BMJ Open

Relationship between Framingham Cardiovascular Risk Score and cognitive performance among ageing rural Indian participants: a cross-sectional analysis

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To cite: Mensegere AL, Sundarakumar JS, Diwakar L, *et al*. Relationship between Framingham Cardiovascular Risk Score and cognitive performance among ageing rural Indian participants: a cross-sectional analysis. *BMJ Open* 2023;**13**:e074977. doi:10.1136/bmjopen-2023-074977

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-074977).

Received 22 April 2023
Accepted 24 October 2023

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ABSTRACT

Objective The burden of cardiovascular risk factors is increasing in India, which, in turn, can adversely impact cognition. Our objective was to examine the effect of cardiovascular risk factors measured by Framingham Risk Score (FRS) on cognitive performance among a cohort of healthy, ageing individuals (n=3609) aged ≥45 years from rural India.

Design A cross-sectional analysis.

Setting A rural community setting in southern India.

Participants Healthy, ageing, dementia-free participants, aged 45 years and above, belonging to the villages of Srinivaspura (a rural community located around 100 km from Bangalore, India), were recruited.

Primary outcome measures Using a locally adapted, validated, computerised cognitive test battery, we assessed cognitive performance across multiple cognitive domains: attention, memory, language, executive functioning and visuospatial ability.

Results The median (IQR) age of the sample was 57 (50.65) and 50.5% were women. Multiple linear regression analysis showed that participants with higher FRS performed poorly in attention (visual attention (β=−0.018, p=0.041)), executive functioning (categorical fluency (β=−0.064, p<0.001)), visuospatial ability (form matching (β=−0.064, p<0.001) and visuospatial span (β=−0.020, p<0.001)), language (reading and sentence comprehension (β=−0.010, p=0.013), word comprehension (β=−0.021, p<0.001) and semantic association (β=−0.025, p<0.001)), and memory (episodic memory IR (β=−0.056, p<0.001), episodic memory DR (β=−0.076, p<0.001) and name-face association (β=−0.047, p<0.001)).

Conclusion Increased cardiovascular risk as evidenced by FRS was associated with poorer cognitive performance in all cognitive domains among dementia-free middle-aged and older rural Indians. It is imperative to design and implement appropriate interventions (pharmacological and lifestyle-based) for cardiovascular risk reduction and thereby, prevent or mitigate accelerated cognitive impairment in ageing individuals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A large sample of a rural Indian population, wherein the role of cardiovascular risk on cognitive performance, has been grossly understudied.

⇒ We included only cognitively normal participants (without dementia or mild cognitive impairment) to demonstrate that cardiovascular risk may start to affect cognitive performance even before the onset of dementia or predementia stages.

⇒ In addition to using a brief global cognitive screening instrument, we used a comprehensive, neuropsychological battery to assess all the individual cognitive domains; this battery was specifically adapted to suit rural community settings, thus minimising literacy and cultural bias.

⇒ The cross-sectional design of our study design prevented us from making causal connections.

⇒ As we used a composite cardiovascular risk score, it was not possible to delineate which risk factor impacted cognitive performance the most.

INTRODUCTION

Dementia is a complex condition that affects the brain and is characterised by a progressive decline in cognitive function, which can seriously impair an individual's ability to perform activities of daily living. This can have a significant impact on the individual's quality of life, as well as on their family and caregivers. The changes in demographic patterns in India are contributing to a rapid rise in the prevalence of dementia.[1] The number of people living with dementia in India by 2050 is projected to be around 14 million, a threefold increase from the current estimates.[2] The existing treatments available for dementia are not able to reverse the pathological process, hence the focus of research is on the early identification of risk factors and on developing preventive measures.

