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Abstract

Background: Chronic cerebrospinal venous insufficiency (CCSVI) has been proposed as a possible cause of multiple sclerosis (MS).
Objectives: The CoSMo study evaluated the association between CCSVI and MS.
Methods: The primary end-point of this multicentric, case-control study was to compare the prevalence of CCSVI between patients with MS, patients with other neurodegenerative diseases (ONDs) and healthy controls (HCs). Color-coded duplex sonography was performed by a sonologist and the images were sent to one of three central sonologists for a second reading. Agreement between local and central sonologists or, in case of disagreement, the predominant judgment among the three central readers, was required for a diagnosis of CCSVI. All readings, data collection and analysis were blinded.
Results: The study involved 35 MS centers across Italy and included 1874 subjects aged 18–55. 1767 (94%) were evaluable: 1165 MS patients, 226 patients with ONDs and 376 HCs. CCSVI prevalence was 3.26%, 3.10% and 2.13% for the MS, OND and HC groups, respectively. No significant difference in CCSVI prevalence was found amongst the three cohorts (MS versus HC, OR = 1.55, 95%CI = 0.72–3.36, $p = 0.30$; OND versus HC, OR = 1.47, 95%CI = 0.53–4.11, $p = 0.46$; MS versus OND, OR = 1.05, 95%CI = 0.47–2.39, $p = 0.99$). High negative and low positive agreement was found between the local and centralized readers.
Conclusions: CCSVI is not associated with MS.

Keywords

Chronic cerebrospinal venous insufficiency, circulatory system, Italy, multicentric study, multiple sclerosis, neurodegenerative disease, prevalence study, sonography

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Introduction

In 2009, Zamboni et al. proposed that anomalous cerebrospinal venous return due to multiple stenoses of the jugular veins, vertebral veins and azygous veins, a condition called chronic cerebrospinal venous insufficiency (CCSVI), could be the cause or one of the causes of multiple sclerosis (MS).[1] This abnormal condition was detected in almost all MS patients in their study by means of a high-resolution echo color Doppler (ECD) and transcranial color-coded Doppler sonography (TCCS), with a sensitivity, specificity and predictive positive/negative value of 100%. They suggested that the increased venous pressure may result in colloids, lymphocyte and erythrocyte extravasation, with an inflammatory reaction in the brain and spine.[1] The strong association of CCSVI to MS found in this initial study was considered a proof of the pathogenetic theory.[1] Angioplasty of jugular veins, the so-called "liberation therapy," was then proposed to correct these venous abnormalities,[2] with claims of beneficial effects on disease activity and burden.

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The strong impact that these claims had on the MS community hastened attempts to confirm these findings. As a consequence of this pressure, the majority of epidemiological studies on the association between CCSVI and MS were of small sample size and monocentric design. Most were performed by blinded operators, but only few had a second reader to give a diagnosis by double-checking the scans and completely avoiding any contact with the study subject. An extensive overview of the studies performed to date on the possible association between CCSVI and MS is presented in Table 1. The most important limitations of these studies are also summarized.[1,3–24]

Many of these studies failed to confirm the strong association reported by Zamboni.[5–9,12,14] Two independent systematic reviews point towards a possible association between CCSVI and MS; however, owing to the substantial variation in the strength of this association, lack of blinding and heterogeneity between studies, definitive conclusions could not be made.[25,26] Furthermore, the occurrence of serious adverse events following interventional procedures led national health authorities and scientific societies to produce clear statements on this topic.[27–29] Overall, this issue has both concerned and confused the MS community.

In late 2010, the "Fondazione Italiana Sclerosi Multipla" (FISM) funded this large epidemiological study to evaluate the association between CCSVI and MS. The rationale, study design and methodology were recently published.[30] The primary objective of the CoSMo study, named after the Italian words "CCSVI: Studio Osservazionale Sclerosi Multipla e OND," which translates to Observational Study of the prevalence of CCSVI in multiple sclerosis and OND, is to compare the prevalence of CCSVI in MS patients, healthy controls (HCs) and patients with other neurological diseases (ONDs). The secondary objectives are the evaluation of the correlation of CCSVI with demographic and clinical parameters.

