

## PAPER

# Risk factors for acute ischaemic stroke in young adults in South India

K Lipska, P N Sylaja, P S Sarma, K R Thankappan, V R Kutty, R S Vasan, K Radhakrishnan

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See end of article for authors' affiliations

Correspondence to:  
Dr K Radhakrishnan,  
Department of Neurology,  
Sree Chitra Tirunal Institute  
for Medical Sciences and  
Technology, Trivandrum-  
695 011, Kerala, India;  
krk@sctimst.ac.in

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**Background:** Stroke is a leading cause of death and disability in developing countries, afflicting individuals at a young age. The contribution of established vascular risk factors to ischaemic stroke in young adults has not been evaluated systematically in Indians.

**Methods:** We conducted a case control study in 214 South Indian patients with first acute ischaemic stroke that occurred between the ages of 15 and 45 years, 99 age and sex matched hospital controls and 96 community controls. We compared the prevalence of the following risk factors: smoking, elevated blood pressure, high fasting blood glucose and abnormal lipids.

**Results:** Compared with community controls, stroke patients had a higher prevalence of smoking (multivariable adjusted odds ratio (OR) 7.77, 95% CI 1.93 to 31.27), higher systolic blood pressure (OR per SD increment of 1.88, 95% CI 1.01 to 3.49) and fasting blood glucose (OR per SD increment of 4.55, 95% CI 1.63 to 12.67), but lower high density lipoprotein (HDL) cholesterol (OR per SD increment of 0.17, 95% CI 0.09 to 0.30). Compared with hospital controls, stroke patients had a higher prevalence of smoking (OR 3.95, 95% CI 1.61 to 9.71) and lower HDL cholesterol (OR per SD increment 0.27, 95% CI 0.17 to 0.44). The presence of  $\geq 3$  metabolic syndrome components was associated strongly with stroke (OR 4.76, 95% CI 1.93 to 11.76; OR 2.09, 95% CI 1.06 to 4.13) compared with community and hospital controls.

**Conclusions:** Key components of the metabolic syndrome and smoking are associated with ischaemic stroke in young South Indian adults. Our observations underscore the importance of targeting adolescents and young adults for screening and prevention to reduce the burden of ischaemic stroke in young adults.

Stroke is the leading cause of adult disability and is the second commonest cause of death worldwide.<sup>1</sup> More than two-thirds of the global burden of stroke is borne by developing countries, where the average age of patients with stroke is 15 years younger than in developed countries.<sup>2</sup> The available limited data indicate that stroke occurring in young people is more often atherothrombotic in origin in developing countries,<sup>3–5</sup> in contrast with developed countries where arterial dissection and cardioembolic aetiologies predominate.<sup>6–9</sup>

We hypothesised that ischaemic stroke occurring in young Indians may be a manifestation of accelerated cerebrovascular atherosclerosis, paralleling the early age of onset of cardiovascular diseases noted for this population.<sup>10</sup> Additionally, based on prior data on increased propensity for insulin resistance among South Asians,<sup>11 12</sup> we postulated that ischaemic stroke in young adults in India will be associated with the combination of risk factors that identify the metabolic syndrome. We tested our hypotheses by conducting a case control study of adults between the ages of 15 and 45 years belonging to the South Indian state of Kerala with a first ischaemic stroke.

## SUBJECTS AND METHODS

### Study site

This study was conducted at the Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, the capital city of the South Indian state of Kerala, situated on the south west coast of the Indian peninsula. This tertiary referral centre for cardiological, neurological and vascular disorders receives patients from all over Kerala as well as the neighbouring state of Tamil Nadu. All participants provided informed consent, and the study protocol was approved by the institutional review board of SCTIMST.

## Study subjects

### Cases

We recruited 214 consecutive patients, aged 15–45 years, hospitalised to SCTIMST with a first ischaemic stroke during the period 1995–2001. We used the WHO definition of stroke,<sup>13</sup> and the diagnosis of ischaemic stroke was supported in every patient by axial CT and/or MRI. Patients were excluded for the following reasons: prior history of stroke; presentation to the hospital >6 months after stroke onset; haemorrhagic stroke; and intracranial sinus–venous thromboses.

