RESEARCH ARTICLE

Modulatory effect of International Standard Scalp Acupuncture on brain activation in the elderly as revealed by resting-state fMRI

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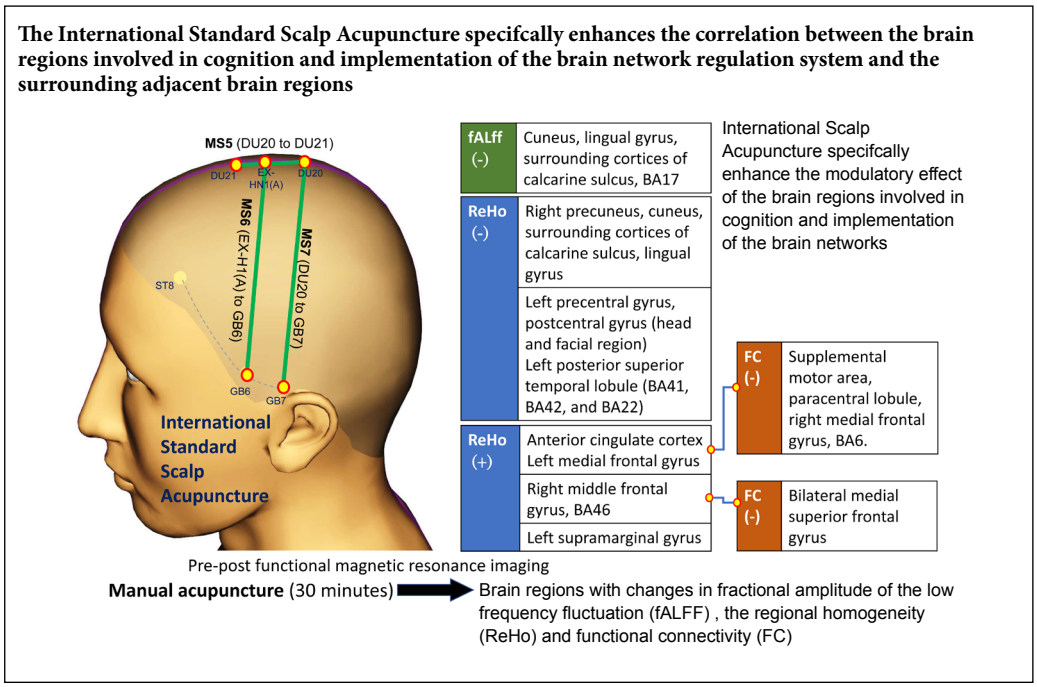
Graphical Abstract



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Abstract

The specific mechanisms by which acupuncture affects the central nervous system are unclear. In the International Standard Scalp Acupuncture system, acupuncture needles are applied at the middle line of the vertex, anterior parietal-temporal oblique line, and the posterior parietal-temporal oblique line. We conducted a single-arm prospective clinical trial in which seven healthy elderly volunteers (three men and four women; 50–70 years old) received International Standard Scalp Acupuncture at MS5 (the mid-sagittal line between *Baihui* (DU20) and *Qianding* (DU21)), the left MS6 (line joining *Sishencong* (EX-HN1) and *Xuanli* (GB6)), and the left MS7 (line joining DU20 and *Qubin* (GB7)). After acupuncture, resting-state functional magnetic resonance imaging demonstrated changes in the fractional amplitude of low frequency fluctuations and regional homogeneity in various areas, showing remarkable enhancement of regional homogeneity in the bilateral anterior cingulate, left medial frontal gyrus, supramarginal gyrus, right middle frontal gyrus, and inferior frontal gyrus. Functional connectivity based on a seed region at the right middle frontal gyrus (42, 51, 9) decreased at the bilateral medial superior frontal gyrus. Our data preliminarily indicates that the international standard scalp acupuncture in healthy elderly participants specifcally enhances the correlation between the brain regions involved in cognition and implementation of the brain network regulation system and the surrounding adjacent brain regions. The study was approved by the Ethics Committee of the China-Japan Union Hospital at Jilin University, China, on July 18, 2016 (approval No. 2016ks043).