Patients and methods

The CoSMo study methods are described in detail elsewhere.[30]

Study design and participants

CoSMo was an observational, case-control, cross-sectional, multicentric study, where MS patients, HCs and patients with ONDs were recruited in a competitive manner from centers throughout Italy. All examiners and data analysts were blinded. Subject recruitment began in November 2010 and ended in June 2012. Male and female individuals aged between 18–55 years were included in the study. Exclusion criteria for all groups were: the presence of any acute or chronic invalidating disease/s which could interfere with the objective of the study.

The MS group included patients with either relapsing–remitting (RR), secondary progressive (SP), or a primary progressive (PP) course, with disease duration between 1 month and 25 years before the screening visit; and patients with clinically-isolated syndrome (CIS) with a maximum disease duration of 5 years. Patients could not be in clinical relapse (at least 30 days since the last relapse). The second group included HCs, namely subjects without any relevant disease and without any family history of MS or family relation to another MS patient. The third group included patients with OND. Two subtypes of patients were included in the OND group: patients with neurodegenerative diseases (ONDn), such as Parkinson's disease or amyotrophic lateral sclerosis; and patients with inflammatory CNS disorders (ONDi), such as neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), encephalitis and neuro-systemic lupus erythematosis.

This study was approved by the Ethics Committee of each study center. We obtained written informed consent from all patients and healthy controls participating in the study. The CoSMo study was registered at ClinicalTrials.gov (NCT01384825).

Procedures

The primary end-point of the CoSMo study was to compare the prevalence of CCSVI among the three study subgroups. In order to have a positive CCSVI diagnosis, study subjects needed to fulfill at least two of the five criteria previously described by Zamboni[1]:

- Reflux in the internal jugular veins (IJVs) and/or vertebral veins (VVs);
- Reflux in deep cerebral veins;
- Presence of proximal IJV stenosis or other anatomical abnormalities;
- Absence of flow in IJVs and/or VVs; or
- Negative difference between the cross-sectional area (CSA) of the IJV in the supine position and the CSA in the upright position.

CCSVI assessment was performed after color-coded duplex (CCD) examination, carried out by a trained sonologist in a blinded manner. To maintain blinding, we instructed subjects not to communicate with the examiner and their bodies were covered to avoid revealing any evidence of medication by injection. The sonologist entered the examination room only after the patient was positioned on the bed. A specific training and final examination were required for each sonologist, in order to address possible limitations attributed to poor training and to guarantee uniform behavior in performing the examination. After the local sonologists performed the investigation and made their diagnoses, all images and video clips of the CCD examination were

Table 1. Studies on the association between CCSVI and MS.

Study		Number of patients			Single or multi-centric	Blinding	Criteria adopted	Method adopted	Inter-observer variability assessed	Conclusion	CCSVI associated with MS (Y/N)
First author	Yr	MS	HC	OND							
Zamboni[1] (First paper published about CCSVI link to MS)	2009	65	190	45	Single	Ultrasound techs and MDs who interpret data are blinded to patient diagnosis	Zamboni's	TCCS-ECD	No	CDMS is strongly associated with CCSVI	Yes
Zamboni[3]	2009	16	8		Two centers	Investigators blinded to subjects' characteristics	Zamboni's	ECD and advanced MRI	No	Venous outflow disturbances in the form of CCSVI significantly impact MS patient's CSF pathophysiology	Yes
Al-Omari[4]	2010	25	25		Single	No	Zamboni's	Doppler ultrasound	No	Hemodynamic abnormalities and morphological changes involving IJVs strongly associate with MS	Yes
Doepp[5]	2010	56	20		Single	No	Zamboni's	Extended extra- and TCCS	No	No evidence that cerebral venous congestion plays a role in MS pathogenesis	No
Worthington[6]	2010	52	1063 (with headache)	286 (siderosis, ME or SAH)	Single	No	CSF ferritin levels	ELISA after lumbar puncture	No	No evidence of etiologic role for CCSVI-related parenchymal iron deposition in MS	No
Baracchini[7]	2011	60	60		Single	Blinded neuro-sonographer	Zamboni's	ECDS-TCDS	No	CCSVI is not a late secondary phenomenon in MS; it is not associated with disability	No
Centonze[8]	2011	86	56		Single	Blinded ECD operators	Zamboni's	ECD evaluation	No	CCSVI has no role in MS risk nor MS severity	No
Mayer[9]	2011	20	20		Single	Sonographer, data analyzer, statistician were blinded to subject status	Zamboni's	CCD sonography	No	No evidence supports presence of CCSVI in MS patients	No
Tsivgoulis[10]	2011	42	43		Single	Blinded sonographers	Zamboni's	CCD sonography	15 patients assessed for intra- and inter-rater reliability of CCSVI ultrasound criteria	No evidence CCSVI is the underlying mechanism of MS	No