### Controls

We recruited two sets of controls: 99 hospital controls and 96 community controls. The hospital controls were gathered prospectively during the period January to June 2002 by two investigators (KL, PNS) from eligible individuals, aged 15–45 years, who presented to SCTIMST without a prior history of stroke or heart disease. They included patients (and their family members) attending the general neurology or epilepsy clinics for follow-up of neurological disorders other than stroke (or transient ischaemic attack) or complications of vascular disease, and patients admitted to general neurology inpatient wards for neurological disorders other than stroke or transient ischaemic attack, or complications of vascular disease, and who were not currently receiving steroid treatment. Hospital controls were matched to cases for age (within 5 years) and sex. As community controls, we recruited 96 subjects from a community based sample of individuals aged 20–45 years residing in the Trivandrum city, who were recruited in 1999

**Abbreviations:** HDL, high density lipoprotein; SCTIMST, Sree Chitra Tirunal Institute for Medical Sciences and Technology; TOAST, Trial of Org 10172 in Acute Stroke Treatment

**Table 1** Characteristics of stroke cases and controls

	Community controls (n = 96)	p Value	Cases (n = 214)	p Value	Hospital controls (n = 99)
Age (y)*	33 (8)	0.04	35 (7)	0.03	33 (8)
Men (%)	42	<0.001	66	0.52	63
Current smoking (%)	6	<0.001	37	<0.001	12
Blood pressure					
Systolic blood pressure (mm Hg)	122 (12)	0.008	127 (17)	0.44	125 (14)
Diastolic blood pressure (mm Hg)	81 (7)	0.25	82 (11)	0.14	80 (9)
Hypertension (%)	17	0.001	36	0.09	25
Hypertension treatment (%)	5	0.10	12	0.10	5
Lipids					
Serum total cholesterol (mmol/l)	5.55 (1.14)	0.41	5.38 (1.89)	0.79	5.32 (1.21)
HDL cholesterol (mmol/l)	1.40 (0.33)	<0.001	0.94 (0.30)	<0.001	1.24 (0.32)
Non-HDL cholesterol (mmol/l)	4.15 (1.22)	0.36	4.29 (1.20)	.22	4.11 (1.08)
Total cholesterol/HDL ratio	4.2 (1.5)	<0.001	5.9 (1.9)	<0.001	4.5 (1.2)
Hypercholesterolaemia (%)	33	0.50	29	0.41	24
Treatment for dyslipidaemia	Nil	1.000	1	0.04	5
Triglycerides (mmol/l)	1.23 (0.76)	<0.001	1.61 (0.94)	0.19	1.47 (0.68)
Glycaemia					
Fasting blood sugar (mmol/l)	4.34 (1.03)	<0.001	5.26 (2.53)	0.52	5.09 (1.83)
Diabetes mellitus	4	0.02	14	0.13	7
Treatment for diabetes (%)	1	0.01	8	0.36	5
Metabolic syndrome traits (%)					
BP $\geq$ 130/85 mm Hg or on antihypertensive treatment	26	<0.001	50	0.81	49
HDL <40 (men), <50 mg/dl (women) or lipid lowering treatment	26	<0.001	65	<0.001	35
Triglycerides $\geq$ 150 mg/dl	18	0.02	31	0.35	25
Fasting blood sugar $\geq$ 100 mg/dl or on treatment	4	<0.001	23	1.000	23
$\geq$ 3 ATP III criteria	6	<0.001	27	0.008	13

BP, blood pressure; HDL, high density lipoprotein.

Values are mean (SD), unless indicated otherwise.

Smoking was defined as current use of inhaled tobacco.

Hypercholesterolaemia was defined as (1) previously diagnosed by a physician or (2) receiving lipid lowering treatment or (3) total cholesterol  $\geq$ 240 or low density lipoprotein  $\geq$ 160.

Diabetes mellitus was defined as (1) previously diagnosed by a physician (prescribed treatment) or (2) on oral hypoglycaemic agents or insulin or (3) fasting blood sugar >126, single measurement available only.

Hypertension was defined as systolic blood pressure  $\geq$ 140 or diastolic blood pressure  $\geq$ 90 or any treatment for high blood pressure.

ATP III criteria: triglycerides  $\geq$ 150, high density lipoprotein <40 for men or <50 for women, blood pressure  $\geq$  130/85 or on treatment, fasting blood sugar  $\geq$ 100 or on treatment.

p values are based on t test for comparison of means, and Fisher's exact test for proportions.

