26, 88.5%, 33.6 (10.7) Controls: 23, 78.3%, 29.9 (7.1)	TTT (710 degrees)
Magnetic resonance imaging (MRI)				
Biswal [21]	ME/CFS (Fukuda 1994)	NG	ME/CFS, 11, NG, NG Controls: 10, NG, NG	NA
Boissoneault [22]	ME/CFS (Fukuda 1994)	NG	ME/CFS: 14, 100%, 48.6 (12.1) Controls: 14, 100%, 49.6 (13.2)	NA
Gay [41]	ME/CFS (Fukuda 1994)	OC	ME/CFS: 19, 100%, 52.3 (10.6) Controls: 17, 100%, 48.8 (11.8)	NA
Li [43]	ME/CFS (CCC 2003, ICC 2011, IOM 2015)	OC	ME/CFS: 31, 87.1%, 42.8 (12.4) Controls: 48, NG, 46.9 (12.0)	NA
Mueller [23]	ME/CFS (Fukuda 1994 & Canadian additional criteria (2010))	NG	ME/CFS: 15, 100%, 40.3 (8.8) Controls: 15, 100%, 40.8 (9.2)	NA
Natelson [24]	ME/CFS with/without a psychiatric diagnosis (Fukuda 1994)	OC	ME/CFS (combined): 43, 60.5%, 42.7 (9.5) ME/CFS (without psychiatric): 27, 62.9%, 41.6 (9.5) ME/CFS (with psychiatric): 16, 56.2%, 44.5 (9.6) Controls: 17, 70.5%, 40.7 (10.4)	NA
Perrin [25]	ME/CFS (Fukuda 1994)	NG	ME/CFS (osteopathic treatment): 9, 44.4%, 35.3 (12.6) ME/CFS (any treatment): 9, 44.4%, 36.1 (12.3) Controls: 9, 44.4%, 36.1 (12.4)	NA
Shan [26]	ME/CFS (Fukuda 1994)	NG	ME/CFS: 45, 73.3%, 47.1 (11.7) Controls: 27, 66.7%, 43.1 (13.8)	NA
Shungu [27]	ME/CFS (Modified Fukuda 1994)	OC	ME/CFS: 15, 80%, 32.7 (8.6) Controls: 13, 53.8%, 27.6 (7.4)	NA
Staud [42]	ME/CFS (Fukuda 1994, CCC 2003)	NG	ME/CFS: 16, 93.6%, 49.3 (11.4) Controls: 15, 100%, 49.0 (10.0)	PASAT
Zeineh [28]	ME/CFS (Fukuda 1994)	OC	ME/CFS: 15, 53.3%, 46.5 (13.2) Controls: 14, 57.1%, 46.6 (14.6)	NA
Single-photon emission computed tomography (SPECT)				
Costa [37]	ME/CFS (CDC Holmes 1988, Oxford 1991, ME Action)	NG	ME/CFS: 24, 54.2%, 36 (13) Controls: 24, 45.8%, 31 (10)	NA
Fischler [36]	ME/CFS (Oxford 1991, CDC Holmes 1988)	OC	ME/CFS: 22, 90.9%, 37.4 (3.8) Controls: 15, 53.3%, 28.5 (5.2)	NA
Fischler [38]	ME/CFS (Modified CDC Holmes criteria 1988)	NG	ME/CFS: 16, 87.5%, 35 (9.6) Controls: 20, 40%, 36 (8.6)	NA
Goldberg [44]	Paediatric ME/CFS (Modified CDC Holmes criteria 1988 & Fukuda 1994)	OC	ME/CFS: 13, 46.2%, 14.2 Controls: 13, 38.5%, 9.3 (3.2)	NA
Ichise [35]	ME/CFS (CDC Holmes 1988)	OC	ME/CFS: 60, 75%, 36 (1) Controls: 14, 50%, 32 (2)	NA
Lewis [29]	Twins with & without ME/CFS (Fukuda 1994)	ME/CFS support group	ME/CFS: 22, 90.9%, 41.4* Controls: 22, 90.9%, 41.4*	NA
Machale [30]	ME/CFS (Fukuda 1994)	OC & support group	ME/CFS: 30, 63.3%, 44.2 (10.3) Controls: 15, 73.3%, 41.1 (12.8)	NA
Peterson [34]	ME/CFS (CDC Holmes 1988)	OC	ME/CFS: 10, 80%, 35.4 (9.5), Controls: 10, 70%, 34.3 (8.3)	Tread-mill walking
Schmaling [31]	ME/CFS (Fukuda 1994)	OC	ME/CFS: 15, 80%, 44.4 (8.4) Controls: 15, 80%, 44.4 (8.4)	PANAS, PASAT
Near infrared spectroscopy (NIRS)				

Table 2 (continued)

First author	Population	Setting	N participants, female %, age (mean (SD))	Protocol
Patrick-Neary [32]	ME/CFS (Fukuda 1994)	NG	ME/CFS: 6, 100%, 39 (13) Controls: 8, 100%, 27 (7)	Maximal cycling test
Xenon computed tomography				
Yoshiuchi [33]	ME/CFS (Fukuda 1994) with/without axis 1 psychiatric disorders	OC	ME/CFS (without axis 1 psychiatric disorders): 16, NG, 38.7 (6.5), ME/CFS (with axis 1 psychiatric disorders): 9, NG, 43.0 (7.1) Controls: 9, NG, 34.9 (9.9)	NA
Extracranial doppler ultrasound (ECD)				
Van Campen [39]	ME/CFS (Fukuda 1994 & ICC 2011)	OC	ME/CFS: 362, 84.8%, 42 (12) Controls: 52, 80.8%, 39 (15)	TTT (70 degrees)
Van Campen [40]	ME/CFS (Fukuda 1994 & ICC 2011)	OC	ME/CFS (abnormal CBF): 488, 86%, 42 (12) ME/CFS (normal CBF): 46, 59%, 44 (11) Controls: 49, 78%, 39 (15)	TTT (70 degrees)
OI only				
Transcranial doppler ultrasound (TCD				
Asahina [55]	MSA (with OH)	NG	MSA: 7, 42.9%, 59 (7) Controls: 9, 44.4%, 56 (8)	TTT (70 degrees)
Baker [102]	POTS	OC	POTS: 25, 100%, 31 (7) Controls: 11, 100%, 31 (8)	TTT (60 degrees)
Camargo [56]	PD	OC	PD (6 with OH, 5 without OH): 11, 37.5%, 67.4 (11.7), Controls: 11, 57.1%, 64.7 (11.9)	Breath holding
Carey [103]	VVS	OC	VVS: 17, NG, 48 (22) Nonsyncopal controls: 17, NG, 55 (22) Syncopal controls: 8, NG, 49 (20)	TTT (70 degrees)
Carey [104]	VVS	OC	VVS: 16, 56.3%, 52 (22) Syncopal controls: 14, 57.1%, 53 (22) Nonsyncopal controls: 51, 52.9%, 53 (22)	TTT (70 degrees)
Castro [116]	VVS & autonomic failure (familial amyloidotic polyneuropathy)	OC	Autonomic failure: 8, 25%, 31.4 (6.5) VVS: 8, 50%, 30.2 (8.7) Controls: 8, 37.5%, 28.3 (5.9)	TTT (70 degrees)
Castro [117]	VVS & Autonomic failure	OC	VVS: 9, 45%, 30.2 (8.7) Autonomic failure: 9, 34%, 31.4 (6.5) Controls: 10, 50%, 29.0 (5.7)	TTT (70 degrees)
Claydon [118]	PRS	OC	PRS: 28, 60.7%, 39.4 (2.7), Controls: 11, 36.4%, 26.3 (3.6)	TTT (60 degrees)
Coelho [133]	OI	OC	OI: 22, 91.3%, 33.1 (12.2) Controls: 19, 78.9%, 39.1 (10.5)	
Delpozzi [87]	POTS	OC	POTS: 11, 72.7%, 19 (3) Controls: 10, 70.0%, 23 (3)	TTT (70 degrees)
Diehl [119]	VVS and POTS	OC	OI (VVS & POTS): 16, 75.0%, 28.5 (10.0) Controls: 20, 50.0%, 29.5 (7.1)	TTT (80 degrees)
Diehl [105]	VVS	OC	VVS: 10, 60.0%, 27.4 (9.8) Controls: 20, 50.0%, 31.2 (11.4)	TTT (80 degrees)
FuenteMora [57]	FD (with OH)	OC	FD: 25, 48%, 23 (2) Controls: 15, 66.7%, 25 (2)	AST
Gonzalez-Hermosillo [106]	VVS	OC	VVS: 14, 50.0%, 24.2 (6.1) Controls (negative tilt): 41, 37%, 24.2 (6.1) Controls (positive tilt): 16, 57%, 23.7 (3.6)	TTT (70 degrees)
Gonzalez-Hermosillo [107]	VVS	OC	VVS: 24, 70.8%, 31 (12) OI no VVS: 25, 72.0%, 33 (14), Controls: 25, 32.0%, 33 (11)	TTT (70 degrees)
Harms [58]	PAF/MSA (with OH)	NG	PAF/MSA: 9, 44.4%, 37–70* Controls: 9, 44.4%, 32–71*	AST
Harms [59]	PAF/MSA (with OH)	NG	PAF/MSA: 6, 50.0%, 55 (10.9) Controls: 6, 50.0%, 55 (10.9)	AST
Haubrich [60]	PD (with OH)	OC	PD with OH (8 symptomatic): 8, 30.7%, 64 (9) PD with OH (asymptomatic): 18, 30.7%, 73 (4) OH (without PD): 8, 40.0%, 66 (20) Controls: 25, 37.5%, 66 (9)	TTT (80 degrees)