Key Words: *nerve regeneration; resting-state functional magnetic resonance imaging; International Standard Scalp Acupuncture; acupoint specificity; brain functional connectivity; healthy elderly volunteers; low frequency fluctuation; regional homogeneity; functional connectivity; neural regeneration*

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Introduction

The International Standard Scalp Acupuncture system proposes that acupuncture needles are placed along "scalp lines", *i.e.*, lines or arcs that connect groups of acupoints related to specific cerebral functional regions, to strengthen the stimulation of such regions (No authors listed, 1990). Scalp acupuncture has been used to treat various brain-related diseases according to the principle of acupoint selection with respect to neighboring brain regions. Considering the increase in stroke cases observed in the aging society in China, the MS5, MS6, and MS7 scalp acupuncture line groups have been frequently selected for the use in the rehabilitation of stroke-related motor and sensory dysfunctions (Wang et al., 2017, 2018; You et al., 2017). However, the mechanisms of action of scalp acupuncture in the central nervous system are unclear, thus limiting the use of this form of acupuncture compared with other methods and treatment options, such as those involving western medicine and rehabilitation.

The theory of acupoint specificity holds that the selection of acupoints is a key factor in the efficacy of acupuncture therapy (Zhao et al., 2012; Zheng et al., 2015) and can be defined according to cerebral function (Lai and Huang, 2007; Rong et al., 2013). As the formulation of targets in scalp acupuncture is based on acupoints, it has been hypothesized that the mechanisms of action of International Standard Scalp Acupuncture (MS5, MS6 and MS7) are associated with changes in the activity of certain cerebral regions.

The development of functional magnetic resonance imaging (fMRI) has made it possible to observe changes in the central nervous system following scalp acupuncture. Resting-state fMRI (rs-fMRI) is obtained when participants are relaxed with their eyes closed, and are not involved in any cognitive task. It is favorable in that it enables a simple study design and minimal instructions for participants compared with task-based fMRI (Lu et al., 2011; He et al., 2015). Generally, regional functional analysis is conducted by obtaining the fractional amplitude of the low frequency fluctuation (fALFF) and the regional homogeneity (ReHo), while linear analysis is obtained *via* functional connectivity (Golestani et al., 2017). This non-invasive technique has been widely adopted in the study of brain physiology and pathologies, such as ischemic stroke (Thiel and Vahdat, 2015; Baldassarre et al., 2016), Parkinson's disease (Cerasa et al., 2016; Tahmasian et al., 2017), and depressive disorders (Deng et al., 2016; Wang et al., 2016; Brakowski et al., 2017). rs-fMRI has been used to examine acupuncture-induced changes in brain function. Specifically, it has been used to assess the effects of various manipulation methods, the presence or absence of *Deqi* (needling sensation), sham-vs-verum acupuncture effects, and different acupoint groups (Bai et al., 2014; Goffaux et al., 2014; Zhang et al., 2014, 2016; Shi et al., 2016; Yin et al., 2017; Cai et al., 2018).

In the present study, we investigated the brain-related mechanisms of action of International Standard Scalp Acupuncture. We used resting-state fMRI to observe specific changes in brain activity induced by needling in healthy elderly participants.

Participants and Methods

Participants

This study was a single-arm clinical trial. The study was approved by the Ethics Committee of the China-Japan Union Hospital at Jilin University, China on July 18, 2016 (approval No. 2016ks043) and has been registered at the Chinese Clinical Trial Registry (registration number: ChiCTR-IOR-15007672). Ten healthy participants were recruited from January to March 2017 *via* posters. This study followed the Standard Protocol Items: STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidance for study.

The inclusion criteria were (1) age between 50 and 70 years and any gender; (2) no history of hypertension, diabetes, thyroid disease, or cerebral ischemia; (3) normal eating habits without smoking or alcohol consumption, no caffeine intake in the past 24 hours, normal sleeping pattern, normal physical build; (4) no history of acupuncture in the past 1 month; (5) no metallic implants or dentures; (6) right handedness; (7) provision of informed consent.

Of the 10 participants recruited, two were excluded because of excessive head movement over 1.5 mm and 1.5 degrees during scanning, and an additional participant was excluded because they fell asleep during scanning. Thus, we obtained usable data from seven participants. There were three men and four women with a mean age of 56.14 ± 4.06 years (**Figure 1**).

