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Research article

Recurrence of ischaemic stroke using epidemiology and neuroimaging: A retrospective study in Gansu Province

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ABSTRACT

Objectives: This retrospective study aimed to investigate the clinical and imaging recurrence of ischaemic stroke (IS), and to evaluate the risk factors for recurrence. A combined clinical and imaging diagnostic model is important for stroke prevention and management.

Methods and materials: In accordance with the inclusion and exclusion criteria, we retrospectively analysed consecutively hospitalised patients with acute IS at the Affiliated Hospital of Gansu University of Chinese Medicine. Based on the epidemiological and imaging results, stroke episodes were divided into four categories: clinical first episode (CFE), clinical recurrence (CR), imaging first episode (IFE), and imaging recurrence (IR). Based on the above categories and clinical practice, a joint diagnostic system for IS was established for the first time, including the following five types: IFE, IR, CFE and IFE, CFE and IR, and CR and IR. A binomial logistic regression analysis was conducted to determine the factors which contributed to CR and IR.

Results: In total, 280 patients were assessed. The CR rate was 22.9% (64/280) and the IR rate was 62.9% (176/280). The only predictor of CR was hypertension ($P = 0.019$, odds ratio [OR] = 3.041, 95% confidence interval [95%CI] = 1.200–7.704). The factors of hypertension ($P < 0.001$, OR = 3.551, 95%CI = 1.781–7.080) and age ($P = 0.031$, OR = 1.031, 95%CI = 1.003–1.060) were predictors of IR.

Conclusion: The IR rates for IS were three times higher than the CR rates. The key to preventing IR and CR in IS was the management of blood pressure. Neuroimaging examinations were important for the early detection of IFE and IR in elderly patients with hypertension. A combined clinical imaging diagnostic model was developed for the first time.

1. Introduction

China has the highest burden of stroke in the world, which has been increasing over the past 30 years, particularly in rural areas [1]. In addition, an aging population, the persistence of risk factors, inadequate management, and the increasing availability of neuroimaging techniques have led to the over-diagnosis and overtreatment of silent cerebral infarction (SCI) [2]. However, SCI is associated with an increased risk of future symptomatic stroke, independent of other vascular risk factors [3]. In many cases, acute ischaemic stroke (AIS) was overlooked because the atypical manifestations were similar to those of other diseases, such as stroke chameleons, which account for 39.9% of all strokes. Therefore, strategies are required to identify patients with stroke at an early stage [4].

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Therefore, we conducted a single-centre retrospective study on the recurrence of AIS, in conjunction with clinical epidemiology and neuroimaging. This study aimed to establish a joint diagnosis system for ischaemic stroke (IS) using a combination of clinical and imaging analysis, to identify clinical recurrence (CR) and imaging recurrence (IR) risk factors, and to provide information relevant to preventing clinical and imaging stroke events as well as recurrences.

2. Methods

2.1. Patients

The Affiliated Hospital of Gansu University of Chinese Medicine (AHGUCM) is affiliated with Gansu University of Chinese Medicine. A retrospective retrieval of the discharge database from June 2016 to May 2019 was performed using the Disease Classification and Code (GB/T14396-2016), with numbers I63.402, 502, 800, 801, and I63.900 to I63.9007. The ethics review of all charts was approved by the ethics research committee of the AHGUCM (acceptance number: 2022.51). As this was a retrospective study, the data were obtained by consulting the patients' medical history, which meant that informed consent could not be obtained from the patient.

Inclusion criteria: AIS was diagnosed based on the World Health Organization diagnostic criteria, and patients admitted to our hospital during the acute phase were included in the analysis. Exclusion criteria: our hospital receives patients with acute convalescence transferred from other hospitals and patients with chronic cerebral infarctions. These patients were not included.

