

Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study



Martin J O'Donnell, Siu Lim Chin, Sumathy Rangarajan, Denis Xavier, Lisheng Liu, Hongye Zhang, Purnima Rao-Melacini, Xiaohe Zhang, Prem Pais, Steven Agapay, Patricio Lopez-Jaramillo, Albertino Damasceno, Peter Langhorne, Matthew J McQueen, Annika Rosengren, Mahshid Dehghan, Graeme J Hankey, Antonio L Dans, Ahmed Elsayed, Alvaro Avezum, Charles Mondo, Hans-Christoph Diener, Danuta Ryglewicz, Anna Czlonkowska, Nana Pogossova, Christian Weimar, Romaina Iqbal, Rafael Diaz, Khalid Yusoff, Afzalhussein Yusufali, Aytekin Oguz, Xingyu Wang, Ernesto Penaherrera, Fernando Lanas, Okechukwu S Ogah, Adesola Ogunniyi, Helle K Iversen, German Malaga, Zvonko Rumboldt, Shahram Oveisgharan, Fawaz Al Hussain, Daliwonga Magazi, Yongchai Nilanont, John Ferguson, Guillaume Pare, Salim Yusuf; on behalf of the INTERSTROKE investigators*

Summary

Background Stroke is a leading cause of death and disability, especially in low-income and middle-income countries. We sought to quantify the importance of potentially modifiable risk factors for stroke in different regions of the world, and in key populations and primary pathological subtypes of stroke.

Methods We completed a standardised international case-control study in 32 countries in Asia, America, Europe, Australia, the Middle East, and Africa. Cases were patients with acute first stroke (within 5 days of symptom onset and 72 h of hospital admission). Controls were hospital-based or community-based individuals with no history of stroke, and were matched with cases, recruited in a 1:1 ratio, for age and sex. All participants completed a clinical assessment and were requested to provide blood and urine samples. Odds ratios (OR) and their population attributable risks (PARs) were calculated, with 99% confidence intervals.

Findings Between Jan 11, 2007, and Aug 8, 2015, 26 919 participants were recruited from 32 countries (13 447 cases [10 388 with ischaemic stroke and 3059 intracerebral haemorrhage] and 13 472 controls). Previous history of hypertension or blood pressure of 140/90 mm Hg or higher (OR 2.98, 99% CI 2.72–3.28; PAR 47.9%, 99% CI 45.1–50.6), regular physical activity (0.60, 0.52–0.70; 35.8%, 27.7–44.7), apolipoprotein (Apo)B/ApoA1 ratio (1.84, 1.65–2.06 for highest vs lowest tertile; 26.8%, 22.2–31.9 for top two tertiles vs lowest tertile), diet (0.60, 0.53–0.67 for highest vs lowest tertile of modified Alternative Healthy Eating Index [mAHEI]; 23.2%, 18.2–28.9 for lowest two tertiles vs highest tertile of mAHEI), waist-to-hip ratio (1.44, 1.27–1.64 for highest vs lowest tertile; 18.6%, 13.3–25.3 for top two tertiles vs lowest), psychosocial factors (2.20, 1.78–2.72; 17.4%, 13.1–22.6), current smoking (1.67, 1.49–1.87; 12.4%, 10.2–14.9), cardiac causes (3.17, 2.68–3.75; 9.1%, 8.0–10.2), alcohol consumption (2.09, 1.64–2.67 for high or heavy episodic intake vs never or former drinker; 5.8%, 3.4–9.7 for current alcohol drinker vs never or former drinker), and diabetes mellitus (1.16, 1.05–1.30; 3.9%, 1.9–7.6) were associated with all stroke. Collectively, these risk factors accounted for 90.7% of the PAR for all stroke worldwide (91.5% for ischaemic stroke, 87.1% for intracerebral haemorrhage), and were consistent across regions (ranging from 82.7% in Africa to 97.4% in southeast Asia), sex (90.6% in men and in women), and age groups (92.2% in patients aged ≤55 years, 90.0% in patients aged >55 years). We observed regional variations in the importance of individual risk factors, which were related to variations in the magnitude of ORs (rather than direction, which we observed for diet) and differences in prevalence of risk factors among regions. Hypertension was more associated with intracerebral haemorrhage than with ischaemic stroke, whereas current smoking, diabetes, apolipoproteins, and cardiac causes were more associated with ischaemic stroke ($p < 0.0001$).

