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Prevalence of intracranial artery stenosis in a general population using 3D-time of flight magnetic resonance angiography

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ABSTRACT

Background: Data on prevalence of intracranial artery stenosis (ICAS) in Western populations is sparse. The aim of the study was to assess the prevalence and risk factors for ICAS in a mainly Caucasian general population.
Methods: We assessed the prevalence of ICAS in 1847 men and women aged 40 to 84 years who participated in a cross-sectional population-based study, using 3-dimensional time-of-flight 3 Tesla magnetic resonance angiography. ICAS was defined as a focal luminal flow diameter reduction of ≥50 %. The association between cardiovascular risk factor levels and ICAS was assessed by multivariable regression analysis.
Results: The overall prevalence of ICAS was 6.0 % (95 % confidence interval (CI) 5.0–7.2), 4.3 % (95 % CI 3.1–5.7) in women and 8.0 % (95 % CI 6.3–10.0) in men. The prevalence increased by age from 0.8 % in 40-54 years age group to 15.2 % in the 75-84 years age group. The majority of stenoses was located to the internal carotid artery (52.2 %), followed by the posterior circulation (33.1 %), the middle cerebral artery (10.8 %) and the anterior cerebral artery (3.8 %). The risk of ICAS was independently associated with higher age, male sex, hypertension, hyperlipidemia, diabetes mellitus, current smoking and higher BMI.
Conclusions: The prevalence of ICAS in a general population of Caucasians was relatively high and similar to the prevalence of extracranial internal carotid artery stenosis in previous population-based studies.

Introduction

Intracranial artery stenosis (ICAS) is a common cause of stroke in Asians, Hispanics and African Americans[1–4], with high risk of stroke recurrence.[4,5] In Caucasians extracranial carotid artery atherosclerosis has been considered the predominant cause of stroke, whereas ICAS has been of minor importance,[5,6] but the real impact of ICAS in western populations may however have been underestimated.[7–9]

The reported prevalence of ICAS varies with study design and study population and is dependent on diagnostic criteria and examination modality. A French autopsy study of 333 patients with fatal stroke found ICAS in 43 % of the cases[10] and a Chinese autopsy study of 114 patients reported ICAS in 31.4 %.[11] A review of 48 imaging-based studies of patients with TIA or ischemic stroke estimated that 12.1 % of Caucasians had at least one intracranial stenosis.[6,12]

Data on prevalence of ICAS in the general population is limited. Population-based studies have mainly been conducted on Asian populations, with prevalence ranging from 4.7 to 15.7 %.[13,14] The

Abbreviations: ICAS, intracranial artery stenosis; ECAS, extracranial carotid artery stenosis; TOF-MRA, time-of flight magnetic resonance angiography; MRA-WASID method, The Warfarin-Aspirin Symptomatic Intracranial Disease method on TOF-MRA; MRA-VICAST method, Visual grading system for IntraCranial Arterial STenosis on TOF-MRA.

All authors can be contacted by calling the University Hospital of North NorwayThe imaging in this study was performed at the Department of Radiology, University Hospital of North Norway. All authors are academically affiliated to the Department of Clinical Medicine, Faculty of Medicine, UiT The Arctic University of Norway, Tromsø, Norway.Cover title: Prevalence of intracranial artery stenosis in a general population

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Atherosclerotic Risk in Communities (ARIC) study reported a prevalence of 8 % in Caucasians.[15] In the Barcelona-Asymptomatic Intracranial Atherosclerosis (AsIA) study, the reported prevalence of ICAS >50 % was 3.3 %.[16,17]

In the population-based Rotterdam study, calcification of the intracranial internal carotid artery on non-contrast enhanced computer tomography (CT) was used as a surrogate marker for intracranial atherosclerosis, which was found in 82 % of the participants.[18]

In the present study, we aimed to determine the prevalence, distribution and severity of ICAS ≥ 50 % in a general Norwegian population aged 40 years and older using 3D-TOF 3T MRA, and to study the association between presence of ICAS and cardiovascular risk factors.