Hypertension was defined as a systolic blood pressure $\geq$140 mmHg and a diastolic blood pressure $\geq$90 mmHg, or the use of antihypertensive drugs within the preceding 2 weeks [5]. The diagnostic criteria for diabetes were as follows: random blood glucose levels $\geq$200 mg/dL (11.1 mmol/L); fasting blood glucose $\geq$126 mg/dL (7.0 mmol/L) (fasting time 8–12 h); oral glucose tolerance test (OGTT) 2-h venous plasma value $\geq$ 200 mg/dL (11.1 mmol/L); and haemoglobin a1C (Hba1c) $\geq$ 6.5% (48 mmol/mol Hb) [6]. Hospitalised blood pressure measurements and blood glucose, blood lipids, homocysteine, fibrinogen, and platelet values were collected from biochemical, coagulation, and routine blood tests. Whether the patients had smoked was determined by their personal history. The normal ranges of total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein were 2.9–5.72, 0–1.7, 0–3.35, and 0.91–1.74 mmol/L, respectively. Normal plasma fibrinogen levels range between 2.0 and 4.0 g/L. The normal range of plasma homocysteine levels is 0–15 μmol/L. The normal platelet count ranges between 100 and 300 $\times$ 10^9/L.

2.2. Methods of neuroimaging examination

The patients underwent brain computed tomography (CT) scans before and after admission using a Siemens 64-slice spiral CT. We used a 1.5T magnetic resonance imaging (MRI) by the United Imaging Company for MRI scans of the brain, including T1-weighted, T2-weighted, fluid-attenuated inversion recovery, and diffusion-weighted images.

2.3. Diagnostic imaging classification in IS

Imaging first episode (IFE): Single or multifocal cerebral infarction was identified in patients undergoing imaging examinations for medical reasons. Additionally, lesions associated with non-cerebrovascular diseases were excluded.

IR: After undergoing two or more imaging examinations for medical purposes, the patients were diagnosed with multifocal cerebral

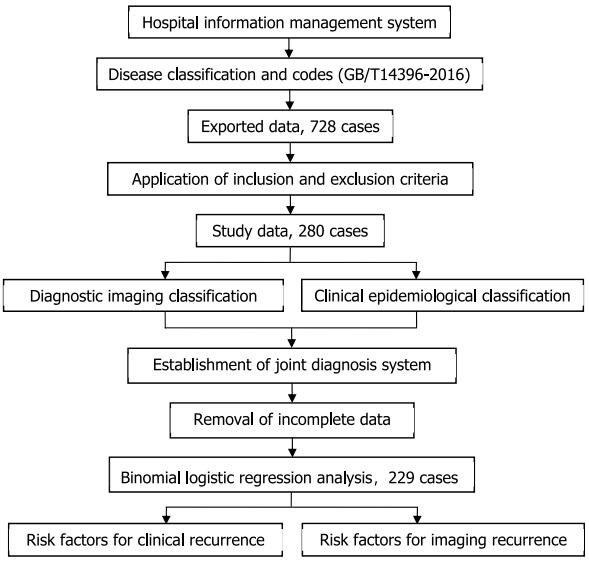

Fig. 1. Study flow chart.

infarction at different locations or at different times. Patients with intracranial lesions caused by non-cerebrovascular diseases were excluded.

2.4. Classification of IS from a clinical epidemiological perspective

Clinical first episode (CFE): IS was initially diagnosed based on neurological or non-neurological symptoms and signs, as well as diagnostic imaging criteria.

CR: IS was diagnosed twice or more based on neurological or non-neurological symptoms and signs, as well as the imaging diagnostic criteria for IS.

2.5. Joint diagnosis system of IS is combined with clinical epidemiology and neuroimaging

According to the above-mentioned clinical epidemiology and neuroimaging, IS can be categorised into four classes: CFE, CR, IFE, and IR. Considering the above types and clinical practice, the joint diagnosis system of IS comprises the following five types: IFE, IR, CFE and IFE, CFE and IR, and CR and IR. Patients with IFE and IR were excluded because the subjects were hospitalised after AIS.

2.6. Flow chart

A flowchart of the complete research process of this study is shown in Fig. 1.

2.7. Statistical analysis

SPSS (IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.) was used for all statistical analyses. The CR and IR component ratios were calculated using the component ratios of the entire group. Binomial logistic regression analysis was used to calculate the odds ratio (OR) and 95% confidence interval (95%CI) of CR and IR. (1) Demographic and clinical characteristics: age, sex, and prior diagnoses (including hypertension, diabetes, coronary heart disease, atrial fibrillation, and a history of long-term smoking); (2) laboratory examination, including measurements of serum blood glucose, plasma total cholesterol, triglycerides, low-density

Table 1
Characteristics of the patients and the current situation of recurrence.