Table 2 (continued)

First author	Population	Setting	N participants, female %, age (mean (SD))	Protocol
Hilz [61]	FD (with OH)	NG	FD: 10, 50.0%, 26.9 (9.4) Controls: 10, 40.0%, 25.2 (12.7)	TTT (80 degrees)
Jacob [130]	OI	OC	OI: 10, 90.0%, 22–47* Controls: 9, 88.9%, 20–42*	TTT (75 degrees)
Jaureguirenaud [120]	POTS, VVS and OI	OC	POTS: 40, 75.0%, 36 (10) VVS: 40, 55.0%, 34 (11) OI: 40, 75.0%, 39 (11)	TTT (70 degrees)
Joo [86]	PD (with OH)	OC	PD no OH: 21, 72.2%, 68.7 (6.3) PD with OH: 10, 100%, 69.6 (3.6) Controls: 11, 83.3%, 69.2 (4.6)	TTT (70 degrees)
Lagi [62]	PAF & MSA	OC	PAF/MSA: 12, 0%, 48.9 (26–72)* Controls: 12, 0%, 48.8 (27–71)*	LBNP
Lin [88]	POTS	OC	POTS: 60, 55.0%, 32.3 (8.5) Healthy youth: 13, 69.2%, 29.3 (7.4) Healthy elders: 10, 20.0%, 56.5 (9.0)	TTT (75 degrees)
Mankovsky [63]	Diabetics (with/without OH)	OC & HI	Diabetics (with OH): 8, 37.5%, 47.3 (12.7) Diabetics (no OH): 7, 14.3%, 46.4 (13.8) Controls: 12, 58.3%, 42.6 (9.7)	AST
Medow [89]	POTS	OC	POTS: 12, 75.0%, 20.8 (16–29)* Controls: 9, 66.7%, 21.4 (17–27)*	TTT (70 degrees)
Medow [121]	VVS & POTS	OC	VVS: 20, 65.0%, 21.2 (1.2) POTS: 20, 80.0%, 22.5 (2.0) Controls: 12, 66.7%, 22.0 (1.1)	TTT (70 degrees)
Medow [90]	Paediatric POTS	NG	POTS: 10, 80.0%, 24.7 (0.5) Controls: 15, 90.0%, 19.5 (1.4)	LBNP
Norcliffe-Kaufmann [91]	POTS	OC	POTS: 28, 89.3%, 31 (2) Controls: 21, 90.5%, 28 (5)	TTT (60 degrees)
Novak [131]	OI	OC	OI: 30, 83.3%, 31.3 (1.2) Controls: 17, 76.5%, 30 (1.6)	TTT (80 degrees)
Novak [64]	OH	OC	OH: 21, 57.1%, 61.8 (2.4) Controls: 14, 57.1%, 61.6 (2.3)	TTT (80 degrees)
Novak [122]	OI	OC	OH-c: 96, 61.4%, 56.9 (17.5) OH-u: 60, 61.7%, 57.7 (17.6) OCHOs: 97, 60.8%, 48.1 (17.6) OHTN: 14, 21.4%, 53.0 (16.1) POTS: 101, 85.1%, 31.1 (9.7) IST: 28, 78.6%, 33.5 (7.5) PST: 12, 83.3%, 37.0 (17.8) Syncope-cardioinhibitory: 4, 75.0%, 39.0 (14.5) Syncope-vasodepressor: 12, 58.3%, 48.3 (22.5) Syncope mixed: 26, 53.8%, 35.2 (17.1) pCAF: 67, 46.3%, 57.9 (17.9) PPS: 8, 87.5%, 53.6 (19.9) Controls: 102, 62.7%, 48.7 (16.7)	TTT (70 degrees)
Novak [123]	OCHOs	OC	OCHOs: 102, 58.8%, 51.1 (14.9) Controls: 102, 58.8%, 49.9 (15.9)	TTT (70 degrees)
Novak [124]	POTS & HYCH	OC	HYCH: 16, 93.8%, 38.6 (8.1) POTS: 16, 87.5%, 33.2 (6.5) Controls: 16, 86.7%, 35.8 (7.6)	TTT (70 degrees)
Novak [92]	Long COVID with POTS	OC	Long COVID: 9, 100.0%, 35.8 (7.3) POTS: 10, 90.0%, 36.3 (9.8) Controls: 15, 86.7%, 40.1 (11.6)	TTT (70 degrees)
Novak [134]	POTS & HYCH	OC	POTS: 125, 92%, 31.5 (7.7) HYCH: 127, 86.6%, 33.2 (8.0) Controls: 42, 85.7%, 33.1 (8.1)	TTT (70 degrees)
Ocon [93]	POTS	OC	POTS: 9, 55.6%, 20.3 (15–29)* Controls: 7, 57.1%, 24.4 (15–29)*	TTT (70 degrees)

Table 2 (continued)