(Continued)

Table 1. (Continued)

Study		Number of patients			Single or multi-centric	Blinding	Criteria adopted	Method adopted	Inter-observer variability assessed	Conclusion	CCSVI associated with MS (Y/N)
First author	Yr	MS	HC	OND							
Zivadinov[11]	2011	310	163	26	Single	Rater-blinded	Zamboni's	ECD evaluation	No	Increased prevalence of CCSVI in MS, but with modest sensitivity/ specificity. No evidence CCSVI has a primary causative role in MS development	Y/N
Amato[12]	2012	15	16		Single	Blinded local and central neuro-sonologists	Zamboni's	CCD sonography	Yes	Evidence against a causative role of CCSVI in MS	No
Barreto[13]	2012	206	11	37 + 22 CVD	Single	Blinded neurosonologist	Zamboni's	High resolution B-mode image, with color, spectral Doppler	No	CCSVI not causally associated with MS	No
Blinkenberg[14]	2012	24	15		Single	Blinded MRI and ultrasound investigators	Zamboni's	Extra-cranial high-resolution US-CD, TCDS, MRI, and PC-MR	No	No evidence of vascular pathology in RRMS; no evidence to support CCSVI hypothesis	No
Chambers[15]	2012	70	70		Single	Blinded ultrasound operators	Zamboni's	Doppler ultrasound	No	CCSVI is not present in CIS and mild RRMS, but apparent increase in IJV variation	Y/N
Ciccone[16]	2012	277			Single	Blinded ECD operators	Zamboni's	ECD evaluation	32 patients assessed	MS and CCSVI associated	Yes
Floris[17]	2012	40	34		Single	Blinded operators	Zamboni's	CDUS	No	Slight difference in CCSVI prevalence between MS and HC, but not statistically significant	Y/N
McTaggart[18]	2012	19	20		Single	Blinded neuroradiologists	Flattening and collaterals of IJV	2D-TOF neck MRV and TRICKS MRV	Assessed between two local neuroradiologists	MS patients have > IJV flattening and a trend toward more non-IJV collaterals than HCs	Yes
Patti[19]	2012	168	172	40	Single	Blinded central expert evaluators and blinded local evaluator	Zamboni's	ECD evaluation	No	Found higher frequency of CCSVI in MS patients, more evident if advanced MS. Suggests that CCSVI could be related to MS disability	Yes

Table 1. (Continued)

Study		Number of patients			Single or multi-centric	Blinding	Criteria adopted	Method adopted	Inter-observer variability assessed	Conclusion	CCSVI associated with MS (Y/N)
First author	Yr	MS	HC	OND							
Zaniewski[20]	2012	181	50		Single	No	Outflow disturbances, morphological abnormalities present in IJVs, VVs	Doppler ultrasound	No	Possible connection between MS and CCSVI	Yes
Imperiale[21]	2013	80	41	26	Single	Blinded sonographer	Zamboni's	Trans-cranial and extra-cranial ECD	No	No association between MS and CCSVI	No
Lanzillo[22]	2013	146	38		Single	Off-line reading by 2 blinded sonographers, ECD images collected by an un-blinded sonographer	Zamboni's	Color Doppler sonography	Yes	CCSVI associated with patients' age	Y/N
Leone[23]	2013	68	68		Single	Blinded neurosonologists	Zamboni's	ECD examination	No	No association of CCSVI with MS, nor its severity	No
Van den Berg[24]	2013	90	41		Single	Rater-blinded	Zamboni's	Extra- and trans-cranial ECD + iron metabolism + peripheral signs of impaired venous flow	No	CCSVI is uncommon, is a secondary epi phenomenon in MS	No
Comi (present CoSMo study)	2013	1165	376	226	Multicentric	Blinded local and central readers, data analyzers, statistician	Zamboni's	CCD sonography	Variability assessed between local and central reader	CCSVI prevalence is very low; not significantly associated with MS nor OND	No