\*Age distribution of cases, n (%): 15–20 years 13 (6); 21–30 years 49 (23); 31–40 years 104 (49); 41–45 years 48 (22). Age distribution of hospital controls, n (%): 15–20 years 9 (9); 21–30 years: 28 (28); 31–40 years 42 (43); 41–45 years 20 (20). Age distribution of community controls, n (%): 15–20 years 3 (3); 21–30 years 36 (37); 31–40 years 37 (39); 41–45 years 20 (21).

by one of the authors (VR) for a separate investigation of serum lipids and other risk factors for ischaemic heart disease.<sup>14</sup>

### Data collection

For cases, using a structured proforma, the investigators (KL, PNS) abstracted demographic, clinical and investigative data, and stroke risk factors from the medical records. We ascertained blood pressure, fasting lipids and fasting blood glucose at approximately a week or later after stroke onset, as elevations in blood pressure, hyperglycaemia and lower blood lipids are well documented during the acute phase of stroke.<sup>15–17</sup> While hospital controls were personally interviewed to gather the required data, the same were accessed from the data already available for community controls.<sup>14</sup> Blood glucose, total and high density lipoprotein (HDL) cholesterol, and triglycerides were estimated on automated systems with standardised kits using enzymatic methods for both cases and controls (glucose oxidase, cholesterol oxidase, precipitation method and glycerol phosphate oxidase, respectively). Non-HDL cholesterol was estimated by subtracting HDL cholesterol from total cholesterol.

### Categorisation of stroke subtypes

Stroke subtypes were assigned independently by two investigators (KL, PNS; kappa 0.82) according to the TOAST (Trial of

Org 10172 in Acute Stroke Treatment) criteria.<sup>18</sup> All disagreements between the two investigators were resolved through discussion with the senior neurologist (KR).

### Statistical analyses

We assessed statistical significance of the risk factors between cases and either of the controls (table 1). The variables for multiple logistic regression modelling were selected based on the significance in bivariate analyses and low intercorrelations among them. Two sets of analyses were conducted: one evaluating all ischaemic strokes and another excluding patients with cardioembolism and stroke due to other determined aetiology. Unconditional logistic regression adjusting for matching variables was used because perfect matching was not possible for hospital controls, and community controls were not matched. We adjusted all models for age and sex, and evaluated the following vascular risk factors: systolic and diastolic blood pressure, smoking, blood glucose, serum total cholesterol, HDL cholesterol, non-HDL cholesterol and triglycerides. Other than sex and smoking, all variables were modelled as continuous variables. In additional analyses, we evaluated risk factors as categorical variables using standardised definitions of hypertension (systolic blood pressure  $\geq$ 140 or diastolic blood pressure  $\geq$ 90 mm Hg or treatment),<sup>19</sup> hypercholesterolaemia ( $\geq$ 6.22 mmol/l (240 mg/dl))<sup>20</sup> and diabetes

**Table 2** Risk factors associated with ischaemic stroke: results of multivariable logistic regression

	Compared with community controls		Compared with hospital controls	
	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value
<b>All ischaemic strokes</b>				
(A) Models with individual risk factors				
Fasting blood sugar	4.55 (1.63, 12.67)	0.004	1.17 (0.68, 2.02)	0.57
Total cholesterol	0.86 (0.44, 1.68)	0.66	1.92 (0.97, 3.82)	0.06
HDL cholesterol	0.17 (0.09, 0.30)	<0.001	0.27 (0.17, 0.44)	<0.001
Triglycerides	0.70 (0.37, 1.32)	0.27	0.67 (0.40, 1.11)	0.12
Smoking	7.77 (1.93, 31.27)	0.004	3.95 (1.61, 9.71)	0.003
Systolic blood pressure	1.88 (1.01, 3.49)	0.045	1.13 (0.74, 1.73)	0.57
(B) Models with clustering of metabolic syndrome components				
≥3 components	4.76 (1.93, 11.76)	<0.001	2.09 (1.06, 4.13)	0.03
<b>Strokes excluding cardioembolic and strokes due to other aetiologies</b>				
(A) Models with individual risk factors				
Fasting blood sugar	4.33 (1.45, 12.96)	0.009	1.12 (0.58, 2.19)	0.73
Total cholesterol	1.10 (0.51, 2.39)	0.80	2.45 (1.09, 5.51)	0.03
HDL cholesterol	0.15 (0.07, 0.30)	<0.001	0.26 (0.15, 0.46)	<0.001
Triglycerides	0.77 (0.39, 1.50)	0.44	0.77 (0.42, 1.42)	0.41
Smoking	8.73 (2.14, 35.68)	0.003	5.38 (2.01, 14.39)	0.001
Systolic blood pressure	2.35 (1.11, 4.96)	0.03	1.29 (0.79, 2.12)	0.31
(B) Models with clustering of metabolic syndrome components				
≥3 components	5.75 (2.24, 14.76)	<0.001	2.38 (1.16, 4.87)	0.02

HDL, high density lipoprotein.