First author	Population	Setting	N participants, female %, age (mean (SD))	Protocol
Ocon [108]	VVS	OC	VVS: 12, 58.3%, 17 (1) Controls: 12, 50%, 18 (1)	TTT (70 degrees)
Ocon [109]	OI	OC	Fainters: 16, 68.8%,16 (1), Controls: 15, 66.7%, 17 (1)	TTT (70 degrees)
Park [65]	PD (with/without OH)	OC	PD (with dizziness & OH): 22, 39.1%, 68.0 (8.8) PD (with dizziness & no OH): 23, 27.3%, 71.5 (9.3) PD no dizziness: 13, 27.3%, 63.9 (9.9) Controls: 10, 40.0%, 58.4 (15.6)	TTT (80 degrees)
Petersen [125]	OHTN	OC	OHTN: 17, 100%, 37 (14) OI symptoms: 12, 100%, 32 (12) Controls: 16, 100%, 31 (11)	TTT (70 degrees)
Riberholt [66]	SCI (with OH)	OC	SCI with OH: 14, 50%, 64 (49–69)* Controls: 15, 47%, 31 (27–59)*	TTT (80 degrees)
Schondorf [110]	VVS	OC	VVS: 37, 89.2%, 32.7 (1.2) Controls: 15, 60.0%, 30.7 (1.7)	TTT (80 degrees)
Schondorf [94]	POTS	OC	POTS: 27, 92.6%, 29.2 (1.6) Controls: 17, 64.7%, 30.5 (1.7)	TTT (80 degrees)
Shin [126]	POTS, OH, OI with normal tilt test	OC	OH: 45, 42.2%, 39.6 (15.5) POTS: 33, 75.8%, 24.2 (7.9) OI + normal tilt: 183, 65.0%, 43.7 (11.5) Controls: 50, 60.0%, 42.3 (9.0)	TTT (80 degrees)
Stewart [95]	POTS	NG	POTS: 11, 81.8%, 22.3 Controls: 9, 66.7%, 21.4	TTT (60 degrees)
Stewart [96]	POTS	NG	POTS: 58, 93.1%, 18.1 (1.2) Controls: 16, 93.8%, 19.4 (2.4)	TTT (70 degrees)
Stewart [101]	POTS	OC	POTS low end-tidal CO_2: 26, 92.4%, 18 (3) POTS normal end-tidal CO_2: 28, 92.9%, 19 (3) Controls: 32, 90.7%, 19 (2)	AST
Sung [111]	VVS	OC	VVS: 32, 71.9%, 12.2 (2.8), Controls: 23, 47.8%, 12.0 (2.6)	AST & TTT (80 degrees)
Tang [135]	OI (OH, POTS, OHT, OCHOs)	OC & HI	OI: 85, 38.8%, 58.4 (16.5) Controls: 20, 25%, 55.6 (16.5)	AST & Valsalva manoeuvre
Tantucci [67]	DAN (with OH)	OC	No DAN: 15, 0%, 44.1 (3.2) DAN no OH: 15, 0%, 46.3 (2.7) DAN + OH: 15, 0%, 46.3 (2.5) Controls: 15, 0%, 41.0 (1.6)	Seated CO_2 rebreathing
Treger [68]	Stroke (with/without OH)	RI	Stroke (with OH): 5, 40%, 59.9, Stroke (without OH): 8, 37.5%, 55.2 Controls: 13, 69.2%, 51 (10.4)	TTT (80 degrees)
Tugba [112]	VVS	OC	VVS positive tilt: 31, 51.6%, 13.3 (2.5) VVS negative tilt: 21, 52.4%, 13.9 (2.3) Controls: 22, 50%, 13.6 (2.6)	TTT (80 degrees)
VanVliet [69]	PAF & MSA (with OH)	OC	Autonomic failure: 10, 10%, 66.2 (9.1) Controls: 10, 10%,: 65.9 (8.4)	TTT (60 degrees) & cognitive testing
Wells [97]	POTS	OC	POTS: 22, 86%, 29 (11) Controls: 18, 72%, 28 (3)	Cognitive challenge followed by AST
Wells [98]	POTS	NG	POTS: 11, 82%, 28 (19–37)* Controls: 8, 50%, 31 (26–35)*	Visual & neuro-cognitive testing

Table 2 (continued)

First author	Population	Setting	N participants, female %, age (mean (SD))	Protocol
Xing [70]	PD	HI	PD (total): 90, 38.8%, 58.8 (10.8) PD + OH: 16, 31.2%, 63.7 (7.7) PD no OH: 74, 40.5%, 57.7 (11.1) Controls: 20, 50%, 61.6 (5.9)	AST
Xu [71]	MSA (with OH)	OC	MSA: 38, 78.9%, 55 (7) Controls: 31, 67.7%, 52 (10)	AST
Magnetic resonance imaging (MRI)				
Foster-Dingley [85]	Older adults using antihypertensives	OC	OH: 199, 57.3%, 81.4 (4.6) No OH: 221, 63.3%, 81.5 (4.7)	AST
Skow [100]	POTS	OC	POTS: 11, 90.9%, 17 (1) Controls: 10, 90.0%, 18 (2)	LBNP
Trujillo [84]	PAF (with OH)	OC	PAF: 17, 29.4%, 70.1 (5.6) Controls: 17, 47.1%, 66.8 (5.5)	TTT (60 degrees)
Van Osch [83]	OH	NG	OH: 9, 55.6%, 80.7 (4.3) Controls: 8, 25%, 75 (7)	TTT (90 degrees)
Single-photon emission computed tomography (SPECT)				
Hayashida [82]	OH	OC	OH: 6, 50.0%, 60 (10) Controls: 6, 66.7%, 56 (7)	AST
Joo [115]	VVS	NG	VVS: 35, NG, 36.6 (13.8) Controls: 35, NG, 36.6 (13.8)	TTT (70 degrees)
Matsui [81]	PD (with/without OH)	OC	PD with OH: 15, 66.7%, 70.4 (6.9) PD without OH: 13, 61.5%, 66.2 (6.1)	AST
Passant [80]	OH	OC	OH: 7, 100%, 43 (16.3) Controls: 21, 57.1%, 49.9 (17.5)	TTT (70 degrees)
Passant [79]	Alzheimer's (with/without OH)	OC	AD with OH: 13, 23.1%, 72 (66–85)* AD no OH: 5, 40%, 77 (72–83)*	AST
Siennikki-Lantz [78]	Alzheimer's (with/without OH)	RI	AD with OH: 4, 100%, 79.1 (76.0–82.6)* AD without OH: 8, 100%, 83.0 (81.7–89.9)* OH only: 9, 100%, 82.6 (75.9–90.1)* Controls: 6, 100%, 81.8 (84.4)*	TTT (90 degrees)
Near infrared spectroscopy (NIRS)				
Cheng [114]	Healthy adults	NG	Presyncopal: 6, 66%, 46.7 (14.7) Controls: 8, 50%, 45.6 (11.0)	TTT (70 degrees)
Hunt [77]	PAF/MSA (with OH)	OC	PAF/MSA: 18, 27.8%, 61 (42–79)* Controls: 10, 50.0%, 60 (46–68)*	TTT (60 degrees)
Kharraziha [99]	POTS	OC	POTS: 34, 76.5%, 29.1 (9.5) Controls: 34, 76.5%, 29.4 (9.0)	TTT (70 degrees)
Kim [129]	Paediatric OI	Public schools	iOH: 9, 40.8%, 10–15 years* POTS: 3, 40.8%, 10–15 years* VVS: 3, 40.8%, 10–15 years* dOH: 1, 40.8%, 10–15 years* Normal HR & BP: 33, 40.8%, 10–15 years*	AST
Kim [128]	OI	OC	VVS: 4, 25.0%, 30.0 (23–72)* POTS: 2, 50.0%, 31.0 (20–42)* OH: 7, 42.9%, 72.0 (42–83)* OHTN: 5, 80.0%, 66.0 (38–73)* OI + normal tilt: 16, 68.8%, 54.0 (22–79)* Controls: 8, 37.5%, 67.5 (57–74)*	TTT (70 degrees)
Kim [76]	PD (with/without OH)	OC	PD with OH: 10, 50.0%, 71.9 (9.1) PD no OH: 29, 31.0%, 68.7 (9.2) Controls: 7, 57.1%, 68.1 (4.5)	TTT (70 degrees)
Rodriguez-Nunez [113]	Paediatric VVS	OC	Positive tilt: 19, 40%, 11.6 (2.4) Negative tilt: 6, 40%, 11.6 (2.4)	TTT (80 degrees)
Shinoura [132]	Autonomic dysfunction (with OI)	OC	OI: 6, 33.3%, 35 (1.5), Controls: 17, 35.3%, 34 (1.6)	Head down manoeuvre
Suzuki [75]	MSA (with OH)	NG	MSA: 19, 36.8%, 66.6 (8.3) Controls: 10, 60%, 66.5 (8.5)	TTT (70 degrees)
Extracranial Doppler ultrasound (ECD)				

Table 2 (continued)