Interpretation Ten potentially modifiable risk factors are collectively associated with about 90% of the PAR of stroke in each major region of the world, among ethnic groups, in men and women, and in all ages. However, we found important regional variations in the relative importance of most individual risk factors for stroke, which could contribute to worldwide variations in frequency and case-mix of stroke. Our findings support developing both global and region-specific programmes to prevent stroke.

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*See appendix for a full list of study investigators

Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (M J O'Donnell PhD, S L Chin, S Rangarajan MSc, P Rao-Melacini MSc, X Zhang MSc, S Agapay BSc, Prof M J McQueen MBChB, M Dehghan PhD, G Pare MD, Prof S Yusuf DPhil); Health Research Board Clinical Research Facility, Department of Medicine, NUI Galway, Galway, Ireland (M J O'Donnell, J Ferguson PhD); St John's Medical College and Research Institute, Bangalore, India (Prof D Xavier MD, Prof P Pais MD); National Center of Cardiovascular Disease, Beijing, China (Prof L Liu MD); Beijing Hypertension League Institute, Beijing, China (Prof H Zhang MD, Prof X Wang PhD); Instituto de Investigaciones FOSCAL, Escuela de Medicina, Universidad de Santander, Bucaramanga, Colombia (Prof P Lopez-Jaramillo PhD); Eduardo Mondlane University, Maputo, Mozambique (A Damasceno MD); Academic Section of Geriatric Medicine, Glasgow Royal Infirmary, University of Glasgow, Glasgow, UK (Prof P Langhorne PhD); Sahlgrenska University Hospital and Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

(Prof A Rosengren PhD); School of Medicine and Pharmacology, The University of Western Australia, Perth, WA, Australia (Prof G J Hankey MD); College of Medicine, University of Philippines, Manila, Philippines (Prof A L Dans MD); Alzheim Alazhari University, Khartoum North, Sudan (Prof A Elsayed MD); Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil (Prof A Avezum PhD); Uganda Heart Institute, Mulago Hospital, Kampala, Uganda (Prof C Mondo PhD); Department of Neurology, University Hospital, Essen, Germany (Prof H-C Diener MD, Prof C Weimar MD); Institute of Psychiatry and Neurology, Warsaw, Poland (Prof D Ryglewicz MD, Prof A Czlonkowska MD); National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russia (Prof N Pogossova MD); Department of Medicine, Aga Khan University, Karachi, Pakistan (R Iqbal PhD); Estudios Clinicos Latinoamerica, Rosario, Argentina (Prof R Diaz MD); Universiti Teknologi MARA, Selayang, Selangor, Malaysia (Prof K Yusoff MB); UCSI University, Cheras, Kuala Lumpur, Malaysia (Prof K Yusoff); Dubai Health Authority, Dubai Medical College, Dubai, United Arab Emirates (Prof A Yusufali MD); Department of Internal Medicine, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey (Prof A Oguz MD); Department of Cardiology, Hospital Luis Vernaza, Guayaquil, Ecuador (E Penaherrera MD); Faculty of Medicine, Universidad de La Frontera, Temuco, Chile (Prof F Lanas MD); Division of Cardiovascular Medicine, Department of Medicine, University College Hospital, Ibadan, Nigeria (O S Ogah MD, Prof A Ogunniyi MD); Stroke Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark (H K Iversen MD); Universidad Peruana Cayetano Heredia, Lima, Peru (Prof G Malaga MD); Department of Medicine, University of Split, Split, Croatia (Prof Z Rumboldt MD);