Cardiovascular risk factors are increasingly being implicated in the pathogenesis of dementia. There is a strong correlation between cardiovascular risk factors and cerebrovascular dysfunction, which, in turn can contribute to dementia. According to the Lancet Commission 2020, out of 12 potentially modifiable risk factors, six are cardiovascular risk factors (physical inactivity, hypertension, obesity, diabetes, smoking and excessive alcohol consumption).[3] Moreover, around two-thirds of people diagnosed with dementia show vascular pathology at autopsy.[4]

Cardiovascular diseases (CVDs) are one of the leading causes of mortality in India.[5] Compared with Europeans, Indians have earlier onset by a decade[6] and Indians tend to have higher case fatality and increased premature mortality compared with individuals from high-income countries.[7] This burden of CVD is seen across India, with significant variation across regions and communities. Rural Indians bear a considerable burden due to this CVD epidemic as their health awareness is poor, and their access to modern healthcare is limited. Further, given the low insurance coverage in rural areas, these individuals have to rely on out-of-pocket expenditures towards medical treatment, making them highly vulnerable to financial crises.

It is well known that cardiovascular risk factors tend to cluster together as they are often interrelated. Hence, the utility of multivariable, composite cardiovascular risk prediction scores is becoming increasingly recognised. One such score which is widely used and well-validated is the Framingham Cardiovascular Risk Score (FRS).[8] This is a sex-specific multivariable risk factor algorithm that was developed from the Framingham Heart Study and Framingham Offspring Study. FRS was built on the previous cardiovascular risk algorithms from the Framingham Heart Study and can be used to assess general CVD risk as well as the risk of individual CVD events, such as heart attack, stroke or death, from CVD over 10 years.

In the above scenario, some studies have investigated the association between FRS and cognitive impairment; however, the bulk of this research has been conducted on Western populations.[9] Given the ethnic differences in the effects of these risk factors on cognitive functions, this research evidence may not be generalisable to the Indian population. Further, though two-thirds of India's population is rural-dwelling, there is a dearth of such studies on rural Indians. Therefore, exploring whether there is an association between FRS and cognitive performance among ageing adults from rural India is of paramount importance while considering dementia prevention strategies in India.

We are conducting a first-of-its-kind, large-scale (projected n=10 000), community-based, prospective cohort study in a rural ageing population in southern India, namely, the Srinivaspura Aging, Neuro Senescence and COGnition (SANSCOG) study. This study is aimed at understanding the diverse patterns of cognitive ageing among rural Indians aged 45 years and above, using multidimensional assessments such as clinical, cognitive, biochemical, genetic and neuroimaging.[10] This, in turn, will help in identifying risk and protective factors for dementia and related disorders. The participants of the SANSCOG cohort are predominantly farmers, who are socioeconomically disadvantaged, have low levels of formal education and have settled in this rural area for several generations.

The current study aims to examine the cross-sectional association between FRS and cognitive performance in

Table 1 Framingham risk score for women

Points	Age	HDL	TC	SBP Not treated	SBP Treated	Smoker	Diabetic
–3				<120			
–2		≥60					
–1		50–59			<120		
0	30–34	45–49	<160	120–129		No	No
1		35–44	160–199	130–139			
2	35–39	<35		140–149	120–129		
3			200–239		130–139	Yes	
4	40–44		240–279	150–159			Yes
5	45–49		≥280	≥160	140–149		
6					150–159		
7	50–54				≥160		
8	55–59						
9	60–64						
10	65–69						
11	70–74						
12	≥75						

HDL, high-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol.

Mensegere AL, et al. BMJ Open 2023;13:e074977. doi:10.1136/bmjopen-2023-074977

various cognitive domains (attention, memory, language, executive functioning and visuospatial ability) among the non-demented participants from the SANSCOG cohort. We hypothesise that higher FRS would be associated with poorer cognitive performance across multiple cognitive domains.

METHODOLOGY

Study setting and participants

SANSCOG cohort comprises rural-dwelling individuals aged 45 years and above recruited from Srinivaspura 'taluk' (an administrative subdivision comprising of several villages) in Kolar district, Karnataka state in southern India. The current study is a cross-sectional analysis of data from SANSCOG participants who completed their baseline study assessments from January 2018 to October 2022. Out of the 4913 participants, 3609 individuals were included in the final analysis and 1304 participants were excluded for various reasons such as Clinical Dementia Rating (CDR) score≥0.5 or no CDR score (463), lack of motivation to do cognitive tests (386) and unavailability of complete data to calculate FRS (454).

Measurements

Study participants underwent a detailed clinical proforma, anthropometric measurements, cognitive assessments and laboratory investigations.