First author	Population	Setting	N participants, female %, age (mean (SD))	Protocol
Matsumura [74]	ODV	OC	ODV (30 with OH-16.6%, 151 without OH-83.4%): 181, 64.6%, 50.9 (1.5) Controls (11 with OH-15.1%, 62 without OH 84.9%): 73, 76.7%, 52.6 (2.0)	AST
Van Campen [127]	Long COVID with POTS and OH	OC	COVID + POTS: 13, 69%, 36 (10) COVID + OH: 5, 80%, 43 (7) COVID + normal HR & BP: 11, 82%, 42 (16)	TTT (70 degrees)
Positron emission tomography (PET)				
Yoo [73]	PD	OC	PD no OH: 53, 56.6%, 69.7 (9.1) PD with OH: 20, 30.0%, 73.8 (7.1)	TTT (60 degrees)
Rheoencephalography				
Khandelwal [72]	OH	OC	OH: 15, 66.7%, 41.8 (12.9) Controls: 15, 66.7%, 42.1 (11.8)	TTT (70 degrees)
ME/CFS and OI combined				
Transcranial doppler ultrasound (TCD)				
Medow [49]	ME/CFS (Fukuda 1994) with POTS	OC	ME/CFS: 15, 93.3%, 21.8 (1.4) Controls: 11, 63.6%, 24.1 (0.6)	TTT (60 degrees)
Ocon [46]	ME/CFS (Fukuda 1994) with POTS	NG	ME/CFS: 16, 66.7%, 21 (1) Controls: 20, 66.7%, 23 (1)	TTT (70 degrees)
Stewart [47]	ME/CFS (Fukuda 1994) with POTS	NG	ME/CFS + POTS: 25, NG, 22 (1) Controls: 20, NG, 23 (1)	TTT (70 degrees)
Near infrared spectroscopy (NIRS)				
Tanaka [48]	ME/CFS (Fukuda 1994) with OI	OC	ME/CFS: 28, 53.6%, 10–22* Controls: 20, 50%, 6–27*	AST
Extracranial Doppler ultrasound (ECD)				
Van Campen [3]	ME/CFS (Fukuda 1994 & ICC 2011) with OI	OC	ME/CFS (247 normal HR & BP, 62 dOH, 120 POTS): 429, 87%, 39 (12) Controls: 44, 87%, 37 (14)	TTT (70 degrees)
Van Campen [50]	Severe ME/CFS (Fukuda 1994 & ICC 2011) with POTS/fibromyalgia	OC	Severe ME/CFS (34 with POTS, 66 with normal HR & BP): 100, 88%, 38 (12) Controls: 15, 86.7%, 38 (15)	Sitting -supine
Van Campen [51]	ME/CFS (Fukuda 1994 & ICC 2011) with OI	OC	ME/CFS normal tilt: 30, 86.7%, 42 (14) ME/CFS + POTS: 26, 84.6%, 36 (10)	TTT (70 degrees)
Van Campen [54]	ME/CFS (ICC 2011, IOM 2015) with POTS, Long COVID with POTS	OC	COVID + POTS: 10, 70%, 30 (7) ME/CFS + POTS: 20, 70%, 30 (7) ME/CFS normal HR & BP: 20, 70%, 30 (7) Controls: 20, 70%, 30 (7)	TTT (70 degrees)
Van Campen [10]	ME/CFS (Fukuda 1994 & ICC 2011) with OI	OC	ME/CFS normal HR & BP: 105, 80%, 41 (9) ME/CFS + POTS: 39, 74.4%, 38 (11) ME/CFS + dOH: 27, 81.5%, 43 (12) ME/CFS OI negative: 28, 57.1%, 44 (10) Controls: 22, 68.2%, 46 (11)	TTT (70 degrees)
Van Campen [53]	ME/CFS (ICC 2011, IOM 2015) with/without PPS	OC	ME/CFS + PPS: 30, 93.3%, 33 (11) ME/CFS without PPS: 30, 93.3%, 33 (11)	TTT (70 degrees)
Van Campen [52]	ME/CFS (Fukuda 1994 & ICC 2011) with POTS	OC	ME/CFS normal HR & BP: 309, 100%, 42 (11) ME/CFS + POTS: 226, 100%, 34 (9) Controls: 34, 100%, 34 (14)	TTT (70 degrees)

AD, Alzheimer's dementia; AST, Active stand test; BP, Blood pressure; CBF, Cerebral blood flow; CCC, Canadian consensus criteria; CDC, Centre for disease control and prevention; CO, Cardiac output; COVID, Corona virus disease; DAN, Diabetic autonomic neuropathy; dOH, Delayed orthostatic hypotension; FD, Familial dysautonomia; HI, Hospital inpatients; HR, Heart rate; HYCH, Hypocapnic cerebral hypoperfusion syndrome; ICC, International consensus criteria; iOH, Initial orthostatic hypotension; IOM, Institute of medicine criteria; IST, inappropriate sinus tachycardia; LBNP, Lower body negative pressure; ME/CFS, Myalgic encephalomyelitis/chronic fatigue syndrome; MSA, Multiple system atrophy; NA, Not applicable; NG, Not given; OC, Outpatient clinic; OCHOs, Orthostatic cerebral hypoperfusion syndrome; ODV, Orthostatic dizziness and vertigo; OH, Orthostatic hypotension; OH-c, Compensated orthostatic hypotension; OH-u, Uncompensated orthostatic hypotension; OHTN, Orthostatic hypertension; OI, Orthostatic intolerance; PAF, Pure autonomic failure; PANAS, Positive and negative affect schedule; PASAT, Paced auditory serial assessment task; pCAF, Primary cerebral autoregulatory failure; PD, Parkinson's disease; POTS, Postural orthostatic tachycardia syndrome; PPS, Psychogenic pseudosyncope; PRS, Postural related syncope; PST, Paroxysmal sinus tachycardia; RI, Rehabilitation inpatients; SCI, Spinal cord injury; SD, Standard deviation; TTT, Tilt table test; VVS, Vasovagal syncope

*Median (range)