Projects	Numerical value
Age (years)	68.60 ± 11.89
Range	32 ~ 90
Sex	
Male (%)	180 (64.3)
Imaging form	
CT (%)	58 (20.7)
MRI (%)	94 (33.6)
CT + MRI (%)	128 (45.7)
Clinical First Episode (%)	216 (77.1)
Clinical Recurrence (%)	64 (22.9)
Frequency of recurrence (range)	2.06 ± 0.43 (1 ~ 3)
Imaging First Episode (%)	104 (37.1)
Imaging Recurrence (%)	176 (62.9)
Classification of cerebral infarction attack	
Clinical First Episode & Imaging First Episode (%)	104 (37.1)
Clinical First Episode & Imaging Recurrence (%)	112 (40.0)
Clinical Recurrence & Imaging Recurrence (%)	64 (22.9)
Hypertension (%)	202 (72.1)
Diabetes (%)	93 (33.2)
Coronary heart disease (%)	38 (13.6)
Atrial fibrillation (%)	28 (10.0)
Smoking history (%)	60 (21.4)
Carotid plaque (%) (235)	195 (83.0)
Systolic pressure (mmHg)	141.03 ± 22.81
Diastolic pressure (mmHg)	83.41 ± 15.09
Primary blood glucose (mmol/L) (279)	7.45 ± 3.22
Total cholesterol (mmol/L) (275)	4.27 ± 1.11
Triglycerides (mmol/L) (277)	1.78 ± 1.42
Low density lipoprotein (mmol/L) (275)	2.40 ± 0.95
High density lipoprotein (mmol/L) (275)	1.17 ± 0.35
Fibrinogen (g/L) (268)	2.85 ± 1.27
Homocysteine (umol/L) (275)	22.38 ± 16.93
Platelet count ($\times 10^9$/L) (275)	190.24 ± 63.91

CT, computed tomography; MRI, magnetic resonance imaging.

lipoprotein, high-density lipoprotein, plasma homocysteine, plasma fibrinogen, and platelet count; and (3) auxiliary examination, CT and/or MR, were used to determine the presence of intracranial infarction. A Siemens Acuson S2000 instrument was used to perform the cervical vascular ultrasonography.

3. Results

3.1. Patient characteristics and current situation of recurrence

A total of 280 patients were assessed, 19 of whom suffered from AIS again during a 3-year follow-up period, so they were finally included in the CR and IR groups. Among the whole group, there were 21 cases with incomplete laboratory data (total cholesterol, five cases; triglycerides, three cases; high-density lipoprotein, five cases; low-density lipoprotein, five cases; homocysteine, five cases; blood glucose, one case; platelet count, five cases; and plasma fibrinogen, 12 cases). Among the 45 patients, colour Doppler ultrasound of the carotid artery were not completed.

An analysis of the 280 cases revealed 64 cases (22.9%) with CRs and 176 cases (62.9%) with IRs (Table 1).

3.2. Factors associated with recurrence in the clinical epidemiology of IS (n229)

In addition to age, sex, hypertension, diabetes, atrial fibrillation, long-term smoking history, carotid plaque formation, total cholesterol, triglycerides, low-density lipoprotein, and homocysteine were possible predictors of CR in IS. To investigate the predictors of CR of IS, a binomial logistic regression analysis was carried out on the CR of IS and the above-mentioned 11 risk factors, six of which categorical variables were sex, hypertension, diabetes, atrial fibrillation, smoking history, and carotid plaque formation, with five continuous variables: age, total cholesterol, triglycerides, low-density lipoprotein, and homocysteine.

In the logistic regression analysis, the ORs for age, sex, hypertension, diabetes, atrial fibrillation, smoking history, carotid plaque, total cholesterol, triglycerides, low-density lipoprotein, and homocysteine were 0.988, 1.211, 3.041, 0.757, 1.016, 0.559, 1.561, 0.825, 0.731, 1.136, and 0.973, respectively. Only hypertension ($P = 0.019$) was statistically significant (OR = 3.041 [1.200–7.704]), indicating that the risk of CR of IS in patients with hypertension was 3.041 times higher than that in patients without hypertension (Table 2).