Material and methods

Study participants

Started in 1974, the Tromsø Study is a large longitudinal and multipurpose population health study of adult inhabitants in the municipality of Tromsø.[19,20] The study design is repeated cross-sectional surveys to which total birth cohorts and selected samples are invited, based on the official population registry. We invited 3027 men and women who participated in the seventh survey in 2015–2016 to participate in a magnetic resonance imaging (MRI) study. Of these, 975 did not respond, 169 were excluded because of contraindications for MRI, and five had moved or died before the MRI examination. We excluded participants with missing images ($n = 8$), insufficient image quality ($n = 16$), extracranial internal carotid artery occlusion evaluated on ultrasound examination ($n = 4$), generalized intracranial artery disease (moya-moya and vasculitis; $n = 2$), and one participant who withdrew his/her consent, leaving 1847 participants in the final analysis. Details on the sampling and flow chart (Supplemental Figure I) of participants are provided in the Supplemental material.

Cardiovascular risk factors

Information on smoking habits, physical activity, use of medication and cardiovascular disease was obtained from questionnaires. Standardized measurements of blood pressure, height and weight were recorded by trained personnel. Serum total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and hemoglobin A1c (HbA1c) were analyzed by standard enzymatic methods. Diabetes was defined as HbA1c ≥6.5 % and/or self-reported diabetes and/or use of diabetes medication. Hypertension was defined as mean systolic blood pressure ≥140 mmHg and/or mean diastolic blood pressure ≥ 90 mmHg and/or use of blood pressure-lowering medication and/or self-reported hypertension. Hyperlipidemia was defined as serum total cholesterol ≥7 mmol/L and/or serum LDL ≥5 mmol/L and/or use of cholesterol lowering medication.

MR angiography and assessment of intracranial artery stenosis

Participants were scanned at the University Hospital of North Norway, Tromsø, with a 3 Tesla (3T) Siemens Skyra MR scanner (Siemens Healthcare, Erlangen, Germany). We used 3D time-of-flight MRA (3D-TOF-MRA) acquired with a 3D transversal fast low angle shot sequence with flow compensation; repetition time/echo time 21/3.43 ms, parallel imaging acceleration factor 3, field of view 200 × 181 mm, slice thickness 0.5 mm, 7 slabs with 40 slices each and reconstructed image resolution of 0.3 × 0.3 × 0.5 mm. Maximum intensity projection (MIP) reconstructions and volume-rendered (VR) reconstructions of the source images were made to optimize stenosis detection.

Images and reconstructions were evaluated by two experienced neuroradiologists (MH and LHJ) on a Sectra workstation, Sectra IDS7 (v22.1.12.4835). ICAS was defined as a ≥50 % focal narrowing of the intracranial arterial flow diameter. Stenosis location was defined as the petrocavernous and the supraclinoid segments of the internal carotid artery (ICA), the A1/A2 segments of the anterior cerebral artery (ACA), the M1/M2 segments of the middle cerebral artery (MCA), the intracranial vertebral arteries, the basilar artery and the P1/P2 segments of the posterior cerebral arteries (PCA).

We used two different grading methods: 1) the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) method,[21] and 2) the MRA-VICAST method.[22] The WASID method, originally developed for digital subtraction angiography (DSA), calculates degree of stenosis by measuring the diameter at the site of the stenosis and at a reference site in the same artery proximal to the stenosis. Measurements were made both on fixed reconstructed MIP images and orthogonal on the vessels with multiplanar reconstructed (MPR) images. The MRA-VICAST method is a recently proposed visual grading system for intracranial arterial stenosis on MRA based on physical characteristics of the TOF-MRA. The signal intensity and flow diameter in the artery distal to the site of stenosis assessed on MIP images is used to evaluate the grade of stenosis which is classified into four groups according to severity of stenosis: < 50 % (mild), 50 %-69 % (moderate), 70-99 % (severe) and 100 % (occlusion). We were not able to successfully apply the MRA-VICAST method in the petrocavernous and supraclinoid part of ICA, consequently only the MRA-WASID method was used in these segments.

Cohen's kappa (κ) for interobserver agreement on ICAS ≥ 50 % was 0.76 (SE 0.02). κ for inter-method agreement (MRA-WASID vs. MRA-VICAST) was 0.81 (SE 0.02). Details on interobserver and inter-method agreement are available in the Supplemental material.

A stenosis measured as ≥45 % by the MRA-WASID method and/or a moderate/severe stenosis assessed by the MRA-VICAST method induced additional assessment by both observers to reach consensus.