All models adjusted for age and sex. Model A also adjusts for antihypertensive treatment, lipid or blood sugar lowering treatment.

OR here should be per 1 SD increment in fasting blood sugar, systolic blood pressure, triglycerides, total and HDL cholesterol (1 SD for cases; see table 1).

mellitus ( $\geq 7.0$  mmol/l (126 mg/dl)).<sup>21</sup> Effect modification by age was evaluated by modelling appropriate interaction terms for each risk factor (eg, age  $\times$  blood pressure). Odds ratios (OR) and their 95% confidence intervals (CI) were estimated for each risk factor. As data on waist circumference were not available in the medical records, we considered the remaining components of the metabolic syndrome based on revised criteria of the International Diabetes Federation<sup>22</sup>: raised triglycerides  $\geq 1.7$  mmol/l (150 mg/dl) or specific treatment for this lipid abnormality; reduced HDL cholesterol  $< 1.03$  mmol/l (40 mg/dl) in men and  $< 1.29$  mmol/l (50 mg/dl) in women or specific treatment for this lipid abnormality; raised blood pressure, systolic  $\geq 130$  or diastolic  $\geq 85$  mm Hg or treatment of previously diagnosed hypertension; raised fasting blood glucose  $\geq 5.6$  mmol/l (100 mg/dl) or previously diagnosed type 2 diabetes.

## RESULTS

### Stroke subtypes

Based on the TOAST criteria,<sup>18</sup> there were 54 (25.2%) patients with cardioembolic stroke (45 major and 9 minor sources of cardiac embolism), 27 (12.6%) with large artery atherosclerosis and 16 (7.5%) with lacunar infarcts. Twenty-four (11.2%) strokes were adjudicated as of other determined aetiology: 15 patients with arterial dissection (7.0%; 8 carotid system and 7 vertebrobasilar system dissections), 3 possibly related to a haematological/immunoinflammatory condition (1 each with lupus erythematosus, primary antiphospholipid antibody syndrome and protein S deficiency), 2 patients with ectasia (one in the vertebrobasilar system, one involving the left middle cerebral artery) and 4 due to other causes (1 case of each: Moya Moya disease, Takayasu's arteritis, fibromuscular dysplasia and nephrotic syndrome). Ninety-three strokes (43.5%) were deemed to be of "indeterminate origin"; of the latter, 23 patients were incompletely investigated (lack of echocardiography and carotid Doppler ultrasonography or angiography), 5 had more than one potential cause for stroke and in 65 patients no cause of stroke was determined despite complete investigation.

### Prevalence of vascular risk factors among cases and controls

The characteristics of the ischaemic stroke cases and the two sets of controls are compared in table 1. Approximately 70% of cases and hospital controls were aged 20–40 years, compared with 76% of community controls. Compared with community controls, cases were more likely to be smokers, had higher systolic blood pressure, fasting blood sugar and lower HDL cholesterol levels, and a greater prevalence of hypertension and diabetes mellitus. Compared with hospital controls, cases were more likely to report smoking and had lower HDL cholesterol levels. Mean serum total cholesterol levels in cases did not differ from that in community or hospital controls. A higher proportion of cases had three or more components of the metabolic syndrome compared with both sets of controls.

### Multivariable analyses

In multivariable logistic regression analyses comparing cases to community controls (table 2), smoking (about 8-fold odds compared with non-smokers), higher fasting blood glucose (4.6-fold odds per SD increment) and systolic blood pressure (1.9-fold odds per SD increment) were all associated with stroke. HDL cholesterol was related inversely to stroke (83% lower odds per SD increment). Triglyceride levels (table 2) and non-HDL cholesterol (adjusted OR per SD increment 0.90, 95% CI 0.65 to 1.25,  $p = 0.55$ ) were not associated with stroke risk. In multivariable models incorporating the ratio of total to HDL cholesterol (instead of the two variables separately), a unit increase in the ratio was associated with a doubling of stroke risk (adjusted OR 2.15, 95% CI 1.55 to 2.96,  $p < 0.0001$ ). These relations were consistent when analyses were repeated excluding individuals with cardioembolic stroke and stroke due to other aetiologies (table 2). In analyses assessing effect modification by age, none of the interaction terms for different risk factors was statistically significant. The presence of three or more components of the metabolic syndrome was associated with an approximately 5-fold stroke risk (table 2). In analyses of risk factors as categorical variables, smoking (adjusted OR 7.14, 95% CI 2.73 to 18.64,  $p < 0.001$ ) and hypertension