3.3. Risk factors for IR of IS (n229)

Other risk factors for IS include age, sex, hypertension, diabetes, atrial fibrillation, smoking history, carotid plaque, total cholesterol, triglyceride, low-density lipoprotein, and homocysteine. Binary logistic regression analysis was performed with the above risk factors to examine the predictors of IR in IS.

Logistic regression analysis indicated that the relative risk factors for the IR of cerebral infarction were age, sex, hypertension, diabetes, atrial fibrillation, smoking history, carotid plaque, total cholesterol, triglycerides, low-density lipoprotein, and homocysteine; the ORs of these risk factors were 1.031, 0.886, 3.551, 1.050, 0.676, 1.798, 0.714, 0.991, 0.777, 0.973, and 0.997, respectively. The OR for age was statistically significant ($P = 0.031$), and the OR of 1.031 (1.003–1.060) indicated that the risk of IR of IS in elderly patients was 1.031 times higher than that in younger patients. Concurrently, hypertension was a statistically significant factor ($P < 0.001$), and the OR of 3.551 (1.781–7.080) indicated that the risk of IR of IS in hypertensive patients was 3.551 times higher than that in patients without hypertension; that is, advanced age and hypertension were risk factors for IR (Table 3).

4. Discussion

Stroke is a major health concern worldwide, particularly in less developed nations; however, even in developed nations, where the

Table 2
Factors associated with recurrence in the clinical epidemiology of ischemic stroke.

Projects	*B*	S.E.	Walsχ^2	*P*	OR	95% C.I. of the OR	
						lower limit	upper limit
Age	−0.013	0.016	0.622	0.430	0.988	0.957	1.019
Sex	0.191	0.385	0.247	0.619	1.211	0.569	2.573
Hypertension	1.112	0.474	5.498	0.019	3.041	1.200	7.704
Diabetes	−0.279	0.374	0.554	0.457	0.757	0.363	1.576
Atrial fibrillation	0.016	0.585	0.001	0.978	1.016	0.323	3.199
Smoking history	−0.582	0.516	1.274	0.259	0.559	0.203	1.535
Carotid plaque	0.445	0.521	0.729	0.393	1.561	0.562	4.336
Total cholesterol	−0.193	0.348	0.307	0.580	0.825	0.417	1.631
Triglycerides	−0.313	0.241	1.689	0.194	0.731	0.456	1.172
Low density lipoprotein	0.127	0.367	0.12	0.729	1.136	0.553	2.332
Homocysteine	−0.027	0.015	3.344	0.067	0.973	0.946	1.002

CI, confidence interval; OR, odds ratio.

Table 3
The risk factors for imaging recurrence of ischemic stroke.

Projects	*B*	S.E.	Walsχ2	*P*	OR	95% C.I. of the OR	
						lower limit	upper limit
Age	0.031	0.014	4.674	0.031	1.031	1.003	1.060
Sex	−0.121	0.350	0.119	0.730	0.886	0.446	1.759
Hypertension	1.267	0.352	12.953	0.000	3.551	1.781	7.080
Diabetes	0.048	0.328	0.022	0.883	1.050	0.552	1.997
Atrial fibrillation	−0.391	0.536	0.531	0.466	0.676	0.236	1.935
Smoking history	0.587	0.405	2.101	0.147	1.798	0.813	3.975
Carotid plaque	−0.337	0.417	0.653	0.419	0.714	0.315	1.617
Total cholesterol	−0.009	0.319	0.001	0.978	0.991	0.530	1.854
Triglycerides	−0.253	0.173	2.128	0.145	0.777	0.553	1.091
Low density lipoprotein	−0.027	0.332	0.007	0.935	0.973	0.507	1.867
Homocysteine	−0.003	0.009	0.123	0.726	0.997	0.980	1.014

CI, confidence interval; OR, odds ratio.