Research in context

Evidence before this study

We searched PubMed with the search terms “stroke”, “ischaemic stroke”, “intracerebral haemorrhage”, “risk factors”, “population attributable risk”, “global”, “international”, “hypertension”, “smoking”, “diet”, “alcohol”, “diabetes”, “atrial fibrillation”, “physical activity”, and “anthropometrical” for articles published in English before Feb 17, 2016. We identified meta-analyses of epidemiological studies, including the Global Burden of Disease 2013 report of global, regional, and national estimates for environmental, occupational, behavioural, physiological, and metabolic risk factors in 188 countries from 1990–2013. Other than phase 1 of INTERSTROKE, we did not identify an international study of risk factors for stroke that used standardised design and methods, and included all major regions of the world.

Added value of this study

This study builds on the first phase of the INTERSTROKE study, which included 6000 participants in 22 countries, by expanding the sample size to 26 919 participants from 32 countries in America, Europe, the Middle East, Africa, Asia, and Australia. Our study also builds on previous meta-analytic studies, including the

Global Burden of Disease study. We confirm our preliminary observation from phase 1 that about 90% of the population-attributable risk of stroke is associated with ten potentially modifiable risk factors: hypertension, smoking, diabetes mellitus, physical activity, diet, psychosocial factors, abdominal obesity, alcohol, cardiac causes, and apolipoproteins. We report that these ten risk factors collectively account for a similar population-attributable risk in different regions of the world, in men and women, and in younger and older populations, which has not been reported previously. Within individual risk factors, we noted differences in magnitude of association with stroke between regions and within key populations.

Implication of all the available evidence

Available evidence suggests that targeting ten modifiable risk factors, especially hypertension, would result in a marked reduction in the global and regional burden of stroke. Regional variations in the relative importance of most individual risk factors for stroke are likely to contribute to worldwide variations in frequency and case-mix of stroke and our findings support developing both global and region-specific programmes to prevent stroke.

Introduction

Stroke is a leading cause of death and disability, making the prevention of stroke a global health priority.^{1,2} In the first phase of the INTERSTROKE study³ (n=6000, 22 countries), ten common, potentially modifiable risk factors were associated with 90% of the population attributable risk (PAR) of acute ischaemic stroke and intracerebral haemorrhage. Although phase 1 of the study provided new information about the composite attributable risk of key risk factors in an international population, the population size was insufficient to reliably describe regional variations in the effect of risk factors, variations within key populations (eg, age, sex), and whether these risk factors varied in their effect on stroke pathological subtypes (ischaemic and haemorrhage stroke).⁴

Detailed assessment of the importance of risk factors within regions of the world is necessary to find out whether approaches to stroke prevention should differ by region or population characteristic (eg, age, sex, and ethnic origin),^{4,5} and whether variations in the importance of risk factors might explain the marked worldwide variations observed in incidence and subtypes of stroke.⁶ The Global Burden of Disease systematic analysis has reported modelled estimates of the contribution of potentially modifiable risk factors to the global and regional burden of stroke.^{7,8} However, estimates are derived from studies of differing methods, with variable use of neuroimaging to establish primary stroke subtype, and under-representation of populations in low-income countries and middle-income countries, where the burden of stroke is largest.^{6,9}

The aim of the second phase of the INTERSTROKE study was to increase and broaden the sample size to more than 13 000 cases of acute stroke and 13 000 controls in 32 countries to test the hypothesis that variations exist in the effect of common risk factors for stroke by major regions of the world, in key populations (eg, ethnic origin, age, sex), and in subtypes of stroke.