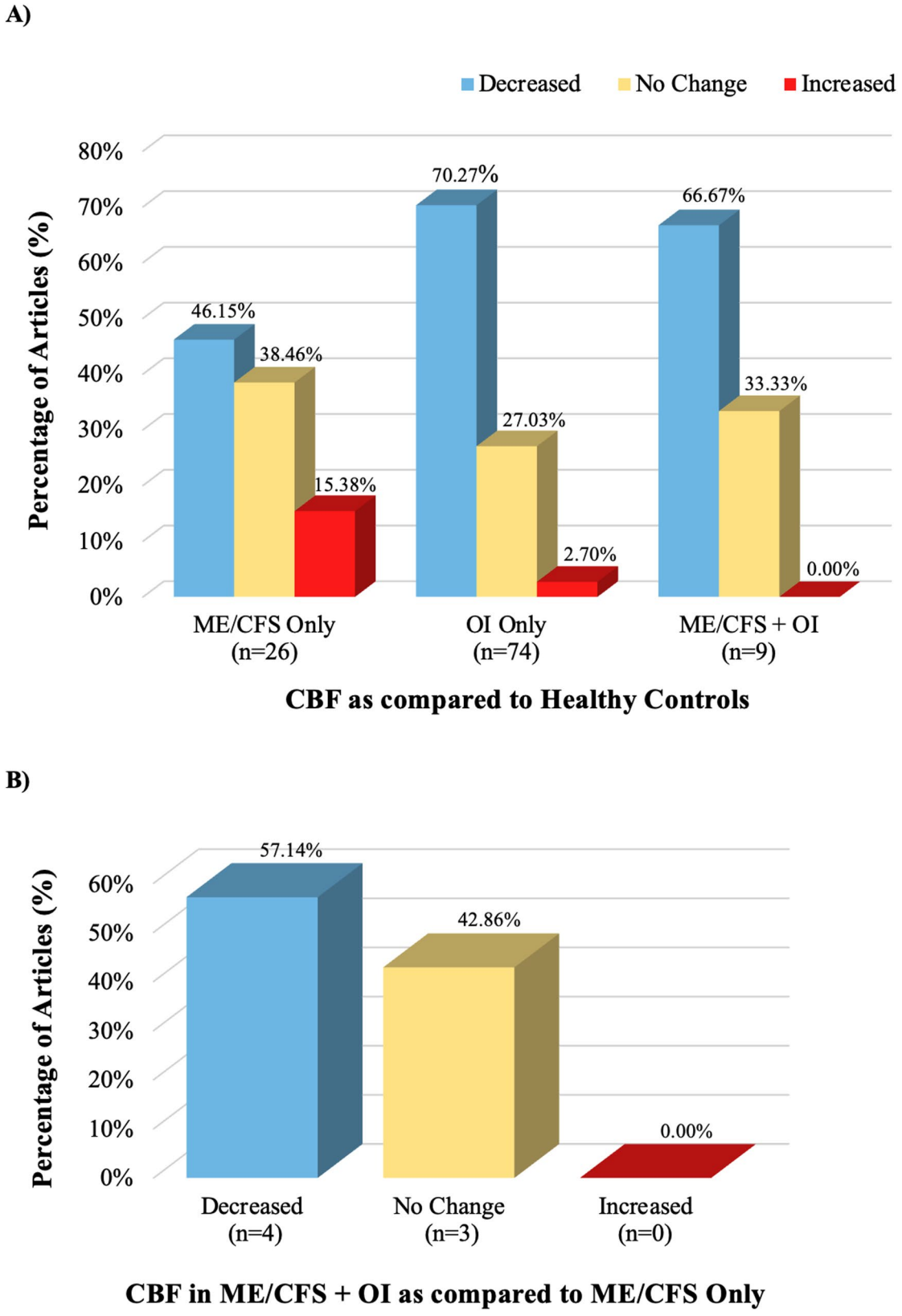

Fig. 2 Cerebral blood flow changes in **A** ME/CFS and OI vs healthy controls, and **B** ME/CFS with OI vs ME/CFS without OI. Seven and 2 articles which studied OI only and ME/CFS + OI combined respectively did not report the difference in cerebral blood flow compared to healthy controls (Panel **A**). Four articles which studied ME/CFS + OI combined did not report the differences in cerebral blood flow between ME/CFS patients with OI compared to ME/CFS without OI (Panel **B**). CBF: cerebral blood flow, ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome, OI: orthostatic intolerance

Table 3 Main findings of cerebral blood flow changes, stratified by type of cerebral blood flow measurement

First author	Main findings	Change versus disease state*	Change versus healthy controls
ME/CFS only			
Transcranial Doppler ultrasound (TCD)			
Malfliet [45]	CBF increased during physical exercise in both ME/CFS patients and controls however there were no significant differences between ME/CFS patients and controls	Not reported	No change
Razumovsky [20]	CBFv did not differ between ME/CFS patients and controls while supine, at 1 or 5 min after tilt, at 5 or 1 min before the end of the tilt, or at termination of the test. CBFv decreased at termination of tilt testing in both patients with ME/CFS and controls	Not reported	No change
Magnetic resonance imaging (MRI)			
Biswal [21]	ME/CFS patients had an overall reduced global CBF than controls (9 of 11 patients reduced CBF). Two of the 11 ME/CFS patients showed increased CBF compared to the control group average	Not reported	↓
Boissoneault [22]	No significant differences in whole brain CBF or between CBFv between ME/CFS patients and controls	Not reported	No change
Gay [41]	Reduced CBF in ME/CFS patients compared to controls while at rest in the occipital gyrus and temporal lobes. No differences in global CBF or in CBF of cortical regions were observed	Not reported	↓
Li [43]	ME/CFS patients showed significant hypoperfusion in several brain regions of the limbic system, including the anterior cingulate cortex, putamen, pallidum, and anterior ventral insular area in comparison to controls	Not reported	↓
Mueller [23]	No differences in CBF between ME/CFS patients and controls in any region of interest that showed changes in metabolite differences between ME/CFS and controls	Not reported	No change
Natelson [24]	CBF was found to be significantly lower in ME/CFS than in controls in only 3 regions: the frontal medial orbital, frontal superior medial and rectus gyri	Not reported	↓
Perrin [25]	No significant differences in CBF were found from baseline to 1 year measurements between ME/CFS with and without osteopathic treatment compared to controls	Not reported	No change
Shan [26]	BOLD signals in the posterior cingulate cortex and the driving hub in the default mode network were more complex in ME/CFS in both resting state and stroop task indicating increased CBF	Not reported	↑
Shungu [27]	Only two regions (the left anterior cingulate cortex and the right lingual gyrus) had statistically significant CBF decreases, however the raw values were highly suggestive of potentially more widespread hypoperfusion in patients with ME/CFS	Not reported	↓
Staud [42]	Global CBF was not different during rest and during a cognitive task (PASAT) between ME/CFS and controls	Not reported	No change
Zeineh [28]	No significant differences in brain perfusion detected	Not reported	No change
Single-photon emission computed tomography (SPECT)			
Costa [37]	Brainstem hypoperfusion was observed in all ME/CFS patients. ME/CFS patients had a generalised reduction in brain perfusion, with a particular pattern of hypoperfusion of the brainstem	Not reported	↓
Fischler [36]	Hyper perfusion was demonstrated in several frontal and temporal regions in patients with ME/CFS compared to controls	Not reported	↑
Fischler [38]	No global or regional CBF differences in ME/CFS patients compared to controls	Not reported	No change
Goldberg [44]	Hypoperfusion was observed in the left and right temporal lobes as well as in both parietal lobes and the frontal lobe of the right hemisphere Hypoperfusion was also seen in bilateral orbitofrontal and anterior temporal regions in addition to the dorsal aspects of both frontal lobes and both parietooccipital lobes	Not reported	↓
Ichise [35]	ME/CFS patients showed significantly lower regional CBF in the cortical and cerebellar regions compared to controls	Not reported	↓
Lewis [29]	No changes in CBF observed between ME/CFS twins vs control twins	Not reported	No change
Machale [30]	Increased perfusion in the right and left thalamus, right pallidum and right putamen in patients with ME/CFS compared to controls	Not reported	↑
Peterson [34]	CBF abnormalities were accentuated post exercise in the ME/CFS group but were not significantly different from the control group. However the effect of exercise on CBF appeared magnified in the ME/CFS patients	Not reported	No change
Schmaling [31]	Both groups showed an increase in CBF, however ME/CFS patients showed significantly larger increases than controls. There also were lateral differences; CFS subjects activated the left, but not the right, anterior cingulate region relatively more during the PASAT than during rest compared to controls	Not reported	↑
Near infrared spectroscopy (NIRS)			

Table 3 (continued)

First author	Main findings	Change versus disease state*	Change versus healthy controls
Patrick-Neary [32]	Prefrontal cortex oxyHb, deoxyHb and totalHb were significantly lower at maximal exercise in ME/CFS versus controls. The ME/CFS subjects exhibited significant exercise intolerance and reduced prefrontal oxygenation and totalHb response when compared with control subjects	Not reported	↓
Xenon computed tomography			
Yoshiuchi [33]	ME/CFS patients with and without axis 1 psychiatric disorders showed decreased CBF in the right MCA and ME/CFS patients without axis 1 psychiatric disorders also showed decreased blood flow in the left MCA compared to controls	Not reported	↓
Extracranial Doppler ultrasound (ECD)			
Van Campen [39]	Significantly lower CBF during end-tilt in ME/CFS compared to controls	Not reported	↓
Van Campen [40]	Significantly lower CBF during the tilt in ME/CFS with lower cardiac output and end-tidal CO_2 levels compared to controls	Not reported	↓
OI only			
Transcranial Doppler ultrasound (TCD)			
Asahina [55]	Mean arterial BP (skull) significantly decreased, heart rate significantly decreased, critical closing pressure was significantly increased and cardiovascular resistance was significantly increased from supine to tilt in MSA patients compared to controls. However there were no significant differences in CBF between MSA patients vs controls	Not reported	No change
Baker [102]	Significantly larger drop in MCA velocity pulsatility index in patients with POTS during tilt compared to controls	Not reported	↓
Camargo [56]	PD patients with OH had higher baseline CBFv compared to PD without OH. PD with OH had a lower percentage increase in mean CBFv during breath holding and a higher post breath hold CBFv compared to controls	No change (PD with OH vs no PD no OH)	↓ (PD with OH vs controls)
Carey [103]	CBFv declined significantly during head up tilt in all groups and mean CBFv was significantly lower in VVS patients than controls at 3 min before syncope and at syncope but was similar at all other times	Not reported	↓
Carey [104]	CBFv declined and critical closing pressure increased during presyncope. Mean CBFv declined at syncope from baseline in both VVS patients and syncopal controls but not in non-syncopal controls at average time to syncope	Not reported	↓ (syncopal patients vs non syncopal controls)
Castro [116]	Decreases in CBFv in all groups (VVS, autonomic failure and controls) from supine to 3 min post tilt were observed and there was a significant decrease in CBFv in autonomic failure patients compared to controls. Increases in critical closing pressure and cerebrovascular resistance index in controls and VVS patients but not autonomic failure patients from baseline to 3 min before tilt were also observed	Not reported	↓ (Autonomic failure vs controls), No change (VVS vs controls)
Castro [117]	CBFv decreased in all groups during tilt but only autonomic failure patients had significant differences in CBFv from a supine to tilted position. No differences were observed between groups	Not reported	No change
Claydon [118]	Patients with PRS had significantly lower CBF than controls	Not reported	↓
Coelho [133]	Significant reduction in systolic CBF velocity while upright and significantly larger maximal decline in CBF velocity while upright in OI patients compared to controls	Not reported	↓
Delpozzi [87]	Significantly lower CBFv in POTS patients vs controls during tilt was observed	Not reported	↓
Diehl [119]	No significant differences between CBFv in VVS + POTS or VVS only patients vs controls during supine or the first few minutes of tilt. Mean CBFV decreased significantly and continuously during tilt in POTS and VVS compared to controls	↓ (VVS + POTS vs VVS only)	No change (POTS and VVS vs controls)
Diehl [105]	CBFv was decreased in VVS patients when tilted compared to while supine, however there were no differences between VVS patients and controls	Not reported	No change
FuenteMora [57]	Significant drop in diastolic MCA velocity and resistance index in FD patients (with OH) when standing but no significant difference between FD patients and controls	Not reported	No change
Gonzalez-Hermosillo [106]	Significantly larger decreases in mean CBFv in patients who have recurrent VVS vs controls	Not reported	↓