2D-TOF; 2-dimensional time-of-flight; CCD: color-coded duplex; CCSVI: chronic cerebrospinal venous insufficiency; CDMS: clinically defined multiple sclerosis, CDUS: color-doppler ultra-sound; CIS: Clinically Isolated Syndrome; CSF: cerebro-spinal fluid; CVD: cerebrovascular disease; ECD: echo color Doppler; ECDS-TCDS: extracranial and transcranial high-resolution venous echo color Doppler sonography; ELISA: enzyme-linked immunosorbent assay; HC: healthy controls; IJV: internal jugular vein; ME: meningo-encephalitis; MRI: magnetic resonance imaging; MRV; magnetic resonance venogram; MS: multiple sclerosis; OND: other neurodegenerative disease; PC-MR: phase-contrast magnetic resonance blow flow measurements; RRMS: relapsing–remitting multiple sclerosis; SAH: subarachnoid hemorrhage; TCCS: transcranial color-coded sonography; TCDS: transcranial color Doppler sonography; TRICKS: time-resolved imaging of contrast kinetics; US-CD: ultrasound color Doppler; VV; vertebral vein; Y/N: yes or no; Yr: year.

Table 2. CoSMo study subjects.

Subjects	*N*	Age (years, mean ± SD)	Women, *n* (%)	Disease duration (years, mean ± SD)	EDSS
MS	1165	39.9 ± 8.6	768 (65.9)	8.1 ± 6.3	2.7 ± 2.0
CIS	104	33.9 ± 8.7	54 (51.9)	1.4 ± 1.4	1.0 ± 0.9
RR	839	38.9 ± 8.2	398 (47.4)	7.9 ± 5.8	2.1 ± 1.5
SP	159	45.7 ± 6.5	109 (68.6)	13.5 ± 6.2	5.7 ± 1.4
PP	63	48.4 ± 4.8	38 (60.3)	7.8 ± 5.6	5.5 ± 1.7
HC	376	37.8 ± 10.1	192 (51.1)		
OND	226	44.3 ± 9.0	122 (54.0)		
Total population[b]	1767	40.0 ± 9.2	1082 (61.2)		

[b]1874 subjects enrolled: 52 were excluded for technical problems and 55 for protocol violations.
CCSVI: Chronic cerebrospinal venous insufficiency; CIS: clinically-isolated syndrome; CoSMo: Italian abbreviation for present study about prevalence of CCSVI as it relates to MS; EDSS, Expanded Disability Status Score; HC: healthy controls; MS: multiple sclerosis; N or n: number of subjects; OND: other neurological disease; PP: primary progressive; RR: relapsing–remitting; SD: standard deviation; SP: secondary progressive.

sent at random to one of the three central expert sonologists (three of the authors), whom performed a second blinded reading. If the CCSVI (presence/absence) diagnosis matched, the final report was issued for that patient. If there was no agreement between the local and central examiners, the other two central readers would perform independent readings and the one which was accepted by at least two of the three central sonologists became the final diagnosis.

Statistical analysis

We calculated study size in order to guarantee a power of 80% at a 5% significance level, to detect an association of CCSVI with MS, described by odds ratios (ORs) ranging from OR = 2 (MS versus HC and MS versus OND) in the case of a low CCSVI prevalence in the HC reference group (5%), to OR = 1.50 in the case of a high prevalence of CCSVI in the HC reference group (30%). We compared CCSVI prevalence in MS patients and HCs or patients with ONDs by the Chi-squared test. CCSVI prevalence was calculated, along with its 95% confidence interval (CI), in the three study groups. We calculated the strength of the association by ORs and their 95% CI. An additional aim of this study was to evaluate CCSVI prevalence in the MS subgroups (CIS, RR, SP and PP). We evaluated differences in CCSVI prevalence among MS subgroups by Chi-squared test for heterogeneity and for trend. The impact of other risk factors (age, sex, sonological center, geographical region, echograph) on CCSVI prevalence was evaluated by logistical regression analysis (a penalized regression model was used to assess the single sonologic center effect). We assessed agreement between the local sonologist and central reader by Cohen kappa statistic, along with positive/negative agreement.[31]

Results

The CoSMo study enrolled 1874 subjects: 52 were excluded for technical reasons related to the CCD exam and registration, and 55 because of protocol violations (age, disease duration, associated pathologies). Therefore, the final analysis was performed on 1767 persons, including 1165 MS patients, 226 patients with ONDs and 376 HCs. Table 2 summarizes the main characteristics of the study subjects. Patients with ONDs were significantly older than both MS and HCs ($p < 0.001$) and, in the MS group, a significantly higher prevalence of females was observed, compared to both groups of HC and OND patients ($p < 0.001$). MS group disability, measured by the "Expanded Disability Status Score" (EDSS), was associated with increased age, and, with the exception of the PP form, with disease duration.