The FRS parameters such as age and smoking status were obtained through self-report. Blood pressure (BP) measurements were performed using a mercurial sphygmomanometer (Diamond Deluxe BP apparatus, Industrial Electronic & Allied Products) in all four limbs in both supine and standing positions; a total of eight readings were obtained (to the nearest 2 mm Hg). Some participants were not comfortable with having multiple BP measurements and for them, BP was measured in the right arm in the supine position. The systolic BP for each participant was taken to be the average of the available systolic BP measurements. Diabetes status was defined as a self-reported diagnosis of diabetes and/or fasting glucose≥126 mg/dL. Trained phlebotomists collected peripheral venous blood samples using vacutainers for the estimation of total cholesterol and high-density lipid (HDL) parameters using a standardised enzymatic method at a partner laboratory that is certified by the National Accreditation Board for Testing and Calibration Laboratories. We calculated FRS based on age, smoking status, systolic BP and medication for hypertension, total cholesterol, HDL cholesterol and diabetes for each participant at baseline separately for men and women.[8] Tables 1 and 2 give details of the score allotted for each cardiovascular risk factor for women and men, respectively.

The cognitive evaluation was performed by trained assessors using a digital neuropsychological battery called the Computerized Assessment of Information Processing (COGNITO),[11] which was adapted to suit our rural setting.[12] The attention domain comprises reaction time, auditory attention and visual attention tests. Reaction

Table 2 Framingham risk score for men

Points	Age	HDL	TC	SBP Not treated	SBP Treated	Smoker	Diabetic
−2		≥60		<120			
−1		50–59					
0	30–34	45–49	<160	120–129	<120	No	No
1		35–44	160–199	130–139			
2	35–39	<35	200–239	140–159	120–129		
3			240–279	≥160	130–139		Yes
4			≥280		140–159	Yes	
5	40–44				≥160		
6	45–49						
7							
8	50–54						
9							
10	55–59						
11	60–64						
12	65–69						
13							
14	70–74						
15	≥75						

HDL, high-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol;

time is measured as the mean latency between the appearance of a stimulus on the screen and the pressing of a key by the participant over multiple trials. The auditory attention test measures sustained attention for auditory stimuli by requiring the participant to report the number of a certain type of sound played over some time amidst another type of sound. The visual attention test assesses the ability to sustain visual attention by scanning a field for two target stimuli among distractors. For both these tests, the number of successful trials is considered the final score.

The executive function domain includes the categorical fluency test, where a participant is required to list as many vegetables as possible within a minute. The number of items recalled constitutes the score on this test. The visuospatial domain consists of form matching and visuospatial span tests. From matching test requires the participants to match a target figure with its clone from a set of six figures that are very similar to the target except for minute differences. The number of correct matches is considered the final score. Visuospatial span is assessed similarly to the Corsi block test[13] wherein a stimulus appears sequentially within blocks and then the participant is required to trace its path in the same order of appearance; visuospatial span is the number of blocks up to which the participant can remember the sequence of appearance.

The language domain includes reading and sentence comprehension, word comprehension, semantic associations and fluency tests. The reading and sentence comprehension test involves reading a sentence and executing the instructions provided in the sentence. The number of correct executions constitutes the final score on this task. The word comprehension test requires the participant to read a word that appears on screen and, subsequently, identify the pictorial representation of the read word from a set of six other pictures with distractors. The number of such correctly matched trials makes up the final score. The semantic associations test involves identifying an object that appears on screen and subsequently matching it with another object that has a functional and/or conceptual association with the target object. The number of right associations made comprises the final score for the task. In the fluency test, the participant is required to list words beginning with the letter ‘p’, within a minute. The number of items recalled constitutes the score on this test.

The memory domain comprises measures of episodic memory and name-face association tests. Episodic memory test measurement is similar to that in Rey Auditory Verbal Learning Test[14]; however, no intervening lists are present and the list learned is constituted by a list of names of persons. The number of names correctly recalled (in free recall), in immediate and delayed recall phases, are considered as measures of the same, respectively. While for the name-face association test, the list of names learned is associated with faces and the test trial requires volunteers to identify faces that they have seen before and learned the names of, from a series of both learned and unlearnt faces. The number of correct responses constitutes the total score on this task.