Table 3 (continued)

First author	Main findings	Change versus disease state*	Change versus healthy controls
Gonzalez-Hermosillo [107]	CBFv was significantly decreased during tilt in patients with OI during the TTT (both patients VVS and without VVS) compared to controls	Not reported	↓
Harms [58]	Significantly lower CBFv and significantly lower oxyHb and higher deoxyHb in PAF/MSA patients vs controls during tilt was observed	Not reported	↓
Harms [59]	CBFv is significantly increased while supine in patients with PAF/MSA and OH compared to controls with no differences when standing observed. No differences in brain oxygenation between PAF/MSA patients and controls were seen	Not reported	No Change
Haubrich [60]	PD with OH who were symptomatic and patients with OH without PD showed significantly larger decreases in CBFv in both the MCA and PCA compared to controls	No Change (PD with OH vs OH no PD)	↓
Hilz [61]	Significantly greater decreases in diastolic and mean CBFv in FD patients vs controls was observed	Not reported	↓
Jacob [130]	Peak and mean MCA velocity was significantly lower in patients with OI compared to controls during tilt	Not reported	↓
Jaureguirenaud [120]	POTS patients showed increased CBFv compared to patients who experienced OI symptoms with normal TTT results	↑ (POTS vs OI symptoms + normal TTT)	NA
Joo [86]	No differences detected in MCA velocity using TCD however there were significantly lower oxyHb in patients with PD with OH compared to PD patients without OH and PD patients with OH when compared to controls	↓	↓
Lagi [62]	Significantly lower mean CBFv in PAF/MSA patients compared to controls was observed	Not reported	↓
Lin [88]	CBFv was significantly higher in POTS patients compared to healthy elders while supine but no significant differences between POTS and healthy youth/elders during tilt was observed	Not reported	No Change during tilt, (increased in POTS while supine vs healthy elders)
Mankovsky [63]	Diastolic and mean CBFv was significantly decreased in diabetic patients with OH vs both diabetics without OH controls during standing	↑ while supine (cardiovascular autonomic neuropathy with OH vs no cardiovascular auto neuropathy)	↓
Medow [89]	No differences in CBFv between POTS vs controls but there was a significant increase in CBFv variability in POTS patients compared to controls	Not reported	No Change
Medow [121]	CBFv significantly decreased in VVS patients in comparison to controls and POTS patients during tilt. The change in oxyHb decreased, totalHb decreased and deoxyHb increased significantly compared to controls during tilt	↓ (VVS vs POTS)	↓ (VVS vs controls)
Medow [90]	In POTS patients following oral rehydration solution but not saline, CBFv was significantly higher compared to POTS patients with no treatment during the tilt. In controls fluid administration did not result in any changes to CBFv	↑ (POTS with oral rehydration vs POTS no treatment)	Not reported
Norcliffe-Kaufmann [91]	Significantly reduced CBF in POTS patients vs controls during tilt was observed	Not reported	↓
Novak [131]	Significantly reduced CBFv in patients with OI compared to controls during tilt was observed	Not reported	↓
Novak [64]	Significantly reduced diastolic CBFv in OH patients during tilt compared to controls was observed	Not reported	↓

Table 3 (continued)

First author	Main findings	Change versus disease state*	Change versus healthy controls
Novak [122]	CBF is significantly reduced in OH-u, OCHOs, POTS, syncope-cardioinhibitory, syncope-vasodepressor, syncope-mixed and pCAF patients in comparison to controls	Not reported	↓ (OH-u, OCHOs, POTS, syncope-cardioinhibitory, syncope-vasodepressor, syncope-mixed and pCAF patients vs controls)
Novak [123]	Significantly decreased CBFv in patients with OCHOs compared to controls	Not reported	↓
Novak [124]	Both POTS patients and HYCH patients had significantly lower CBFv during tilt compared to controls	Not reported	↓
Novak [92]	CBFv significantly decreased in both POTS and long COVID patients compared to controls	Not reported	↓
Novak [134]	Significantly lower CBF velocity during tilt in patients with POTS and HYCH when compared to controls	Not reported	↓
Ocon [93]	Significantly larger decrease in CBF from supine to upright in POTS patients vs controls	Not reported	↓
Ocon [108]	Significant decrease in CBFv during tilt in VVS patients compared to controls	Not reported	↓
Ocon [109]	Significant decrease in mean CBFv during end tilt/faint in VVS patients compared to controls	Not reported	↓
Park [65]	Significantly larger decrease in CBFv in PD with OH compared to those without OH and controls	↓ (PD with OH vs PD no OH)	↓
Petersen [125]	CBF decreased significantly during TTT in OHT, OI and controls, however there were no significant differences between OHT or OI and controls	Not reported	No change
Riberholt [66]	Significant decrease in CBFv in the MCA while supine, however no differences between SCI patients and controls were observed during tilt	Not reported	No change
Schondorf [110]	Decreased CBFv in patients with VVS during early tilt and over the course of the tilt CBFv also decreased significantly but there was no significant differences between VVS patients and controls	Not reported	No change
Schondorf [94]	Decreased average systolic and diastolic CBFv in POTS patients vs controls was observed during the TTT. Increased systolic and diastolic CBFv in POTS vs controls while supine & increased diastolic CBFv in POTS vs controls during late tilt was observed	Not reported	↓
Shin [126]	The drops in systolic CBFv, cerebral perfusion pressure, and cerebral vascular resistance of patients with OI symptoms and normal HR & BP were greater than those of controls. No differences were seen in CBFv between different types of OI groups (POTS, OH, OI symptoms)	Not reported	↓ (OI symptoms with normal HR & BP vs controls)
Stewart [95]	Oscillatory CBFv was significantly increased in POTS patients with increasing tilt angle compared to controls	Not reported	↑
Stewart [96]	CBFv in the MCA was reduced during tilt only in the hyperventilation POTS group in comparison to controls	Not reported	↓ (POTS with hyperventilation vs controls)
Stewart [101]	Significantly lower CBF during the end of the stand test in patients with POTS with low end-tidal CO_2 compared to controls	Not reported	↓
Sung [111]	No significant differences in CBF from supine to 5 min standing or 5 min tilt between VVS and controls were observed. In VVS patients CBF reduced significantly from before presyncope symptoms to the onset of presyncope symptoms	Not reported	No change
Tang [135]	Significantly larger reduction in CBF velocity in patients with an OI diagnosis when compared to controls during a Valsalva manoeuvre	Not reported	↓
Tantucci [67]	MCA CBFv was significantly lower in patients with DAN with OH and without OH as well as in diabetics without DAN compared to controls after rebreathing CO_2	Not reported	↓ (DAN with and without OH and diabetics without DAN vs controls at 50 Torr CO_2)
Treger [68]	No significant differences between hemispheres (damaged & non-damaged) in stroke patients without OH. Stroke patients with OH had significant decrease in CBFv while supine in the damaged vs non-damaged hemisphere and during the tilt test	↓	Not reported