Recruiting centers ($n = 35$) were distributed over the entire Italian territory. For further details on participating centers, see supplemental Table A1 (in Appendix).

CCSVI prevalence for all three study groups, the primary end-point of the CoSMo study, was 3.00%, with a 95% CI = 2.28%–3.93%: Specifically, prevalence was 3.26% in MS patients, 3.10% in OND patients and 2.13% in HC. No statistically significant difference was observed among these three study groups (MS versus HC: OR = 1.55, 95% CI = 0.72–3.36, $p = 0.30$; OND versus HC: OR = 1.47, 95% CI = 0.53–4.11, $p = 0.46$; MS versus OND: OR = 1.05, 95% CI = 0.47–2.39, $p = 0.99$). MS patient subgroup analysis did not reveal an association between CCSVI and disease course (Figure 1). Although the PPMS form had a slightly higher CCSVI prevalence, it did not attain statistical significance.

The overall CCSVI prevalence in the local readings was significantly higher, as compared to the first central reading (14.9% versus 3.2%; $p < 0.001$); however, there was no difference in prevalence among the three groups (MS versus HC: OR = 1.39, 95% CI = 0.98–1.97, $p = 0.07$; OND versus HC: OR = 1.30, 95% CI = 0.80–2.10, $p = 0.28$; MS versus OND: OR = 1.07, 95% CI = 0.72–1.59, $p = 0.84$). Even though CCSVI prevalence among the three study groups was comparable, overall CCSVI prevalence according to

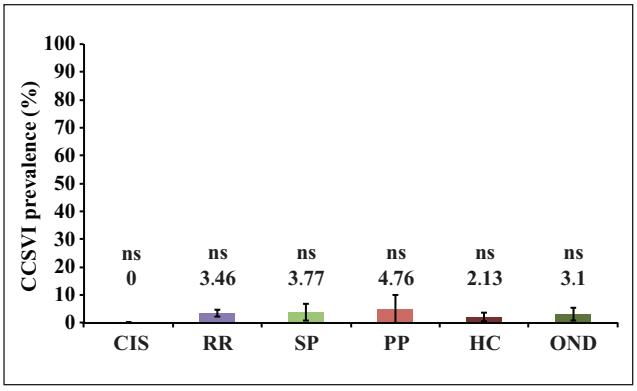

Figure 1. CCSVI prevalence in multiple sclerosis patient subgroups.
CCSVI: Chronic cerebrospinal venous insufficiency; CIS: clinically isolated syndrome; RR: relapsing–remitting (MS subtype); SP: secondary progressive (MS subtype); PP: primary progressive (MS subtype); HC: healthy controls; MS: multiple sclerosis; OND: other neurodegenerative diseases; ns: no statistically significant difference found after chi-square test for heterogeneity.

local readings had a very high degree of variability (p for heterogeneity = 0.013) among sonology centers.

For the central reading, the frequency of CCSVI in the three groups overlapped with results of the primary analysis, with no differences among the three groups (MS versus HC: OR = 1.02, 95% CI = 0.53–1.98, $p = 0.99$; OND versus HC: OR = 0.83, 95% CI = 0.31–2.23, $p = 0.31$; MS versus OND: OR = 1.24, 0.52–2.96, $p = 0.84$), separately.

The CCSVI risk factor analysis, by univariate and multivariate regression, is summarized in Table 3. We grouped sonologic centers according to geographical region, in order to obtain a sufficient number of cases in each group to be included in the multivariate model. Following univariate analysis, factors significantly associated with CCSVI were: geographical region ($p = 0.013$) and the ultrasound machine used for the CCD exam ($p = 0.011$). Multivariate analysis revealed that the only factor associated with CCSVI prevalence was the geographical region ($p < 0.001$). For further details on frequency of CCSVI in the three populations for each of the different regions, see supplemental Table A2 (Appendix).