Methods

Study design and participants

INTERSTROKE is a large, international case-control study.¹⁰ Participants were recruited between Jan 11, 2007, and Aug 8, 2015, from 142 centres in 32 countries in Asia (China, India, Pakistan, Philippines, Thailand, and Malaysia), Africa (Mozambique, Nigeria, South Africa, Sudan, and Uganda), Europe (Croatia, Denmark, Germany, Poland, Russia, Sweden, the UK, Ireland, and Turkey), the Middle East (Iran, Saudi Arabia, Kuwait, and United Arab Emirates), North America (Canada), Australia, and South America (Argentina, Brazil, Chile, Colombia, Ecuador, and Peru; appendix p 1).

Cases were patients with acute first stroke (within 5 days of symptoms onset and 72 h of hospital admission), in whom neuroimaging by CT or MRI brain imaging could be completed within 1 week of presentation. Stroke was defined with the WHO clinical criteria for stroke.¹¹ For patients unable to communicate adequately, proxy respondents were used. Key exclusion criteria and the definition of a suitable proxy respondent are listed in the appendix (p 2). The modified Rankin scale¹² was used to measure stroke severity at baseline and 1 month of

follow-up. We included cases with acute ischaemic stroke and intracerebral haemorrhage in this Article.

Controls were either community-based or hospital-based. Hospital-based controls were patients admitted to hospital or those attending an outpatient clinic for disorders or procedures not related to stroke or transient ischaemic attack, or visitors or relatives of other inpatients.¹⁰ Specific approaches to identifying sources of community-based controls were not prespecified, because standardised approaches might not be feasible in all settings. However, site guidance on preferred and acceptable sources for hospital-based controls were provided at each site (appendix p 3).

Each control was matched for sex and age (± 5 years) with cases; age-matching was extended (± 10 years) for participants older than 90 years.

The study was approved by the ethics committees in all participating centres. All participants, or their proxy, provided written informed consent before taking part in the study.

Measurement of risk factors

Structured questionnaires were administered and physical examinations were done in the same manner in cases and controls. Measurement of key vascular risk factors was consistent with the INTERHEART study¹³ and to phase 1 of INTERSTROKE.³ Further description of risk-factor definitions is given in the appendix. The cutoffs used to divide participants into three tertiles for waist-to-hip ratio were 0.91 and 0.97 in men and 0.86 and 0.93 in women. Hypertension was defined by self-reported history of hypertension or the composite of self-reported hypertension or blood pressure of 140/90 mm Hg or higher. To estimate preadmission blood pressure in cases, we used adjusted blood pressure readings on hospital admission; the adjustment was based on data reported in the Oxford Vascular Study (OXVASC) and Oxfordshire Community Stroke Project (OCSP) prospective cohort studies,¹⁴ which evaluated the relationship between premorbid blood pressure and acute post-stroke blood pressure (appendix pp 4, 15–16). Our primary measure of blood pressure in cases was adjusted blood pressure at the time of admission. Self-reported history of diabetes mellitus or HbA_{1c} of 6.5% or higher was used to define diabetes mellitus. Physically active individuals were defined as being regularly involved in moderate or strenuous leisure activity for 4 h or more per week. Diet quality was defined by the modified Alternative Healthy Eating Index (mAHEI); a higher score indicates a healthier cardiovascular diet than does a low score.^{15,16} Smoking status was defined as never, former, or current smoker. Alcohol use was categorised into never or former, low intake, moderate intake, and high (more than 14 drinks per week in women or more than 21 drinks per week in men) or episodic heavy (more than five drinks in one episode at least once per month) intake.¹⁷ For psychosocial factors,

we used a combined measure of psychosocial stress used in INTERHEART, which combines measures of stress (home and work), life events, and depression.¹³ Atrial fibrillation or flutter was based on previous history, review of baseline electrocardiograph results (for cases and controls), and results of cardiac monitoring (when available). Classification of previous myocardial infarction, prosthetic heart valve, and rheumatic valvular heart disease was based on medical history.