Acupuncture

We focused on the International Standard Scalp Acupuncture lines MS5, left MS6, and left MS7 (No authors listed, 1990). MS5 is located at the mid-sagittal line between *Baihui* (DU20) and *Qianding* (DU21), which are located at 5 *cun* and 3.5 *cun* above the midpoint of the anterior hairline, respectively. MS6 is located at the line joining EX-HN1(A), which is 1 *cun* anterior to DU20, and *Xuanli* (GB6), which is three quarters down the side of the hairline between *Touwei* (ST8) (0.5 *cun* above the corner of the hairline) and *Qubin* (GB7) (located at the vertical line from the hairline anterior to the ear to the level of the apex of the ear). MS7 is located at the line joining DU20 and GB7. A single 30-minute needling session was performed for each participant.

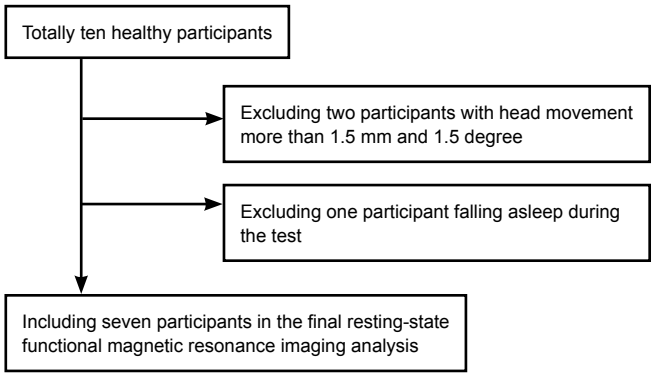

Figure 1 Flow chart of participant inclusion.

Acupuncture and scanning sessions took place in the same facility on the same day, in the following order: 1) pre-acupuncture scanning session, 2) acupuncture treatment, and 3) post-acupuncture scanning session. Following routine local disinfection, stainless steel needles (0.3 mm × 40 mm, Huatuo, Suzhou, China) were inserted at acute angles (15–30 degrees) with respect to the epicranial aponeurosis and left in place for 30 mm. When the participant reported that the needles had elicited *Deqi* sensations, they were twisted at a frequency of 200 turns per minute, causing a distending sensation. Twisting was repeated at 10-minute intervals during the 30-minute period.

fMRI data acquisition

Brain scans were acquired using a MRI system (Siemens 3.0T, Siemens Healthineers, Germany) before and within 20–30 minutes after the acupuncture session. We conducted T1-weighted magnetization-prepared rapid acquisition of gradient-echo and fMRI-BOLD echo-planar images. Each participant lay supine on the examination bed with their head fixed in a coil. We reduced the influence of visual and auditory stimulation by fitting the participants with eye masks and earplugs. They were asked to avoid any active mental activity.

The parameters for T1-weighted magnetization-prepared rapid acquisition of gradient-echo scanning were as follows. We conducted three-dimensional (3D) TFE sequence cross-sectional scans for whole brain high resolution T1WI images with repetition time = 2300 ms, echo time = 2.45 ms, flip angle = 8°, field of view = 250 mm, slice thickness = 1 mm, voxel = 1.0 mm × 1.0 mm × 1.0 mm, and matrix = 256 × 256.

The fMRI-BOLD scanning parameters were as follows. We used a single provocation echo-planar imaging sequence with repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, slice thickness = 3.5 mm, gap = 0.7 mm, voxel = 3.5 mm × 3.5 mm × 3.5 mm, field of view = 224 mm × 224 mm, phases per location = 240, matrix = 64 × 64, and number of slices = 37.

Data analysis

Data were pre-processed using statistical parametric mapping 12 software (https://www.fil.ion.ucl.ac.uk/spm/) and Dpabi software (http://rfmri.org/dpabi) in Matlab 2012a (MathWorks, Natick, MA, USA). Pre-processing included slice time correction, smoothing, motion correction, spatial and temporal filtering, and detrending. We used the resting-state fMRI Data Analysis Toolkit (REST 1.8, http://www.restfmri.net/forum/REST_V1.8) to analyze the data. Post-intervention changes were evaluated using paired *t*-tests, and we generated statistical parameter maps for identification and correction (AlphaSim correction, Cluster Size = 165, cluster connectivity criterion = 4 rmm, $P < 0.05$). We obtained the anatomical locations and activation intensity of clusters with significant changes in fALFF and ReHo. To obtain the functional connectivity, all significant changes in ReHo were further analyzed for consistency with the whole brain data. Post-intervention changes in functional connectivity were analyzed with paired *t*-tests, and statistical parameter maps were constructed. Brain regions were identified and functional connectivity maps were constructed using Brain Net Viewer software (https://www.nitrc.org/projects/bnv/).