Statistical analysis

The data were analyzed with Stata for Mac (version 17: StataCorp LP, TX). Continuous variables are presented as means with standard deviations (SD) and categorical variables as counts (percentages). Differences between participants with and without ICAS were evaluated using a two-sample t-test for summary data, and z-test was used to compare proportions in one sample. Prevalence of ICAS is presented stratified by sex and age groups.

Logistic regression was used for calculating the odds ratio (OR) of the association between cardiovascular risk factors and presence of ICAS. The analyses were performed in univariable models (Model 1), of each variable adjusted for age and sex (Model 2), and in multivariable analyses of all risk factors (Model 3). All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant.

Results

A total of 157 ICAS were found in 111 of the 1847 participants. The mean age of participants was 63.8 (SD ±10.6) years and 53.2 % were women. Participants with ICAS had higher BMI, lower HDL and higher total cholesterol, and higher proportions of hypertension, diabetes, cardiovascular disease and use of lipid-lowering and antihypertensive medication than participants without ICAS (Table 1). LDL levels and current smoking status were similar in the two groups. There was a 15-fold increase in prevalence from the 40-54 years age group to the 75-84 years age group (Table 2). Twelve percent of participants with ICAS reported previous stroke compared to 2.4 % in those without ICAS.

The distribution of ICAS per arterial segment showed that 52.2 % were located to the ICA, 33.1 % in the posterior circulation, 3.8 % in the ACA and 10.8 % in the MCA (Table 3). The degree of stenosis was moderate (50 %–69 %) in the majority of vessels (80.9 %). The per participant prevalence of ICAS was 3.8 % in the ICA, 0.3 % in ACA, 0.8 % in MCA and 2.3 % in the posterior circulation (Table 4).

The risk of ICAS was independently associated with higher age (OR

Table 1
Characteristics of participants with and without intracranial arterial stenosis (ICAS)*.

	All participants (n = 1847)	ICAS* (n = 111)	No ICAS (n = 1736)	p-value
Male sex, n (%)	864 (46.8)	69 (62.2)	795 (45.8)	<0.001
Age (years), mean (SD)	63.8 (10.6)	72.4 (7.5)	63.3 (10.5)	<0.001
Body mass index, kg/m2	27.1 (4.2)	28.2 (3.9)	27.0 (4.2)	0.006
Serum total cholesterol, mmol/L	5.51 (1.10)	5.30 (1.21)	5.53 (1.10)	0.035
Serum HDL cholesterol, mmol/L	1.63 (0.50)	1.45 (0.36)	1.64 (0.51)	<0.001
Serum LDL cholesterol, mmol/L	3.58 (1.02)	3.47 (1.09)	3.58 (1.01)	0.325
Use of cholesterol-lowering medication, %	421 (23.4)	57 (52.3)	364 (21.5)	<0.001
Hyperlipidemia	633 (34.3)	64 (57.7)	569 (32.8)	<0.001
Mean diastolic blood pressure, mmHg	75.2 (9.9)	76.1 (9.3)	75.1 (9.9)	0.274
Mean systolic blood pressure, mmHg	134.0 (20.7)	145.7 (20.5)	133.3 (20.5)	<0.001
Hypertension	988 (53.5)	94 (84.7)	894 (51.5)	<0.001
Use of antihypertensive medication	561 (30.8)	60 (55.0)	501 (29.3)	<0.001
Current smoking	246 (13.3)	19 (17.1)	227 (13.1)	0.224
Cardiovascular disease, %	286 (15.5)	49 (44.1)	237 (13.7)	<0.001
Coronary heart disease, %	207 (11.2)	38 (34.2)	169 (9.7)	<0.001
Stroke, %	53 (3.0)	13 (12.3)	40 (2.4)	<0.001
Diabetes mellitus, %	138 (7.5)	18 (16.2)	120 (6.9)	<0.001

Numbers are means (SD) or n (%)
* Intracranial arterial stenosis was defined as a lumen reduction of ≥ 50%.

1.11, 95 % CI 1.08–1.14) and male sex (OR 1.77, 95 % CI 1.17–2.68) (Table 5). An independent association was also seen for hypertension (OR 2.32, 95 % CI 1.33–4.03), hyperlipidemia (OR 1.66, 95 % CI 1.10–2.51), diabetes mellitus (OR 1.86, 95 % CI 1.04–3.33), current smoking (OR 2.11 CI 95 % 1.20–3.69) and higher BMI (OR 1.05 CI 95 % 1.00–1.11).