Non-fasting blood samples (20 mL) were taken from cases and controls within 72 h of recruitment, separated by centrifugation and aliquoted into six equal volumes, and frozen at -20°C or -70°C immediately after processing. Samples were shipped in nitrogen vapour tanks by courier from every site to a blood storage site, where they were stored at -160°C in liquid nitrogen vapour (Clinical Research Laboratory and Biobank, Hamilton, ON, Canada) or at -70°C in the National Coordinating Offices in India, Turkey, and China. All data were transferred to the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada, where quality-control checks and statistical analysis were done.

Statistical analysis

The sample size for the INTERSTROKE study was based on an intention to include at least 1000 case-control pairs from all major regions in the world, to permit a globally representative sample in the overall study and to provide an estimate of association for common risk factors within each region. The sample size was also determined to be adequate to detect an odds ratio (OR) of 1.2 or greater for minor allele frequencies of 0.1 for all stroke and ischaemic stroke, and OR of 1.3 or greater for minor allele frequencies of 0.3 for each of the ischaemic and haemorrhagic stroke subtypes, assuming an additive genetic model at genome-wide significance. The sample size was calculated on the basis of level of significance, two-sided test at $\alpha=0.01$ for traditional risk factors and $\alpha<5\times 10^{-8}$ for genetic markers (ie, genome-wide significance); power ($1-\beta$) of 80%; and effect size (the minimum OR considered to be clinically important, which is dependent upon the risk factor of interest). For example, to detect a minimum OR of 1.3 for allele frequency of 0.3, we needed a sample size of 3000 case-control pairs, which guided the sample size for intracerebral haemorrhage. The original assumptions underlying the sample size calculation for genetic risk factors were based on knowledge in 2007–08, at which time an OR of 1.2 or 1.3 was considered plausible for common genetic variants.

Means and medians were calculated to summarise continuous variables and were compared with *t* tests or appropriate non-parametric tests if distributional assumptions were in doubt. Categorisation of data by tertiles was based on the control data. We used conditional logistic regression (13 477 matched

Rush Alzheimer Disease Research Center, Rush University Medical Center, Chicago, IL, USA (Prof S Oveisgharan MD); Department of Medicine, University of Limpopo, Pretoria, South Africa (D Magazi MD); Neurology Division, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand (Y Nilanont MD); and King Saud University, Riyadh, Saudi Arabia (F Al-Hussain MD)

Correspondence to: Dr Martin J O'Donnell, Population Health Research Institute, DBCVS Research Institute, McMaster University, 3rd Floor, 237 Barton St East, Hamilton, ON, L8L 2X2, Canada odonnm@mcmaster.ca