Covariates such as literacy and depression were assessed using self-reported years of completed formal education and the Geriatric Depression Scale, 30-item version (GDS-30), respectively.

Ethics

The Institutional Ethics Committee of the Centre for Brain Research, Indian Institute of Science, Bangalore approved the SANSCOG study. All participants provided voluntary, written informed consent for the study procedures.

Patient and public involvement

The residents and the concerned health officials of Srinivaspura help spread awareness of ageing and about the SANSCOG cohort study which is crucial in the recruitment of volunteers for the study. They also provide feedback on the burden of assessments which gets addressed periodically.

Statistical analysis

To examine the cross-sectional effect of FRS on cognitive performance, multiple linear regression analysis was performed where FRS was the independent variable, cognitive tests were the outcome variables, and years of education and GDS scores were used as covariates. Missing data were handled using the pairwise deletion method. All analyses were computed using the Statistical Package for Social Sciences software version.26, IBM Corp, NY, USA.

RESULTS

The sociodemographic information of the cohort is presented in table 3. In a sample of 3609 individuals, 1824 (50.5%) were women and the median (IQR) age of the sample was 57 (50.65). The median (IQR) years of education and GDS was 4 (0.9) and 2 (1.6), respectively. The majority of the cohort (99.2%) belonged to lower-middle and lower socioeconomic status. The median FRS score for the entire sample was 12 (9.16).

Separate multiple linear regression analysis was used to see the association of FRS with various cognitive tests after adjusting for years of education and GDS revealed that individuals with higher FRS performed poorly in all cognitive domains as shown in table 4.

In the attention domain, visual attention was inversely associated with FRS (β=−0.018, p=0.041), indicating that for every point increase in FRS, the visual attention score reduced by 0.018. However, there was no association between FRS and auditory attention (β=−0.001, p=0.982) or reaction time (β=0.234, p=0.128). Executive functioning measured using categorical fluency showed that people with higher FRS had lower categorical fluency (β=−0.064, p<0.001).

Table 3 Study characteristics

Variable (N=3609)	Median or N	IQR or %
Gender		
Male	1785	49.5%
Female	1824	50.5%
Socioeconomic status*		
Upper class (I)	27	0.8%
Middle class (II & III)	2355	67.3%
Lower class (IV & V)	1118	31.9%
Occupation		
Agricultural profession	1919	63.8%
Non-agricultural profession	1088	36.2%
Age (years)	57	50.65
Literacy† (years)	5	0.9
GDS	2	1.6
FRS	12	9.16

*Assessed by Modified Kuppuswamy Scale
†Total years of completed formal education
FRS, Framingham Risk Scores; GDS, Geriatric Depression Scale.

The visuospatial ability domain examined using form matching and visuospatial ability test revealed that with the increase in FRS scores, performance in the form matching test (β=−0.022, p<0.001) and visuospatial ability test reduced (β=−0.018, p=0.041).

In the language domain, there was an inverse correlation of FRS with reading and sentence comprehension (β=−0.010, p=0.013), word comprehension (β=−0.021, p<0.001) and semantic association tests (β=−0.025, p<0.001); no association was found with letter fluency test (β=−0.001, p=0.931).

Finally, in the memory domain, with the increase in FRS, performance in episodic memory-immediate recall (β=−0.056, p<0.001), name-face association (β=−0.047, p<0.001) and episodic memory delayed recall reduced (β=−0.076, p<0.001).

DISCUSSION

In a cohort of 3609 elderly ageing individuals without dementia from a rural Indian setting, we observed that participants with higher FRS had significantly lower cognitive performance across all the cognitive domains assessed—attention, executive functioning, visuospatial ability, language and memory. To the best of our knowledge, this is the first study from rural India examining the association of FRS with cognitive performance in a healthy, ageing cohort.