Agreement between the local sonologists' CCSVI diagnosis and the central expert reader diagnosis was very low. Table 4 displays the frequency of agreement in the positive and negative diagnosis between local and central readers. Kappa statistics test was 13% (standard error = 3%). The negative agreement was 92% and the positive agreement was 18%.

Among the 28 subjects where agreement in CCSVI-positive diagnosis ocurred, single Zamboni's criteria agreement between local and central reading was also variable. Approximately one-half of subjects were diagnosed positive for CCSVI according to the same two criteria, predominantly criteria number one and number three. The rest disagreed on criterion number one.

Discussion

Results from the CoSMo study indicate that the prevalence of CCSVI in patients with MS and ONDs is extremely low (2–3%), and not significantly different among MS patients, OND patients or HCs. A higher frequency of CCSVI in progressive MS compared to RRMS was previously reported,[11] whereas no differences related to disease course emerged in this study, and there was no correlation between CCSVI and disability. These findings do not support an association between MS and CCSVI.

Since Zamboni et al. first reported a high prevalence and strong association between CCSVI and MS,[4,19] other groups tried to replicate these findings, with varying degrees of success. Whilst some investigators claim to confirm Zamboni's findings,[1,10,12,14,18] other groups did not report any abnormality in the cerebrospinal venous outflow in MS patients, providing compelling evidence against a significant contribution of CCSVI in the pathogenesis of MS disease (Table 1).[2,3,5,7,8,16,17] Although two independent systematic reviews point towards a possible association between CCSVI and MS, definitive conclusions could not be made, owing to the substantial variation in the strength of the association, lack of blinding and heterogeneity between studies.[20,25] Previous studies about CCSVI have limitations, such as: lack of an adequate number of controls, monocentric design and incorrect/absent blinding (Table 1). To address these, we adopted a stringent methodology in the design of the CoSMo study, whereby blinding procedures were adopted by local and central readers, a multicentric design was used and the study included a large sample size, appropriate controls and healthy individuals.

In our study, the difference in the prevalence of CCSVI between the participating centers was high, with centers having a prevalence of CCSVI of around 50–60% of examined cases and centers with a prevalence of approximately zero. This variability can be explained by the individual propensity of the local examiner to "see" the ultrasound abnormalities; however, because of the blindedness, this propensity produces the same effects across the three groups. Indeed, in centers with very high levels of CCSVI positivity, "the believers", there never was a difference in CCSVI prevalence among the three groups. Other factors may have contributed to the inter-center variability of results, including examiner expertise and type of instrument used. The multicentric design and large sample size of the CoSMo study partially controlled for instrument variation at the local level, whereas complete blinding of the central reader further controlled for inter-user variability and subjectivity at the local level.

While recruitment of unimpaired or minimally-impaired patients may account, to some extent, for the differences observed between CoSMo and other studies, methodological limitations are the most plausible and robust explanation for the almost unprecedented degree of discrepancy that characterizes the literature on CCSVI. The maintenance of a

Table 3. CCSVI risk factors.

Factor	Risk criteria	OR	*P* value[c]
Group	MS	1 (ref)	0.54[d]
	HC	0.65 (0.30–1.39)	
	OND	0.95 (0.42–2.15)	
Age	Years	0.99 (0.97–1.03)	0.83
Sex	Female versus male	0.97 (0.55–1.67)	0.90
Region[e]	North	1 (ref)	0.013
	Center	0.38 (0.15–0.79)	
	South	0.15 (0.001–1.09)	
	Sardinia	0.41 (0.04–1.57)	
	Sicily	1.29 (0.63–2.48)	
Ultrasound device	Esaote	1 (ref)	0.011
	Acuson	1.88 (0.89–4.00)	
	Toshiba	0.96 (0.36–2.57)	
	Philips	0.35 (0.08–1.55)	
	General Electric	2.37 (1.13–4.93)	

[c]test for heterogeneity
[d]HC versus MS: p = 0.27; OND versus MS: p = 0.90
[e]Sonologic centers grouped according to regions in Italy. The heterogeneity test among single sonologic centers was found to be highly significant (p = 0.013).

Table 4. Agreement on CCSVI diagnosis between local and central readers.