Table 3 (continued)

First author	Main findings	Change versus disease state*	Change versus healthy controls
Tugba [112]	CBF was significantly decreased during upright tilt in VVS patients (both asymptomatic and symptomatic patients) compared to controls. Symptomatic patients experienced further decreases in the right MCA compared to asymptomatic VVS patients	↓ (Symptomatic positive TTT vs asymptomatic negative TTT patients during tilt)	↓
VanVliet [69]	No change in CBFv between autonomic failure patients with OH and controls during head up tilt and sustained attention to response task test	Not reported	No change
Wells [97]	No changes in CBFv in POTS patients after 5 min of standing compared to controls was seen, however there was a significant decrease in CBF in POTS patients after a prolonged cognitive challenge compared to controls	Not reported	↓
Wells [98]	No significant differences in CBF between POTS patients and controls in response to visual stimuli and neurocognitive testing when seated	Not reported	No change
Xing [70]	No changes in CBFv between Parkinson's patients with and without OH were observed	No change	No change (PD with and without OH vs controls)
Xu [71]	Significantly lower CBF was observed in MSA patients (with OH) compared to controls while in the upright position after standing	Not reported	↓
Magnetic resonance imaging (MRI)			
Foster-Dingley [85]	No difference in CBF between OH vs no OH was observed	Not reported	No change
Skow [100]	No significant changes in CBF between patients with POTS and controls during LBNP	Not reported	No change
Trujillo [84]	Grey matter CBF was significantly increased in PAF patients compared to controls	Not reported	↑
Van Osch [83]	CBF did not differ in white or grey matter but cerebral blood volume was significantly decreased in patients with OH in the white matter in comparison to controls	Not reported	↓
Single-photon emission computed tomography (SPECT)			
Hayashida [82]	Significant decrease in cerebral perfusion in the frontal area in patients with OH vs controls were observed	Not reported	↓
Joo [115]	Significantly decreased rCBF in VVS patients in the anterior insular cortex, basal and lateral temporal lobes, medial parieto-occipital area and the cerebellum compared to controls	Not reported	↓
Matsui [81]	Decreased perfusion in PD patients with OH in the bilateral medial frontal areas and the bilateral cingular gyrus compared to PD patients without OH	↓	Not reported
Passant [80]	No significant difference in CBF between OH vs controls was observed	Not reported	No change
Passant [79]	No significant differences between CBF in Alzheimer's patients with and without OH were observed	No change	Not reported
Siennikki-Lantz [78]	Patients with Alzheimer's dementia and OH had significantly lower CBF in frontal and parieto-frontal regions, compared with Alzheimer's patients without OH. In the controls, no significant differences in CBF with respect to the presence of OH were observed	↓ (Alzheimer's with OH vs no OH)	No change (OH vs controls)
Near infrared spectroscopy (NIRS)			
Cheng [114]	Presyncopal patients had significantly lower CBF than controls during tilt	Not reported	↓
Hunt [77]	Significantly larger decreases in oxyhemoglobin, deoxyhemoglobin and total haemoglobin in PAF/MSA patients compared to controls were observed	Not reported	↓
Kharraziha [99]	Significantly larger decrease in cerebral tissue oxygenation in POTS patients vs controls from supine to 10 min tilt was observed	Not reported	↓
Kim [129]	Children with OI (abnormal tilt response) experienced significantly larger decreases in oxyhemoglobin than controls during active standing and significantly decreased total haemoglobin at min 4–7 of standing vs controls was observed	Not reported	↓
Kim [128]	Significantly decreased totalHb and oxyHb in OH patients and VVS patients vs controls was observed	Not reported	↓ (OH vs controls & VVS vs controls)
Kim [76]	PD with OH showed significantly decreased oxyhemoglobin during the tilt compared to controls	Not reported	↓
Rodriguez-Nunez [113]	Significantly larger decreases in the difference between baseline and minimum brain oxygen saturation between patients with positive and negative tilt tests was observed	↓	Not reported
Shinoura [132]	Decrease in right-sided totalHb concentration in symptomatic patients compared to controls but no effect was seen on left-sided totalHb in either group. Five of 6 patients showed a gradual decrease in right-sided totalHb levels when assuming a sitting position	Not reported	↓

Table 3 (continued)

First author	Main findings	Change versus disease state*	Change versus healthy controls
Suzuki [75]	Cerebral tissue oxygen saturation decreased slightly in both MSA patients (with OH) and controls but did not differ significantly. Presyncopal MSA patients had significantly larger decreases in cerebral tissue oxygenation than the non-presyncopal MSA patients and controls. OxyHb and deoxyHb levels did not significantly change during the tilt in MSA patients or controls	↓ (MSA with OI symptoms vs no symptoms)	↓ (MSA with OI symptoms vs controls)
Extracranial doppler ultrasound (ECD)			
Matsumura [74]	Vertebral artery blood flow velocity was significantly decreased in patients with OH vs controls when standing	Not reported	↓
Van Campen [127]	No significant differences between long COVID with POTS, long COVID with OH or long COVID with normal HR & BP in CBF while supine or while tilted	No change	Not reported
Positron emission tomography (PET)			
Yoo [73]	Early phase (30 min) standardised uptake value ratios were significantly higher in the precentral gyrus, dorsolateral superior frontal gyrus, inferior frontal gyrus (opercular part), supplementary motor area, medial superior frontal gyrus, middle cingulate/paracingulate gyrus, superior parietal gyrus, and inferior parietal gyrus in PD patients with OH than in PD patients without OH, indicating increased CBF. However late phase (90 min) standardised uptake ratios were not significantly different between groups	↑ (PD with OH vs PF no OH)	Not reported
Rheoencephalography			
Khandelwal [72]	No difference in CBFv in OH patients vs controls was observed	Not reported	No change
ME/CFS and OI combined			
Transcranial doppler ultrasound (TCD)			
Medow [49]	Significantly lower CBF velocity in the MCA during tilt in ME/CFS patients with POTS compared to controls	Not reported	↓
Ocon [46]	No significant differences between CBF in ME/CFS + POTS patients and controls during tilt/cognitive test were observed	Not reported	No change
Stewart [47]	CBF was not significantly different in ME/CFS + POTS vs controls during tilt & a cognitive test	Not reported	No change
Near infrared spectroscopy (NIRS)			
Tanaka [48]	Cerebral oxyHb was decreased in patients with ME/CFS & OI during active stand in comparison to controls while deoxyHb showed no differences between ME/CFS/OI and controls during stand	Not reported	↓
Extracranial Doppler ultrasound (ECD)			
Van Campen [3]	CBF was significantly decreased at all timepoints apart from supine in ME/CFS patients with normal HR & BP during the tilt compared to controls. CBF was significantly lower in patients with ME/CFS with POTS and dOH compared to ME/CFS with normal HR & BP	↓ (ME/CFS with POTS or dOH vs ME/CFS normal HR/BP)	↓ (ME/CFS normal HR & BP vs controls)
Van Campen [50]	CBF during sitting was significantly lower in severe ME/CFS patients in comparison to controls while supine CBF did not differ. ME/CFS patients with POTS had significantly larger % change in CBF compared to ME/CFS patients without POTS. ME/CFS patients with daily OI symptoms (regardless of a POTS diagnosis) had a significantly larger decrease in CBF compared to ME/CFS patients without daily OI symptoms	↓ (ME/CFS with POTS vs ME/CFS normal HR/BP)	↓ (ME/CFS- all patients vs controls)
Van Campen [51]	No differences in CBF between ME/CFS patients with normal HR and BP during tilt vs ME/CFS with POTS during tilt	No change	Not reported
Van Campen [54]	All COVID patients developed POTS during tilt. CBF was significantly reduced in patients with COVID + POTS, ME/CFS + POTS and ME/CFS normal HR & BP compared to controls during tilt. The reduction in CBF was larger in COVID patients with POTS compared to ME/CFS patients with normal HR & BP	↓ (COVID + POTS vs ME/CFS normal HR & BP)	↓ (ME/CFS + POTS, COVID + POTS, ME/CFS normal HR & BP, vs controls)
Van Campen [10]	No significant differences in CBF between baseline, end tilt or %CBF reduction between ME/CFS patients with normal HR & BP (with abnormal CBF reduction during tilt), ME/CFS with POTS or ME/CFS with dOH. No significant differences between controls and ME/CFS patients without OI (normal HR & BP and CBF reduction during tilt)	No change (ME/CFS with POTS or dOH vs ME/CFS with normal HR & BP)	No change (ME/CFS with normal HR & BP vs controls)