The findings of our study are in line with other studies worldwide among diverse populations. A cross-sectional, population-based study conducted among a large sample of adults with a mean age of 54 years demonstrated that higher FRS scores were associated with poorer cognitive functioning.[15] A recent multicentric study from middle-aged and older Latinos from the USA revealed that higher FRS was associated with poorer cognitive performance in global cognition as well as in learning and memory, verbal fluency and psychomotor speed.[16] On the other hand, a community-based study on normal ageing women from Australia showed that greater midlife scores on FRS

Table 4 Results of multiple linear regression analysis examining the association between Framingham Risk Scores and various cognitive domains

			95% CI for β			
Cognitive domain	Cognitive test	β	Lower	Upper	p	R^2
Attention	Reaction time	0.234	−0.068	0.536	0.128	0.010
	Auditory attention	−0.001	−0.062	0.060	0.982	0.006
	Visual attention	−0.018	−0.035	−0.001	**0.041**	0.235
Executive functioning	Categorical fluency	−0.064	−0.088	−0.040	**<0.001**	0.024
Visuospatial ability	From matching	−0.022	−0.034	−0.011	**<0.001**	0.264
	Visuospatial span	−0.020	−0.029	−0.011	**<0.001**	0.100
Language	Reading and sentence comprehension	−0.010	−0.017	−0.002	**0.013**	0.111
	Word comprehension	−0.021	−0.030	−0.012	**<0.001**	0.274
	Semantic association	−0.025	−0.035	−0.014	**<0.001**	0.303
	Letter fluency	−0.001	−0.014	0.013	0.931	0.276
Memory	Episodic memory IR	−0.056	−0.065	−0.047	**<0.001**	0.292
	Name-face association	−0.047	−0.056	−0.037	**<0.001**	0.231
	Episodic memory DR	−0.076	−0.088	−0.065	**<0.001**	0.313

Multiple linear regression models were constructed for each cognitive test (kept as outcome) while FRS was loaded as an independent variable along with years of education and Geriatric Depression Scale scores. Emboldened p values indicate statistical significance at p<0.05.
DR, delayed recall; IR, immediate recall; R^2, R square/R^2 coefficient; β, unstandardised coefficients.

were associated with poorer performance only in specific domains such as episodic memory but not in the other domains.

Further, longitudinal studies among Caucasian populations have also shown that worse scores on cardiovascular risk indices such as the FRS are associated with greater cognitive decline over time.[9 17 18] Further, a recent study from the Rush Memory and Aging project revealed that participants with the higher cardiovascular burden (higher FRS) not only had faster cognitive decline but also smaller total brain, grey matter and hippocampal volumes along with a higher burden of white matter hyperintensities.[19] A hospital-based cross-sectional study in China examined the effect of FRS on global cognition and found that participants with higher FRS had poorer cognitive performance.[20] A community-based study in Korea that examined the effects of cardiovascular risk factors on cognitive performance among dementia-free individuals concluded that individuals with high cardiovascular risk were associated with poorer cognitive function than those with low risk, especially older women.[21]

Current evidence suggests that cardiovascular risk factors play an important role in cognitive performance. While the mechanisms linking these risk factors to cognitive performance are clear for few, the association is more complex for others and needs further research to completely understand. Insulin resistance and dysregulation of glucose metabolism, and high BP could lead to abnormal cerebral perfusion and cortical atrophy.[22 23] High cholesterol levels are associated with the dysfunction of cleavage enzymes such as β-secretase and γ-secretase leading to increased production of B-amyloid which is usually modified with the presence of apolipoprotein four allele.[24] Smoking is postulated to cause inflammation and oxidative stress resulting in neuronal damage.[25]

A very large cohort study from India with a sample size of around 65 000 people demonstrated that the prevalence of CVD is high in India and women when compared with men have a higher risk of developing CVD.[26] Results from the same cohort study revealed that physical inactivity and obesity increased the likelihood of CVD by 22% and 60%, respectively.[27] Lifestyle-based interventions are the need of the hour to address these risk factors so that their impact on cognitive performance can be reduced.