Finally, experienced neurologists verified significant post-intervention changes in fALFF, ReHo, and functional connectivity based on anatomical knowledge and clinical experience.

Results

After acupuncture, fALFF decreased at the right cuneus, surroundings cortices of the calcarine sulcus, and BA17. This change in activity extended to the bilateral lingual gyrus as well as the left cuneus, surroundings cortices of the calcarine sulcus, and BA17.

ReHo decreased at the right precuneus and cuneus. This decrease extended to the right cortex surrounding the calcarine sulcus and lingua gyrus. ReHo also decreased at the left precentral gyrus and postcentral gyrus (representing the head and facial region), and extended to the left posterior superior temporal gyrus (BA41, BA42, and BA22). ReHo increased at the left anterior cingulate cortex (BA32), which extended to the left medial frontal gyrus and right anterior cingulate cortex. ReHo also increased at the right middle frontal gyrus extending to the right inferior frontal gyrus (BA46) and at the left supramarginal gyrus (BA40).

Based on the seed region at the left anterior cingulate cortex (–6, 33, –3), functional connectivity decreased at the left supplementary motor area extending to the bilateral paracentral lobule, and also decreased at the right supplementary motor area, medial frontal gyrus, and BA6. Functional connectivity based on the seed region at the right middle frontal gyrus (42, 51, 9) decreased at the left medial superior frontal gyrus, extending to the right medial superior frontal. Changes in functional connectivity based on all other ReHo clusters were not significant.

The brain regions with changes in fALFF, ReHo, and functional connectivity are shown in **Table 1** and **Figures 2** and **3**.

Discussion

Our data indicate that scalp acupuncture at MS5, the left MS6, and the left MS7 led to a decreased fALFF value (indicating negative activation) in a number of brain regions. fALFF represents the intensity of regional brain activity. We found decreased fALFF values mainly at the bilateral occipital lobe, including the lingual gyrus, cuneus, and the surrounding cortices of the calcarine sulcus, as well as the BA17. We found these areas, together with the right precuneus, to have decreased ReHo values. The ReHo represents the level of synchronous neuronal activity with respect to neighboring neurons. The cuneus and precuneus are integral parts of the default-mode network, which is involved in several cognitive functions including self-reflection, environment detection, and emotions. Downward activation in the default-mode network is observed when activation in other

Table 1 Brain regions and locations in healthy elderly participants with changes in fALFF, ReHo, and functional connectivity after International Standard Scalp Acupuncture

Parameter	Effect	Brain region	MNI coordinate			Intensity (T-value)
			X	*Y*	*Z*	
fALFF	Reduced	Bilateral cuneus, lingual gyrus, surrounding cortices of calcarine sulcus, BA17	18	–96	–6	–5.8991
ReHo	Reduced	Right precuneus, cuneus, surrounding cortices of calcarine sulcus, lingual gyrus	15	–72	21	–6.996
	Reduced	Left precentral gyrus and postcentral gyrus (representing head and facial region), left posterior superior temporal lobule (BA41, BA42, BA22)	–48	–12	27	–7.3221
	Enhanced	Bilateral anterior cingulate cortex, left medial frontal gyrus	–6	33	–3	8.9454*
	Enhanced	Right middle frontal gyrus, inferior frontal gyrus (BA46)	42	51	9	14.5384#
	Enhanced	Left supramarginal gyrus (BA40)	–48	–48	39	8.558
Functional connectivity	Reduced*	Bilateral supplemental motor area and paracentral lobule, right medial frontal gyrus and BA6	0	–12	57	–9.7768
	Reduced#	Bilateral medial superior frontal gyrus	0	54	3	–9.0382

X, *Y*, *Z* coordinates represent the left-right, anterior-posterior, and superior-inferior axes in MNI space, respectively. The left anterior cingulate cortex *(–6, 33, –3) and right medial frontal gyrus #(42, 51, 9) were used as the seed regions for functional connectivity analysis. fALFF: Fractional amplitude of low frequency fluctuation; ReHo: regional homogeneity; MNI: Montreal Neurological Institute.