Table 3 (continued)

First author	Main findings	Change versus disease state*	Change versus healthy controls
Van Campen [53]	CBF in ME/CFS patients with PPS was significantly decreased during tilt compared to ME/CFS patients without PPS	↓	Not reported
Van Campen [52]	Significantly lower CBF velocity during end-tilt in both ME/CFS patients with normal HR & BP and POTS when compared to controls	No change	↓

AST, Active stand test; BP, Blood pressure; CBF, Cerebral blood flow; CBFv, Cerebral blood flow velocity; CO, Cardiac output; COVID, Corona virus disease; DAN, Diabetic autonomic neuropathy; DeoxyHb, deoxygenated haemoglobin; dOH, Delayed orthostatic hypotension; FD, familial dysautonomia; HR, Heart rate; HYCH, Hypocapnic cerebral hypoperfusion syndrome; iOH, Initial orthostatic hypotension; IST, inappropriate sinus tachycardia; LBNP, Lower body negative pressure; MCA, Middle cerebral artery; ME/CFS, Myalgic encephalomyelitis/chronic fatigue syndrome; MSA, Multiple system atrophy; OCHOs, Orthostatic cerebral hypoperfusion syndrome; ODV, Orthostatic dizziness and vertigo; OH, Orthostatic hypotension; OH-c, Compensated orthostatic hypotension; OH-u, Uncompensated orthostatic hypotension; OHTN, Orthostatic hypertension; OI, Orthostatic intolerance; OxyHb, Oxygenated haemoglobin; PAF, Pure autonomic failure; PANAS, Positive and negative affect schedule; PASAT, Paced auditory serial assessment task; PCA, Posterior cerebral artery; pCAF, Primary cerebral autoregulatory failure; PD, Parkinson's disease; POTS, Postural orthostatic tachycardia syndrome; PPS, Psychogenic pseudosyncope; PRS, Postural related syncope; PST, Paroxysmal sinus tachycardia; RI, Rehabilitation inpatients; SCI, Spinal cord injury; SD, Standard deviation; TotalHb, Total haemoglobin; TTT, Tilt table test; VVS, Vasovagal syncope

*Any other disease group (apart from healthy controls)

influenced by a range of comorbidities, possibly including undiagnosed ME/CFS.

Comparisons between ME/CFS patients with OI and normal orthostatic responses

ME/CFS patients without an OI diagnosis, where heart rate and blood pressure remain normal upon standing may still experience OI symptoms while upright [3]. This suggests that the pathophysiology of OI symptoms in these patients may be similar and potentially linked to a reduction in CBF. In ME/CFS patients without OI reduced CBF may be attributed to orthostatic hypocapnia [124], which is characterised by hyperventilation when in an upright position (leading to cerebral vasoconstriction). Alternatively, it could be related to orthostatic cerebral hypoperfusion syndrome, associated with abnormal orthostatic cerebral autoregulation resulting in vasoconstriction of the cerebral arteries. Further decreases in CBF in ME/CFS patients with OI compared with ME/CFS patients with normal orthostatic responses may indicate that ME/CFS symptom severity may be increased in the patients who have both conditions comorbidly [51]. This may play a key factor in PEM severity, particularly after exertion while upright, and could also contribute to the 'brain fog' that is commonly reported by ME/CFS patients [11]. Often, individuals with severe ME/CFS are highly affected by OI symptoms and they are evoked when transitioning to an upright position [50]. These symptoms, in addition to severe fatigue, pain and PEM upon exertion, restrict functional capacity [139, 140] and these patients are typically not included in studies which involve exercise or tilt table testing as it is not well tolerated and can result in severe OI symptoms and PEM; therefore it is impossible to accurately capture CBF in the entire ME/CFS patient population.

Cerebral blood flow measurement techniques

Various techniques utilised to measure CBF between studies may have influenced the results of CBF in participants with ME/CFS and/or OI, as different techniques measure different variables or regions of the brain. For example we cannot directly compare CBF using TCD ultrasound, which measures the speed of blood flow (in cm/s) in a single artery (a relative measure of CBF) in the brain with arterial spin labelling (ASL)-MRI which, quantifies the rate of arterial blood flow to the capillaries (in mL/100 g of brain tissue per minute) in the brain (an absolute measure of CBF) [13], as these two techniques measure different variables in different regions of the brain. OI symptoms are likely associated with a lack of global CBF, however some techniques (such as NIRS or TCD) only measure CBF in a specific region or artery of the brain and therefore may not adequately capture all the changes in CBF. Therefore techniques which can observe global CBF such as ECD ultrasound and MRI are preferred [141], however these techniques are often difficult to implement in studies and particularly in those which involve upright exercise or tilt tables which are commonly used to assess orthostatic tolerance. Future use of these global CBF measurement techniques in ME/CFS and OI research needs to be refined to include a component of orthostatic tolerance testing with an alternative to the tilt table such as lower body negative pressure during an ASL-MRI scan [100].

Strengths and limitations

This review includes a large number of articles and is the first review to our knowledge that looks at CBF in ME/CFS patients with and without OI. However, due to the different techniques utilised to measure CBF and not having enough articles that employed the same technique in a similar population, we were not able to perform a

meta-analysis. Furthermore, factors such as medications, time of the day or hydration levels will likely influence CBF which were not controlled for in the majority of the studies. Additionally, heterogeneity between the populations and types of OI studied in the included articles may limit the generalisability of the results.

Conclusions

CBF is reduced in patients with ME/CFS or OI alone or having both of these conditions as comorbidities significantly reduces CBF even further when compared to having only one condition. Therefore, monitoring CBF in ME/CFS patients with and without OI may be important in monitoring disease severity and predicting PEM events. Understanding how both ME/CFS and OI affect CBF is crucial for improving time to diagnosis, development of targeted therapies and enhancing patient quality of life.

Abbreviations

ASL	Arterial spin labelling
CBF	Cerebral blood flow
CCC	Canadian Consensus Criteria
CDC	Centers for Disease Control and Prevention
ECD	Extracranial Doppler
ICC	International Consensus Criteria
IOM	Institute of Medicine
ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
MRI	Magnetic resonance imaging
NIRS	Near infrared spectroscopy
NOS	Newcastle–Ottawa scale
OH	Orthostatic hypotension
OI	Orthostatic intolerance
PEM	Post exertional malaise
POTS	Postural orthostatic tachycardia syndrome
SPECT	Single photon emission computed tomography
TCD	Transcranial Doppler
VVS	Vasovagal syncope

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06954-w.

Supplementary Material

Acknowledgements

Not applicable.

Author contributions

EMC conceived and designed research, analysed data, interpreted results of experiments, prepared figures and drafted the manuscript. DT and KH analysed the data. KJM, PRG and EKS edited and revised manuscript. CWA conceived and designed the research, edited and revised the manuscript. All authors read and approved the final version of manuscript.

Funding

This research was funded by a philanthropic grant received by Christopher W. Armstrong that was provided by the Open Medicine Foundation Australia and by a philanthropic grant received by Elena M. Christopoulos that was provided by the Australian POTS Foundation.

Availability of data and materials

All data related to this study are available in the public domain.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 15 April 2025 / Accepted: 30 July 2025
Published online: 26 August 2025

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