Discussion

In this study, the overall prevalence of ICAS in the middle-aged and elderly population was 6.0 %. The majority of ICAS were located to the intracranial ICA. Age, male sex, hypertension, hyperlipidemia current smoking and BMI were independently associated with presence of ICAS.

The prevalence of ICAS in our study is lower than the previously reported prevalence of 8.0 % in Whites in the population-based US ARIC Study,[15] but higher than the prevalence of 3.3 % in the Spanish AsIA Study.[16] Differences both in inclusion criteria and imaging methodology can probably explain the variation in prevalence between the studies. The ARIC study participants were 67 to 90 years old with a mean age of 76 (SD±5) years, which is approx. 12 years higher than the mean age in our study (63.8, SD ±10.6 years) and 10 year more than in the AsIA study (66.3 years). The AsIA Study included subjects with a moderate to high vascular risk but excluded subjects with a history of stroke or transient ischemic attack or a history of coronary disease. Stenosis was assessed by transcranial color-coded duplex (TCCD), which is likely to be less sensitive for detection of stenosis than MRI.[23] Like our study, ARIC used a 3T scanner using 3D-TOF MRA, but included more peripheral segments of the arteries and performed additional high-resolution MRI sequences to identify and measure the intracranial vessel wall, which may have increased the possibility to detect stenotic plaques.

DSA remains the gold standard in assessment of stenosis against which 3D-TOF-MRA, contrast enhanced MRA (CE-MRA), TCCD and CT angiography (CTA) are compared.[24] TCCD estimates grade of stenosis based upon the flow velocity in the artery across a stenosis, whereas CTA, CE-MRA and DSA are visualizing the contrast enhanced blood in the arterial lumen. 3D-TOF-MRA is depicting an inflow-enhancement effect which is dependent on flow velocity, repetition time and cross-sectional area of the vessel.[25] This inflow is strongly influenced by hemodynamics and has limited ability for visualization of the fine

Table 3
Distribution of intracranial arterial stenosis per arterial segment and across categories of degree of stenosis.

Vessel location	≥50% stenosis, n (%)	50-69% stenosis, n	70-99% stenosis, n	Occlusion, n
ICA	82 (52.2)	70	12	0
ACA	6 (3.8)	4	2	0
MCA	17 (10.8)	11	5	1
VA	26 (16.6)	22	1	3
BA	2 (1.3)	2	0	0
PCA	21 (13.4)	17	4	0
PCOM	3 (1.9)	1	2	0
Number (%) of vessels with ICAS	157	127 (80.9)	26 (16.6)	4 (2.5)
Per participant (prevalence, %)	111 (6.0)	88 (4.8)	20 (1.1)	3 (0.2)

Table 4
Per-participant location of intracranial arterial stenosis in men and women.

Stenosis site	Women	Men	Total
Internal carotid artery	26 (2.6)	44 (5.1)	70 (3.8)
Anterior cerebral artery	4 (0.4)	2 (0.2)	6 (0.3)
Middle cerebral artery	8 (0.8)	6 (0.7)	14 (0.8)
Posterior cerebral/vertebrobasilar artery	16 (1.6)	26 (3.0)	42 (2.3)

Values are number (percentage) of stenosis ≥50 %.

Table 2
Prevalence (%) of intracranial stenosis ≥50 % stratified by age group and sex.

	Total	40–54 years	55–64 years	65–74 years	75–84 years
Men					
No. with stenosis/No. of participants	69/864	1/156	10/233	29/323	29/152
Proportion with stenosis (95% CI)	8.0 (6.3–10.0)	0.6 (0.00– 3.5)	4.3 (0.2–7.8)	8.9 (6.1–12.6)	19.1 (13.2–26.2)
Women					
No. with stenosis/No. of participants	42/983	2/222	5/277	20/346	15/138
Proportion with stenosis (95% CI)	4.3 (3.1–5.7)	0.9 (0.1–3.2)	1.8 (0.6–4.2)	5.8 (3.6–8.8)	10.9 (6.2–17.3)
Total					
No. with stenosis/No. of participants	111/1847	3/378	15/510	49/669	44/290
Proportion with stenosis (95% CI)	6.0 (5.0–7.2)	0.8 (0.2–2.3)	2.9 (1.6–4.8)	7.3 (5.5–9.6)	15.2 (11.2–19.8)

Table 5
Association between cardiovascular risk factors and presence of intracranial arterial stenosis.