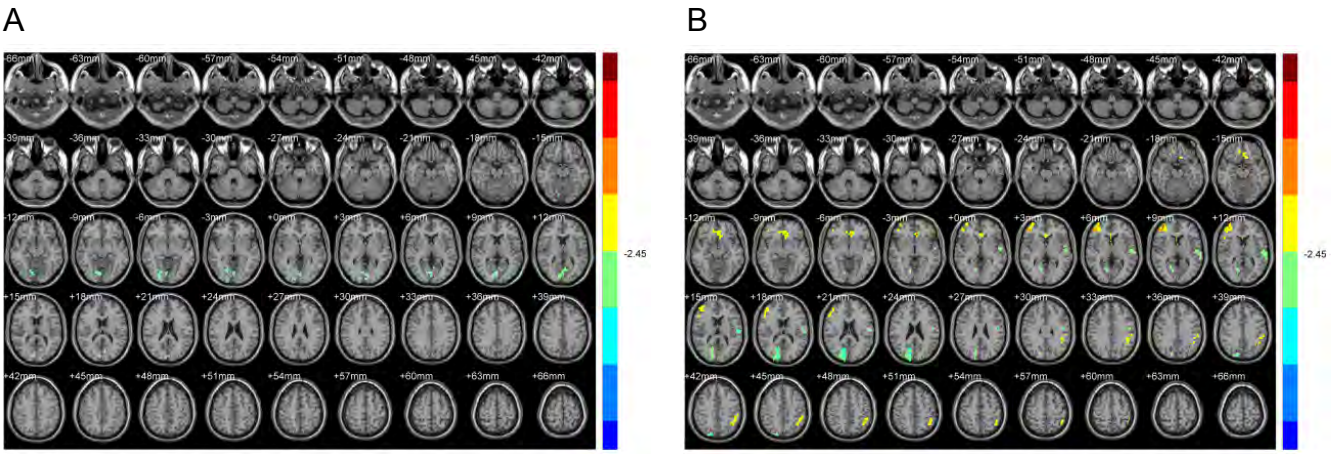

Figure 2 Brain regions with changes in fALFF (A) and ReHo (B) values after international standard scalp acupuncture.
Transition from yellow to red indicates differences in activation. Transition from green to blue indicates differences in deactivation. fALFF: Fractional amplitude of low frequency fluctuation; ReHo: regional homogeneity.

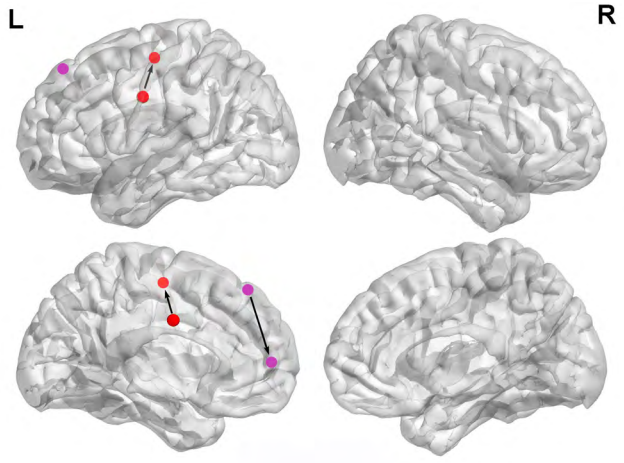

Figure 3 Regional changes in functional connectivity after international standard scalp acupuncture in healthy elderly participants.
The red dots and connecting line represent the functional connectivity based on the seed point at the left anterior cingulate cortex (–6, 33, –3). The purple dots and connecting line represent the functional connectivity based on the seed point at the right middle frontal gyrus (42, 51, 9).

brain regions is evoked during the transition from a resting state to a task state (Cavanna and Trimble, 2006; Zhong et al., 2011; Goffaux et al., 2014).