Several intervention studies targeting cardiovascular risk factors have shown promising results in reducing dementia risk and/or improving cognition among ageing individuals. However, the majority of these trials focussed on individual risk factors—for example, hypertension,[28] diabetes[29] and so on. However, it is vital to have multimodal interventions that target multiple risk factors owing to their synergistic effects on dementia risk, implying that even a small reduction in multifactorial risk could substantially decrease overall risk. Further, such multidomain interventions would also be cost-effective and easily translatable into national-level public health strategies. Of late, the importance of such multidomain, lifestyle-based interventions is being increasingly recognised, owing to large, international studies, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability,[30] the Multidomain Alzheimer Preventive Trial[31] and the Prevention of Dementia by Intensive Vascular Care study.[32]

However, such multimodal, lifestyle-based interventions cannot be directly translated to the Indian scenario for various reasons. For example, dietary recommendations, such as the Mediterranean diet, may not be culturally accepted, and it is costly. Similarly, vigorous aerobic exercises may not be suitable for ageing individuals in India and these may need to be substituted with milder exercises such as Yoga or brisk walking. Cognitive training needs to be adapted to the rural Indian population, where the majority have low levels of formal education. Additionally, such interventions should be tailored in a way that they can be implemented in a situation where the public healthcare system is resource-limited. Furthermore, factors such as low levels of health awareness and poor access to modern technology among rural Indians should also be considered. For example, a small study from India that employed a short-term, Yoga-based lifestyle intervention programme demonstrated a lowering of FRS after the intervention.[33]

The strengths of our study include a large sample size of a rural population, whose cardiovascular risk profile could be different from that of their urban counterparts, and understanding the impact of these cardiovascular risk factors on cognition is very crucial in this population. Also, the study sample included only participants without dementia and mild cognitive impairment to demonstrate that cardiovascular risk may start to affect cognitive performance even before the onset of dementia or predementia syndromes. Finally, unlike most of the previous studies which used brief global cognitive measures or a few selected cognitive domains, we used a comprehensive, neuropsychological battery that was adapted to suit rural community settings to assess all the individual cognitive domains. The effect of FRS on most cognitive tests was quite significant as demonstrated by decent effect sizes (R^2 coefficient around 0.30), except for categorical fluency, visuospatial span, and reading and sentence comprehension tests.

Our study does have a few limitations, and the major one is the cross-sectional study design, which prevents us from making causal connections. Furthermore, the FRS algorithm that we used was originally developed based on data from a Caucasian population and it would have been better if a cardiovascular risk score specific to the Indian population was applied. Finally, a disadvantage of using composite risk scores is that it is not possible to delineate which risk factor impacted cognitive performance the most. We intend to follow these participants for over a decade and explore the relationship between cardiovascular risk factors and cognitive decline, also we would like to explore how these CVD risk factors affect brain morphology using structural MRI. India is a diverse country with different ethnic and racial groups. Our results may not be generalisable to entire India, and we recommend such studies be replicated in other parts of India.

In conclusion, our findings suggest that the FRS could be a simple and useful tool for assessing or predicting risk for cognitive impairment among ageing individuals. We recommend routine screening for these cardiovascular risk factors, periodic monitoring of risk scores and aggressive management of these risk factors. There is an urgent need to address these cardiovascular risk factors through public policy measures to mitigate the rising burden of dementia in India.

Acknowledgements We are grateful to the volunteers who participated in the SANSCOG study.

Collaborators SANSCOG Study Team: BN Gangadhar, NIMHANS, Psychiatry; Girish N Rao, NIMHANS, Public Health; Naren P Rao, NIMHANS, Psychiatry; Palanimuthu T Sivakumar, NIMHANS, Psychiatry.

Contributors ALM: conceptualisation, methodology, validation, formal analysis, data curation, writing—original draft preparation, visualisation. JSS: conceptualisation, methodology, validation, writing—review and editing, project administration and is responsible for the overall content as guarantor. LD: conceptualisation, methodology, validation, writing—review and editing. TGI: conceptualisation, methodology, validation, writing—review and editing, project administration. SANSCOG Study Team: conceptualisation, methodology, data collection and project administration. All authors approved the final version of the manuscript for publication. All authors had full access to the data in the study and take responsibility for data integrity and accuracy of data analysis.

Funding The SANSCOG study is funded by Pratiksha Trust through the Centre for Brain Research. The funding source did not have any role in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript and in the decision to submit the article for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by CBR Institutional Ethics Committee. IEC Number: CBR/42/IEC/2022-23. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author, JSS, upon reasonable request.

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