	Model 1			Model 2			Model 3		
	OR	95 % CI	p-value	OR	95 % CI	p-value	OR	95 % CI	p-value
Male Sex	1.94	1.31-2.89	0.001	1.79	1.19-2.69	0.005	1.77	1.17-2.68	0.007
Age, years	1.11	1.09-1.14	<0.001	1.11	1.08-1.14	<0.001	1.11	1.08-1.14	<0.001
BMI, kg/m^2	1.06	1.02-1.11	0.006	1.08	1.03-1.13	0.003	1.05	1.00-1.11	0.026
Hypertension	5.21	3.08-8.80	<0.001	2.87	1.67-4.95	<0.001	2.32	1.33-4.03	0.003
Diabetes mellitus	2.61	1.52-4.46	<0.001	2.42	1.39-4.24	0.002	1.86	1.04-3.33	0.036
Hyperlipidemia	2.79	1.89-4.12	<0.001	2.01	1.34-3.01	0.001	1.66	1.10-2.51	0.016
Current smoking	1.37	0.82-2.29	0.226	1.90	1.11-3.26	0.020	2.11	1.20-3.69	0.009

OR: odds ratio, CI: confidence interval
Model 1: univariable analysis, Model 2: each variable adjusted for age and sex, Model 3: multivariable model with all variables included.

structures in the arteries, especially where the hemodynamics is complex and vessels change direction, such as the carotid siphon and at junctions of arteries.[26] When applied on TOF-MRA, the WASID method tends to exaggerate the severity of ICAS, resulting in low positive predictive value.[22,24] The MRA-VICAST method was developed to compensate for this weakness of the MRA-WASID method. The MRA-VICAST method bases grading of stenosis on assessment of reduction of the flow signal. A stenosis of a certain severity will induce an irregular flow distal to the stenosis that will cause a reduced flow signal in the post-stenotic segment with the consequence that the flow diameter appears thinner than the actual luminal diameter. According to MRA-VICAST, this means that a stenosis is considered as ≥50 % if the flow signal is thread-like or invisible in the stenotic segment, and the flow diameter distal to the site the stenosis is reduced (pseudo-narrowing) or even absent. In the present study, assessment of ICAS in the ACA, MCA and the posterior circulation was made by comparing the evaluation of stenosis vs. no-stenosis by using both the WASID and MRA-VICAST methods. Decision on stenosis and grading was made after consensus between the observers and the assessment by the MRA-VICAST method was weighted heaviest. This may have contributed to the lower prevalence of ICAS in the ACA and MCA in our study compared to studies that have used the MRA-WASID method alone.[12,15]

Stenosis in the ICA was assessed only by the MRA-WASID method as we were not able to detect ICAS which met the criteria of the MRA-VICAST method despite strong indication of ≥50 % stenosis on 3D-reconstructions, MIP and MPR caliper flow diameter measurements. This might be related to the slab thickness of the TOF-MRA, which can cause the post-stenotic signal to be unreliable as the carotid siphon has to be covered by more than one slab. Thus, the signal on both sides of a stenosis may be the same even in cases with highly suspicious stenosis (Supplemental Figure II).

Because of its tortuosity the flow diameter in ICA siphon is difficult to measure. The WASID method requires that in cases of precavernous, cavernous and postcavernous stenosis, the normal diameter of ICA (D_{normal}) should be measured at the "widest, non-tortuous, normal portion of the petrous carotid artery that have parallel margins".[21] As the caliber of the ICA normally decreases on its intracranial course from the petrous segment to the terminus,[27] especially distal to the origin of the ophthalmic artery,[21] both the lumen diameter of the D_{normal} in DSA-WASID and the flow diameter of the D_{normal} in MRA-WASID will consequently be larger than the lumen diameter/flow diameter just proximal to a supraclinoid stenosis. This might, both in assessment of stenosis on DSA and MRA, lead to an overestimation of the grade of a stenosis in the postcavernous ICA. But on TOF-MRA, the assessment is even more challenging due to loss of laminar flow which is especially pronounced in irregular, atherosclerotic vessels. Hence, the flow diameter may additionally be reduced in the postcavernous segment compared to the flow diameter at the site of the D_{normal}, either giving an illusion of a stenosis or exaggerate it. The relatively high proportion of ICA stenosis in the present study might partially be explained by this.