		Central reading		
		No	Yes	Total
Local reading	No	1475	28	1503
	Yes	236	28	264
	Total	1711	56	1767

Cohen Kappa = 13% (SE = 3%)
Negative agreement = 92% (90%–93%)
Positive agreement = 18% (13%–22%).
CCSVI: Chronic cerebrospinal venous insufficiency; SE: standard error

local and central blinded analysis is a significant improvement over previous studies, where often the real blindness of the sonologist was uncertain. Ultrasound investigation of veins is susceptible to rater bias, because of the unfavorable signal-to-noise ratio of the vein signals. Moreover, many factors influence the results of the ultrasound examination of neck veins, including hydration status and level of compression by the ultrasound transducer.[32] Therefore, blinding of the rater is fundamental. Some involuntary unblinding may have occurred in the local analysis, because the examiner may have perceived some level of disability in patients with MS or ONDs; on the contrary, the central reader was completely blind. The results of the central readings show almost identical prevalence in HCs and MS (3.19% versus 3.26%). Interestingly, local readings show almost identical prevalence in the MS and OND groups (15.8% versus 15.0%, respectively), with a trend toward lower prevalence in HCs (11.9%).

While there was good agreement between the local and central examiners with regard to the absence of CCSVI, there was, on the contrary, poor agreement in the positive diagnosis of CCSVI. It is likely that this problem is related to the already discussed problems of the CCD examination; however, the intrinsic characteristics of the criteria proposed by Zamboni for the diagnosis of CCSVI may represent another factor accounting for the variability of these results. Most of these criteria have been criticized both for conceptual and technical reasons.[9,32] The absence of an abnormality is easily recognized, but the presence of a change is not uniformly evaluated by ultrasound readers. In this context, it is worth noting that results variability in the literature, but also within a single multicentric study, and the very low presence of CCSVI when confounders are controlled through central reading, pose the basic question of whether CCSVI does exist as a syndrome,[33] i.e. an association of clinically-recognizable features that, together, are linked to a disease state. At present, the answer is no.

Conclusions

Findings from the CoSMo study do not support the role of CCSVI as a recognizable clinical condition that is causally related to the development or progression of MS. The prevalence of CCSVI, detected in a multicentric setting by a shared local and central assessment, was very low and was not significantly associated with MS. Based on the lack of evidence of CCSVI in MS that emerged from this CoSMo study, we do not recommend vascular intervention in MS patients.

Declaration of conflicting interests

GC received consulting fees for participating on advisory boards from Novartis, TEVA, Sanofi-Aventis, Merck-Serono and Bayer-

Schering; lecture fees from Novartis, TEVA, Sanofi-Aventis, Merck-Serono, Biogen-Dompè, Bayer-Schering and Serono Symposia International Foundation. He is a member of the Board of the Italian MS Foundation.

LT, MAB and PZ are members of the Board of the Italian MS Foundation.

AB has been on steering committees in clinical trials sponsored by Biogen-Idec and Roche; has received speaker's honoraria from Biogen-Idec, Merck-Serono, TEVA, Bayer-Schering, Sanofi-Aventis and Novartis; has received research support from Biogen-Idec, Bayer-Schering, Merck-Serono, Sanofi-Aventis, the Italian Multiple Sclerosis Society and the European Union Sixth Framework Program.

GM, ES and MDS report no disclosures.

AG received speaker's honoraria from Bayer-Schering, Biogen-Dompè, Merck-Serono, Novartis, Sanofi-Aventis and Allergan; payment for consulting from Actelion, Merck-Serono, TEVA and Novartis; support for participating in National and International Congresses from Bayer-Schering, Biogen-Dompè, Merck-Serono, Novartis and Sanofi-Aventis.

MS receives grant support from Bayer-Schering, Merck-Serono, Sanofi-Aventis and Biogen-Idec.

MPS received consulting fees or honoraria from Biogen-Idec, Merck-Serono, Actelion, Synthon and TEVA.

GLM received honoraria for lecturing; travel expenses for attending meetings and financial support for research from Bayer-Schering, Biogen-Idec, Sanofi-Aventis, Novartis and Merck-Serono. He is a member of the Board of the Italian MS Foundation.

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Notes

There were many contributors to the study. All authors read and approved the final manuscript. GC and GLM were the principal investigators of the CoSMo study. GC, MAB, AB, MDS, AG, GM, MS, MPS, LT, ES, PZ and GLM were members of the steering committee. MDS, ES and GLM were the expert central examiners for the centralized readings. MPS performed all statistical analysis.

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