See Online for appendix

	Overall (n=13 447)	Western Europe, North America, Australia (n=1917)	Eastern and central Europe, Middle East (n=1394)	South America (n=1471)	China (n=3987)	South Asia (n=2850)	Southeast Asia (n=855)	Africa (n=973)
Age, years	62.2 (13.6)	66.7 (13.4)	63.9 (13.4)	65.8 (14.3)	61.9 (12.5)	59.6 (12.9)	56.6 (13.0)	58.7 (15.2)
Age ≤45 years	1582 (11.8%)	141 (7.4%)	143 (10.3%)	123 (8.4%)	364 (9.1%)	451 (15.8%)	156 (18.3%)	204 (21.0%)
Women	5434 (40.4%)	781 (40.7%)	556 (39.9%)	652 (44.3%)	1606 (40.3%)	1017 (35.7%)	352 (41.2%)	470 (48.3%)
Intracerebral haemorrhage	3059 (22.7%)	128 (6.7%)	117 (8.4%)	348 (23.7%)	1102 (27.6%)	785 (27.5%)	285 (33.3%)	294 (30.2%)
Ischaemic stroke	10 388 (77.3%)	1789 (93.3%)	1277 (91.6%)	1123 (76.3%)	2885 (72.4%)	2065 (72.5%)	570 (66.7%)	679 (69.7%)
OCSP classification*								
Total anterior circulation infarct	673/10 388 (6.5%)	71/1789 (4.0%)	72/1277 (5.6%)	176/1123 (15.7%)	127/2885 (4.4%)	105/2065 (5.1%)	33/570 (5.8%)	89/679 (13.1%)
Partial anterior circulation infarct	4872/10 388 (46.9%)	809/1789 (45.2%)	631/1277 (49.4%)	404/1123 (36.0%)	1306/2885 (45.3%)	945/2065 (45.8%)	383/570 (67.2%)	394/679 (58.0%)
Posterior circulation infarct	1509/10 388 (14.5%)	353/1789 (19.7%)	265/1277 (20.8%)	146/1123 (13.0%)	372/2885 (12.9%)	258/2065 (12.5%)	63/570 (11.1%)	52/679 (7.7%)
Lacunar infarction	2789/10 388 (26.9%)	536/1789 (30.0%)	267/1277 (20.9%)	212/1123 (18.9%)	1051/2885 (36.4%)	549/2065 (26.6%)	79/570 (13.9%)	95/679 (14.0%)
Undetermined	545/10 388 (5.3%)	20/1789 (1.1%)	42/1277 (3.3%)	185/1123 (16.5%)	29/2885 (1.0%)	208/2065 (10.1%)	12/570 (2.1%)	49/679 (7.22%)
Modified Rankin scale score (1-month follow-up)								
0-1	4907 (36.5%)	900 (47.0%)	596 (42.8%)	376 (25.6%)	1865 (46.8%)	759 (26.6%)	286 (33.5%)	125 (12.9%)
2-3	5994 (44.6%)	850 (44.3%)	606 (43.5%)	632 (43.0%)	1638 (41.1%)	1355 (47.5%)	404 (47.3%)	509 (52.3%)
4-5	1397 (10.4%)	136 (7.1%)	130 (9.3%)	248 (16.9%)	384 (9.6%)	299 (10.5%)	60 (7.0%)	140 (14.4%)
6	1149 (8.5%)	31 (1.6%)	62 (4.5%)	215 (14.6%)	100 (2.5%)	437 (15.3%)	105 (12.3%)	199 (20.5%)
Modified Rankin 3-6	5061 (37.6%)	483 (25.2%)	392 (28.1%)	758 (51.5%)	1169 (29.3%)	1381 (48.5%)	299 (35.0%)	579 (59.5%)
CT or MRI of brain	13 441 (99.9%)	1917 (100%)	1394 (100%)	1471 (100%)	3987 (100%)	2845 (99.8%)	855 (100%)	972 (99.9%)
Time to CT or MRI of brain, h†	8.61 (18.17)	7.98 (13.71)	4.24 (12.26)	8.89 (16.73)	4.86 (14.38)	7.95 (14.83)	9.36 (14.54)	30.64 (35.08)
ECG	13 341 (99.2%)	1908 (99.5%)	1391 (99.8%)	1442 (98.0%)	3986 (99.9%)	2820 (98.9%)	855 (100%)	939 (96.5%)
Vascular imaging*‡	4155/10 354 (40.1%)	1505/1786 (84.3%)	829/1274 (65.1%)	398/1104 (36.1%)	1033/2885 (35.8%)	311/2063 (15.1%)	63/570 (11.1%)	16/672 (2.4%)
Transthoracic echocardiography*‡	1191/10 356 (11.5%)	415/1787 (23.2%)	259/1274 (20.3%)	140/1106 (12.7%)	280/2885 (9.7%)	16/2061 (0.8%)	9/570 (1.6%)	72/673 (10.7%)
Holter monitor*‡	750/10 356 (7.2%)	442/1787 (24.7%)	198/1274 (15.5%)	67/1106 (6.1%)	38/2885 (1.3%)	2/2061 (0.1%)	3/570 (0.5%)	0/673

Data are n (%) or mean (SD). Western Europe, North America, Australia includes Australia, Canada, Denmark, Germany, Sweden, UK, and Ireland. Eastern and central Europe, Middle East includes Croatia, Poland, Russia, Turkey, Iran, Saudi Arabia, Kuwait, and United Arab Emirates. South America includes Argentina, Brazil, Chile, Colombia, Ecuador, and Peru. South Asia includes India and Pakistan. Southeast Asia includes Philippines, Thailand, and Malaysia. Africa includes Mozambique, Nigeria, South Africa, Sudan, and Uganda. OCSP=Oxfordshire Community Stroke Project. ECG=electrocardiogram. *Percentages are calculated based on the totals from ischaemic stroke. †Mean time for hospital admission to completion of CT or MRI of brain. ‡Diagnostic testing, where test was completed and report available at 1-month follow-up.