population is ageing, it remains an issue [7]. China accounted for 18% of the world's population in 2019. With a population of 164.5 million people aged 65 and older and 26 million people aged 80 and older, China has entered into the ageing society. As ageing continues, the burden on existing families and the public health system increases [8]. The highest incidence of stroke, adjusted for age, was observed in East Asia, particularly in China [9]. More than 2 million new cases of stroke are identified in China annually, and the incidence of stroke is increasing; therefore, the implementation of preventive measures must be strengthened [2]. Currently, advanced and effective recanalisation therapy is available for AIS, but most patients do not receive it [4]. Stroke is currently the fifth leading cause of death in the United States, and the incidence of both new and recurrent strokes has decreased by 10% [10]. However, a recent study showed that while the post-stroke all-cause mortality rate decreased, stroke recurrence increased significantly among stroke patients from rural areas between 2004 and 2018 [11]. The rate of IS recurrence in China is higher than that reported in the West, and failure to control certain modifiable risk factors may account for this difference [12].

Although stroke treatment has advanced rapidly, the most effective medical measure is prevention, particularly primary and secondary prevention, to prevent the occurrence and recurrence of stroke [13]. With the continued reform of the Chinese national healthcare system, the efficacy of stroke treatment and hospital admission has significantly improved, especially with the implementation of secondary prevention. The continued use of secondary prophylactic drugs has also been associated with lower rates of recurrent stroke, compound events, all-cause death, and disability in patients with AIS [1,14]. Non-medical prevention strategies are needed to improve stroke recurrence in the future, such as physical activity, lifestyle changes, and improved patient compliance [15]. Identifying patients who need prevention should be a top priority to effectively implement prevention. Patients with clinically confirmed stroke are the targets of secondary prevention, but patients for primary prevention are sometimes indistinct. Young and middle-aged patients or asymptomatic stroke patients would theoretically benefit from earlier prevention, but compliance remains low. The high global prevalence of stroke suggests that primary prevention strategies are either insufficient or ineffective. In addition to addressing behavioural risk factors, effective screening is crucial [9]. Therefore, it is vital to develop a preventive screening mechanism that combines clinical epidemiology and imaging.

In AIS management, the 2018 American Heart Association/American Stroke Association guidelines reflect a paradigm shift from "time is brain" to "imaging is brain" [16]. Imaging has become an indispensable diagnostic and therapeutic tool for stroke [17]. Although stroke has a variety of clinical symptoms, the use of neuroimaging in patient examination, diagnosis, and treatment is a major theme in modern IS care, and neuroimaging is widely used to assess vascular patency and tissue vitality. For instance, data from CT imaging have significantly improved the discriminatory performance and reclassification for predicting IS recurrence beyond a model incorporating clinical risk factors only [15,18–20]. Regional data in China revealed that the rate of neuroimaging diagnosis and hospitalisation of stroke patients have increased significantly over the past three decades, with an annual increase of 4.0% and 11.2%, respectively [21]. The diagnosis of IS has become a combination of clinical and imaging diagnoses due to the development of China's economy and the improvement of medical care, the increase in social awareness of stroke, and the popularity of imaging examinations.

Overlaps and divergence were observed in the actual diagnosis; for example, imaging examination identified new lesions with or without previous cerebral infarction in patients with CFE. The formation of cerebral infarction was discovered during the annual check-up or outpatient imaging examination, without symptoms or signs, and patients with CR had both new and old lesions on imaging examination. Therefore, in accordance with the clinical situation and imaging interpretation, the CFE and CR cases, as well as the IFE and IR cases of IS, were described. This retrospective study revealed that 64 of the 280 patients had CR (22.9%), and 176 patients had IR (62.9%). The results indicate that the IR rate is greater than the CR rate. Similar to the findings of this study, approximately 800,000 IS patients are diagnosed in the United States each year, with a recurrence rate of approximately 25% [22]. Moreover, this study revealed that the number of CRs was 2.06 ± 0.43, and previous research has demonstrated that IS patients have the highest rate of recurrence. If recurrence occurs, the number of recurrences will rise [23] Therefore, IS patients, particularly those with more than one CR, should, in addition to strengthening preventive measures, be informed of the severity of recurrence, as well as the disability and possibility of death caused by recurrence, in order to improve adherence to prevention measures.