We found negative activation, indicated by a decline in both fALFF and ReHo values, in the right lingual gyrus, surrounding cortices of the calcarine sulcus, and BA17. The lingual gyrus is located between the calcarine sulcus and the collateral sulcus, and is a processing center for visual information, particularly visual memory and visual imagery (Bogousslavsky et al., 1987; Olivetti Belardinelli et al., 2009). The cortices surrounding the calcarine sulcus process visual signals. BA17 is the primary visual cortex. The observed decrease in activation in these two sites was likely caused by the lack of visual sensation, induced by the presence of the eye mask.

We found negative activation in terms of ReHo values in the left precentral gyrus, postcentral gyrus (representing the head and facial region), and posterior superior temporal gyrus (BA41, BA42, and BA22). The precentral gyrus and postcentral gyrus are known as the somatic motor and sensory cortices, respectively. The left BA41 and BA42 are known as

the primary and secondary auditory cortices. When grouped with BA22, which is involved in language processing, these regions form Wernicke's area (Lichteim, 1885). We found that synchronous activity was reduced among the sensory language center, the motor cortex, and the sensory cortex, which are all associated with pronunciation. We speculate that this reduction in activation was due to the experimental conditions, particularly, the participants wore earplugs and were asked to remain silent.

Conversely, we found enhanced local synchronous neuronal activity among the bilateral anterior cingulate cortex (BA32), left medial frontal gyrus, supramarginal gyrus (BA40), right middle frontal gyrus, and inferior frontal gyrus (BA46). The anterior cingulate cortex is thought of as a high-level functional unit in the frontal parietal network, where it allocates attentional resources and coordinates decision-making when there is a conflict among external/internal cognition and mentally-derived outcomes (Vincent et al., 2008). The left medial frontal gyrus plays a high-level role in coordinating execution, fear control, adjustment, language processing, and recognition of auditory signals (Talati and Hirsch, 2005; Tomoda et al., 2012; Frascarelli et al., 2015; Myung et al., 2016). The left supramarginal gyrus, positioned in the parietal lobe, is implicated in the integration of conceptual knowledge and motor representations into meaningful actions (Króliczak et al., 2016). BA46 is also involved in working memory, attention, behavioral control, and emotions (Zhang et al., 2003; Koike et al., 2011). Taken together, our data indicate that International Standard Scalp Acupuncture modulated the experience of being in the scanner, and enhanced the synchronous activities of several brain areas associated with cognitive and executive control networks.

In addition, we found that activation of the seed region at the anterior cingulate cortex and nearby regions suppressed functional connectivity among the bilateral supplementary motor area, paracentral lobule (which is involved in the regulation of defecation and micturition), and the left BA6, which is associated with the right premotor cortex. This implies that International Standard Scalp Acupuncture specifically enhanced the regulation of cognitive and executive control networks without further engaging the above-mentioned areas. Furthermore, that we found enhanced connectivity in the left medial frontal gyrus but reduced connectivity in the right medial frontal gyrus relative to the seed region at the anterior cingulate cortex indicates that International Standard Scalp Acupuncture had a major regulatory effect on activity in the dominant hemisphere.

Relative to that at the seed region at the right middle frontal gyrus (BA46), we found reduced functional connectivity at the bilateral medial superior frontal gyrus, which is connected anatomically to the anterior and middle cingulate cortices and involved in various cognitive control processes (Li et al., 2013). This implies that International Standard Scalp Acupuncture may activate neural networks at BA46 that are independent of the medial superior frontal gyrus.

The current study is limited in that we used a pre-post comparison with a small sample that had an unequal male-to-female ratio. Our study also lacked a control group with sham needles and participants with a medical condition. Thus, further investigation of scalp acupuncture is necessary in other participant groups.

This study preliminarily indicates that the international standard scalp acupuncture in healthy elderly participants specifically enhanced the correlation between the brain regions involved in cognition and implementation of the brain network regulation system and the surrounding adjacent brain regions.

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Declaration of participant consent: *The authors certify that they have obtained all appropriate participant consent forms. In the forms, the participants have given their consent for their images and other clinical information to be reported in the journal. The participants understand that their names and initials will not be published and due efforts will be made to conceal their identity.*
Reporting statement: *This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidance.*
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