MRI techniques such as intracranial high-resolution vessel wall imaging has proven to be reliable for assessing the arterial vessel wall and is a promising tool for detection and especially verification of stenosis which can complement TOF-MRA or CE-MRA.[28,29] CE-MRA offers better diagnostic accuracy than TOF-MRA when compared to DSA and provides an advantage in evaluating ICAS and large artery occlusion.[30]

The traditional cardiovascular risk factors age, male sex, hypertension, hyperlipidemia, current smoking, BMI and diabetes mellitus were all independently associated with presence of ICAS. Apart from age and sex, these are modifiable risk factors which are associated with cardiovascular disease and could be responsive to preventive measures.[31] The proportion with a history of cardiovascular disease was higher in participants with ICAS, most pronounced for stroke. Due to the cross-sectional design, no inferences can be made with regards to the temporal relationship between history of stroke and ICAS.

The definition of what should be regarded as an intracranial artery is not consistent across prevalence studies. While we and others defined the petrocavernous segment as intracranial,[12,18] others have excluded the petrous part, but not the cavernous segment.[15,16] Still others have included only the intradural segment.[6] If we exclude participants with the main stenosis in the petrous segment of the ICA, the overall prevalence is essentially unchanged (from 6.0 % to 5.9 %), while the prevalence of intradural stenosis is 5.6 %.

The prevalence of 8.0 % in men and 4.3 % in women in our study is similar to the estimated prevalence of extracranial carotid stenosis (ECAS) in the Tromsø population (5.3 % in men and 2.7 % in women).[32] A meta-analysis from four population-based studies ($n = 23{,}706$) reported that the prevalence of ECAS≥50 % increased from 0.3 % in men aged <50 years to 10.6 % in men ≥80 years, and from 0 % to 5.9 % in women in the same age groups.[33] This might suggest that the impact of ICAS could be stronger than previously assumed, especially in the elderly, and may be a target for primary prevention.

Strengths and limitations

The strength of this study is the population-based study design, with a balanced age distribution.[34] Still, the number of participants in this study was limited, resulting in relatively wide confidence intervals for the age- and sex-specific prevalence estimates, especially for the oldest age groups. Lower participation rate in the oldest age groups due to disease or disability may have led to underestimation of the prevalence of ICAS in the elderly. The mean age and the proportion of women were somewhat higher in non-attendees (mean age 65.0 years, 55.0 % women) than in attendees of the MRI study (mean age 63.8 years, 53.2 % women).

As DSA is an invasive method not feasible in population-based studies, we used 3D-TOF-MRA in our study with the limitations discussed above. However, we believe that the combined use of the MRA-VICAST and MRA-WASID methods has reduced the likelihood of errors in the assessment of stenosis. We are not aware of any population-based validation studies of TOF-MRA, but the MRA-WASID and MRA-VICAST methods have both been validated against DSA in clinical studies.[22,35]

Conclusions

The overall of prevalence of ICAS ≥50 % in our population was 6.0 %. The prevalence is relatively high and similar to the prevalence of extracranial internal carotid stenosis in previous population-based studies. This might suggest that the impact of ICAS could be stronger than previously assumed and may be a target for primary prevention.

Ethical approval

The Tromsø Study was approved by the Norwegian Data Inspectorate. The 7th survey of the Tromsø Study (REK Nord 2014/940) and the MRA study was approved by the Regional Committee for Medical and Health Research Ethics, North Norway (REK Nord 2014/1665). Participants gave informed consent to participate in the study before taking part. The study adheres to the tenets of the Declaration of Helsinki.

Author contributions

Conceptualization: EBM and JGI; Data curation: LHJ, TV and EBM; Formal analysis: LHJ and EBM; Funding acquisition; EBM; Methodology: LHJ, MH and EBM; Project administration: EBM; Supervision: EBM, TV, JGI and MH; Validation: LHJ and MH; Writing-original draft: LHJ; Writing-review & editing: LHJ, MH, TV, JGI and EBM. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2023.107399.

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