(adjusted OR 2.46, 95% CI 1.25 to 4.84) were associated with increased stroke risk, whereas a borderline significant association with diabetes was observed (adjusted OR 2.94, 95% CI 0.93 to 9.30,  $p = 0.07$ ).

In analyses comparing cases with hospital controls (table 2), smoking was positively related to stroke (near 4-fold odds compared with non-smokers), whereas HDL cholesterol was inversely related (73% lower odds per SD increment). A unit increase in the ratio of total to HDL cholesterol was associated with a more than 2-fold stroke risk (adjusted OR 2.36, 95% CI 1.68 to 3.32). High systolic blood pressure, blood sugar, triglyceride levels (table 2) and non-HDL cholesterol (adjusted OR per SD increment 1.06, 95% CI 0.77 to 1.47,  $p = 0.71$ ) were not associated with stroke risk. We did not observe any effect modification by age (all interaction terms were non-significant). The presence of three or more components of the metabolic syndrome was associated with an approximately 2-fold stroke risk (table 2). These findings were consistent when analyses were restricted to individuals without cardioembolic stroke or stroke due to other aetiologies (table 2). In analyses of risk factors as categorical variables, only smoking was associated with increased stroke risk (adjusted OR 5.22, 95% CI 2.49 to 10.94,  $p < 0.001$ ).

## DISCUSSION

To our knowledge, the present investigation is the first case control study that has evaluated risk factors for ischaemic stroke in young adults in India. Two previous case control studies, one in the Parsi community of Bombay (present Mumbai), Central India,<sup>23</sup> and the other in the South Indian population of Madras (present Chennai),<sup>24</sup> included completed ischaemic strokes in all age groups.

The selection of controls is usually the most difficult aspect of the case control study design. Although several strategies for control selection are possible, all have certain limitations.<sup>25</sup> The use of more than one set of controls can test concordance of results across control groups, which increases the validity of the results.<sup>25</sup> This prompted us to use both community and hospital based controls to investigate the contribution of established vascular risk factors to the development of stroke risk in young adults. The two sets of our controls yielded mostly consistent findings (both in the overall sample and in analyses excluding individuals with cardioembolic and strokes of other aetiology): smoking, low HDL cholesterol levels and the presence of three or more components of the metabolic syndrome emerged as key risk factors for stroke. A stronger association of hyperglycaemia and higher systolic blood pressure with stroke risk was observed in analyses comparing cases with community controls. One potential explanation may be that hospital controls had higher blood sugar and blood pressure levels relative to community controls, in part related to the stress of the hospital environment, diminishing the ability of these factors to distinguish them from cases. Other investigators have reported that hospital controls may resemble cases more, and differ from community controls.<sup>26 27</sup>

Although observational studies from Western countries have emphasised the preponderance of cardiogenic embolism, arterial dissection, procoagulant states and non-atherosclerotic vasculopathies as possible aetiologies,<sup>6-9</sup> careful analytic comparisons have shown the importance of traditional risk factors in the pathogenesis of stroke in the young adults.<sup>28 29</sup> In the Baltimore-Washington Cooperative Young Stroke Study,<sup>28</sup> which compared 296 cases of incident ischaemic stroke among black and white adults aged 18-44 years with 1220 community based adults of the same age group, hypertension, diabetes mellitus and current smoking emerged as important risk factors. Similarly, in a comparison of 201 consecutive patients

with first onset stroke due to cerebral infarction aged 15-55 years and the same number of matched neighbourhood control subjects conducted as part of the Melbourne Risk Factor Study,<sup>29</sup> hypertension, diabetes mellitus, current smoking, heart disease and long term heavy alcohol consumption were major risk factors. The two case control studies from India that included ischaemic stroke in all age groups suggested that hypertension, diabetes mellitus and smoking are important risk factors for stroke in India as they are worldwide.<sup>23 24</sup> Our observation of the association of the traditional risk factors with stroke in the young adults emphasises their role in the pathogenesis of ischaemic stroke in this age group.