Table 1: Demographic and clinical characteristics of cases

case-control pairs for primary analysis of all stroke), other than for subgroup analyses, for which we used unconditional logistic regression. We observed consistent results between conditional and unconditional analyses, for analyses of potentially modifiable risk factors, including the entire cohort (appendix p 5). All

unconditional regression analyses were adjusted for age, sex, and geographical region, and all conditional analyses were stratified on the matching criteria. In the multivariable models, we sought to establish the association between common risk factors, identified in the INTERHEART study and INTERSTROKE phase 1

studies (hypertension, smoking, diabetes mellitus, physical activity, diet, psychosocial factors, abdominal obesity, alcohol, cardiac causes, and apolipoproteins), and all stroke, ischaemic stroke, and intracerebral haemorrhage, for the entire cohort, by region, self-reported ethnic origin, sex, and age group. We included the entire INTERSTROKE population in analyses, but analysed the two phases of the study separately, to establish consistency of findings (appendix p 6). We collapsed several cardiac causes into one cardiac cause variable, because of the low prevalence of some cardiac causes (other than atrial fibrillation) in the cohort, and also reported on atrial fibrillation alone (which included atrial flutter). To optimise power to detect associations, we used the pool of controls for ischaemic stroke to match additional controls to intracerebral haemorrhage cases, with a target ratio of 1:4 for case-control pairing. We used the same approach for ischaemic stroke (ie, used an intracerebral haemorrhage control pool to increase the number of controls), with a target ratio of 1:2. Adjusted ORs for combinations of risk factors were derived from their model coefficients in the multivariable logistic model. To find out whether individual vascular risk factors were more significantly associated with ischaemic stroke than intracerebral haemorrhage, we did a case-case analysis, which matched participants with ischaemic stroke to participants with intracerebral haemorrhage, matched for site, age, and sex. Estimates of ORs and accompanying 99% CIs are presented for every risk factor and their combinations, and the $p_{\text{interaction}}$ value is reported for individual risk factors by region, sex, and age group. Our primary approach to univariate and multivariable estimation of PAR for each risk factor, and combination of risk factors, was the method described by Benichou and Gail,¹⁸ and used in INTERHEART and

phase 1 of INTERSTROKE. More detailed description of the analytical approach to estimating PARs was reported in the INTERHEART study report.¹³ Using this method, addition of PARs for individual risk factors usually exceeds 100%, although the overall PAR for the composite of these risk factors is less than 100%. An alternative approach to estimating PAR, which ensures that adding estimates for individual risk-factor multivariable estimates equals the PAR for the composite of these risk factors, is average PAR (APAR). Using this approach, described by Eide and Heuch,¹⁹ each risk factor is added to the model in every possible order (1–10), and the APAR for all risk factor permutations is calculated. To calculate APAR, we used the method described by Ferguson and colleagues.²⁰ The advantage of this approach is that it allows measurement of the independent proportion of PAR that each risk factor contributes to the overall PAR for all risk factors. However, the disadvantage is that this approach might underestimate the effect of removing some individual risk factors on disease burden. All statistical tests of hypotheses are two-sided. Statistical analyses and graphics were produced with SAS (version 9.2), R statistical program (version 3.2.4), and TIBCO Spotfire S-Plus (version 8.2) for Windows.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

26 919 participants were recruited from 32 countries from Jan 11, 2007, to Aug 8, 2015, comprising 13 447 cases of