Fisher [24] first described cerebral infarction in the absence of any obvious clinical stroke, namely SCI, which is a common imaging manifestation in the absence of corresponding clinical symptoms. These are classified as IFE or IR in this study. Prior research

demonstrated that the recessive aetiology was prevalent in the population of patients with transient ischaemic attacks and minor strokes, which displayed a high rate of asymptomatic imaging recurrence [25]. Recently, imaging and laboratory biomarkers have been proposed to improve the stratification of stroke aetiology, and build a more robust and precise risk prediction model for stroke survivors with atrial fibrillation. Clinical and radiological markers of confirmed cerebrovascular disease and stroke aetiology were better predictors than the usual demographic vascular risk factors [26–28]. Therefore, IR and CR should be emphasised in preventive strategies. To provide pertinent information for the prevention of recurrence, this study investigated both CR and IR, as well as the associated predictors of recurrence, in addition to gaining an understanding of CR.

The risk factors for CR and IR in the 229 patients with complete clinical data were analysed using binomial logistic regression. Hypertension was a predictor of CR and IR. Hypertension was also a predictive factor for CR ($P = 0.019$, OR = 3.041, 95%CI = 1.200–7.704). Hypertension ($P < 0.001$, OR = 3.551, 95%CI = 1.781–7.080) and age ($P = 0.031$, OR = 1.031, 95%CI = 1.003–1.060) were predictors of IR. While 31.1% of adults worldwide had hypertension in 2010, the prevalence declined by 2.6% in high-income countries between 2000 and 2010, but it increased by 7.7% in low and middle-income countries [29]. Of Chinese adults above 18 years of age, 23.2% (244.5 million) had hypertension, while 41.3% (443.5 million) had pre-hypertension, 46.9% of whom were aware of their condition and 40.7% took anti-hypertensive prescription medications. Only 15.3% had controlled hypertension[5]. Systemic hypertension is the most common, most easily diagnosed, and one of the most reversible risk factors for neurologic pathologies that increase stroke risk by three to five fold; thus, primary prevention is essential as three-fourth of strokes are incident events [30]. According to the findings of this study, hypertension, previous symptomatic stroke, chronic infarction on MRI, and age were independently associated with the recurrence of IS [31]. Therefore, blood pressure management should be improved to reduce the burden of stroke.

According to epidemiological estimates, SCI is strongly associated with age and hypertension in the assessed population, and is an independent predictor of stroke incidence [32]. Approximately one-fifth of elderly individuals without a history of stroke have SCI, which is associated with a high risk of future stroke [33]. It is necessary to further examine risk assessment strategies and strengthen preventive measures for patients with clinically undetected but imaging-observable cerebral infarctions. The hypertensive population is the target population for stroke prevention in China, as emphasised by the country's guidelines [34]. A recent systematic review and meta-analysis revealed that the use of blood pressure-lowering drugs in patients with IS is associated with a 1.9% reduction in strokes [35]. Thus, the results of this study suggest that active monitoring and control of hypertension is a crucial measure for preventing both CR and IR, while elderly patients should be aware of IR and undergo neuroimaging, if necessary.

IFE, IR, CFE and IFE, CFE and IR, and CR and IR were the five subtypes that resulted from the combination of clinical and neuroimaging analyses in the initial establishment of a joint diagnostic system. Therefore, it is necessary to further investigate the diagnostic system established by the combined clinical and imaging analyses, and to use this system to score and grade patients to adopt early, tailored, and graded prevention strategies in order to determine whether it will help reduce the incidence and recurrence of stroke.

5. Conclusion

The IR rate was significantly higher than the CR rate among AIS patients. The management of blood pressure should be strengthened to prevent IR and CR of AIS. Moreover, as hypertensive patients age, they should undergo neuroimaging examination or review to detect IFE or IR of IS early; a joint diagnostic system for IS has been established.

6. Limitations

1. The research participants were selected from regional single centres, necessitating additional multicentre and prospective studies.
2. Owing to the retrospective nature of the study and the inclusion of hospitalised patients with AIS, we lacked data on IFE and IR in joint diagnosis systems.
3. The participants' Trial of Org 10172 in Acute Stroke Treatment classification was not assessed.
4. The data in this retrospective study were relatively incomplete and insufficient.

Author contribution statement

Honghui Bao: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Qitao Yin: Performed the experiments.
Danbi Tian: Performed the experiments; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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