The role of dyslipoproteinaemia in the pathogenesis of cerebrovascular disease is less certain than for coronary artery disease; more consistent association has been noted with low HDL cholesterol and high total cholesterol to HDL cholesterol ratio than with total cholesterol, low density lipoprotein cholesterol and triglycerides.<sup>30 31</sup> Low HDL cholesterol was the only serum lipid index associated with an increased risk of ischaemic stroke among 94 consecutive patients under 45 years admitted to a tertiary care facility in Toulouse, France, when compared with 111 controls of the same age.<sup>32</sup> In a case control study involving 204 patients with acute ischaemic stroke of all ages from Madras, South India, the authors found that while low HDL cholesterol and high total cholesterol to HDL cholesterol ratio were more frequent among patients, total serum cholesterol, triglycerides and low density lipoprotein cholesterol levels did not significantly differ.<sup>24</sup> Our results among stroke in young adults are consistent with these observations. HDL cholesterol plays a fundamental role in the regulation of atherogenesis via its effects on reverse cholesterol transport<sup>33</sup> and vascular remodelling.<sup>34</sup>

Even though fasting blood glucose, systolic blood pressure and lipid profile were not consistently different between cases and the two control groups, the strong association of the conjoint presence of multiple components of the metabolic syndrome with stroke in young adults is a striking observation of the present report. Although several prior reports have associated the metabolic syndrome with stroke risk in middle aged to older adults,<sup>35-37</sup> to our knowledge, such an association has not been established for stroke in young adults. Overall, our observations add to the growing body of evidence implicating insulin resistance, a precursor of the metabolic syndrome, in the development of vascular disease in young people of South Asian origin.<sup>11 12</sup> Metabolic syndrome in the South Indian population has recently been reported to be associated with Thr54 allele carriers of the Ala54Thr variant of FABP2 gene.<sup>38</sup> The relative contribution of genetic predisposition and extraneous influences such as food, tobacco and meteorological factors in the pathogenesis of metabolic syndrome among the South Indian population is at present unknown.

The use of standardised criteria for ischaemic stroke, two sets of controls, controls of similar ethnicity and from a limited geographic region strengthen the present investigation. However, we acknowledge the following limitations of our approach. The study was conducted in a tertiary care referral centre for neurological and cardiovascular diseases and may therefore be biased towards more disabling and complicated disease processes. Strokes of indeterminate origin were overrepresented in the sample, presumably because of incomplete investigation of our cases. The modest sample size for controls might have diminished our statistical power to detect more moderate associations with selective risk factors. Additional limitations include the retrospective abstraction of data from medical records, use of single occasion measurements of risk factors, limited ability to characterise a dose-response for key variables such as smoking and lack of waist circumference measurement.

Despite these limitations, our study incriminates known vascular risk factors in the pathogenesis of ischaemic stroke in young adults, raising the possibility that accelerated atherosclerosis may be the underlying substrate, rather than rarer aetiologies commonly sought in such individuals. Tobacco smoking<sup>39</sup> and diabetes<sup>40</sup> are growing problems in the developing countries. Our findings suggest that smoking cessation, identification and treatment of elevated blood pressure, dyslipidaemia and diabetes are critical measures for preventing ischaemic stroke in young adults seen in this geographical region.

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## Authors' affiliations

**K Lipska**, Department of Medicine, Brigham and Women's Hospital, Boston University School of Medicine, Boston, Massachusetts, USA  
**P N Sylaja, K Radhakrishnan**, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India  
**P S Sarma, K R Thankappan**, The Achutha Menon Centre For Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India  
**V R Kutty**, Health Action by People, Kerala, India  
**R S Vasan**, Cardiology Section and Preventive Medicine and Epidemiology, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA

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Individual author's contribution to this research and responsibilities: Drs Lipska, Sylaja, Radhakrishnan and Vasan were involved in study conception and design, analysis and interpretation of the data, including writing and critical revision of the report. Dr Sarma provided statistical expertise and directed the analysis and interpretation of the data, and participated in the writing and critical revision of the report. Dr Kutty participated in the collection of data on community controls, the analysis and interpretation of data, and the writing and critical revision of the report. Dr Thankappan contributed to the interpretation of the data, including writing and critical revision of the report. The corresponding author, Dr Radhakrishnan, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

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