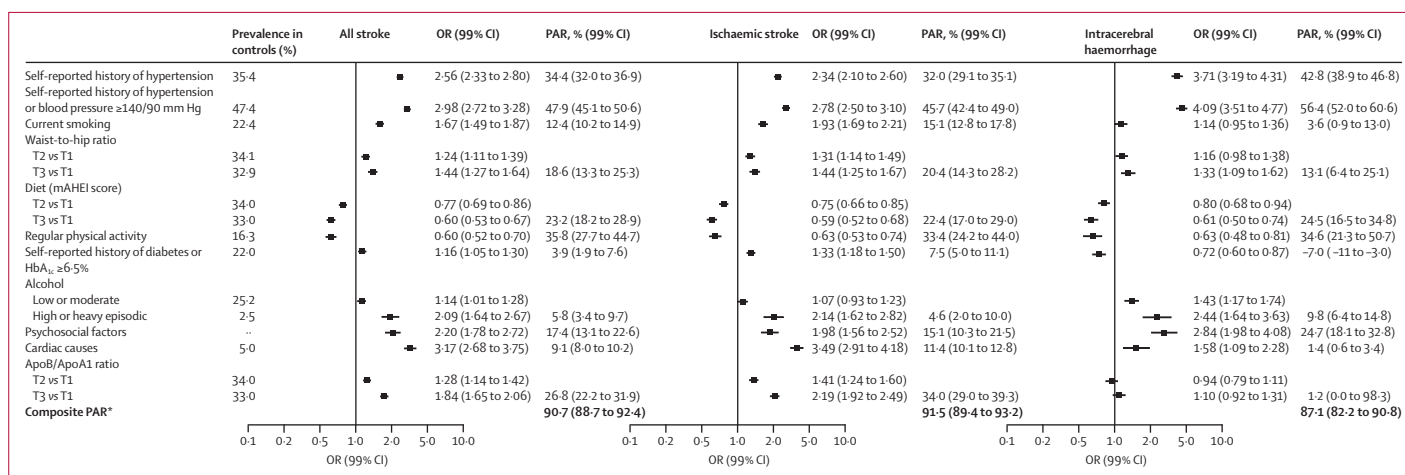


Figure 1: Multivariable analysis of prevalence of risk factors, OR, and PAR for ten risk factors

Cardiac sources include atrial fibrillation or flutter, previous myocardial infarction, rheumatic valve disease, or prosthetic heart valve. For tertiles, PAR was calculated using T2 + T3 versus T1, other than diet, where PAR was calculated using T1 + T2 versus T3. For physical activity, OR is reported for physically active versus other, and PAR is calculated for the inverse. For alcohol, OR is reported for high or heavy episodic, low or moderate vs former or never drinker, PAR is reported for current alcohol intake vs former or never drinker. For psychosocial factors, additional adjustment for education and income (purchasing power parity) reported a PAR 16.1% (99% CI 11.6–21.9) for all stroke. Apo=apolipoprotein. mAHEI=modified Alternative Healthy Eating Index. OR=odds ratio. PAR=population attributable risk. T=tertile. *Composite PAR includes all ten risk factors; self-reported history of hypertension or blood pressure ≥140/90 mm Hg was used for hypertension variable.

acute first-ever stroke and 13472 controls (403 [3.0%] of controls had chronic bronchitis, 948 [7.0%] had malaria, 263 [2.0%] had tuberculosis, 127 [0.9%] had venous thrombosis, and 107 [0.8%] had peripheral vascular disease; appendix p 14). Neuroimaging was completed in 13441 (99.9%) of 13447 cases. Questionnaires were

completed by patients (5573 [41.4%]), proxy respondents (4953 [36.8%]), or both together (2917 [21.7%]); missing for four participants. Descriptive characteristics of cases are reported in table 1. The proportion of patients undergoing diagnostic testing, to identify a source of thromboembolism, varied between regions (table 1). The

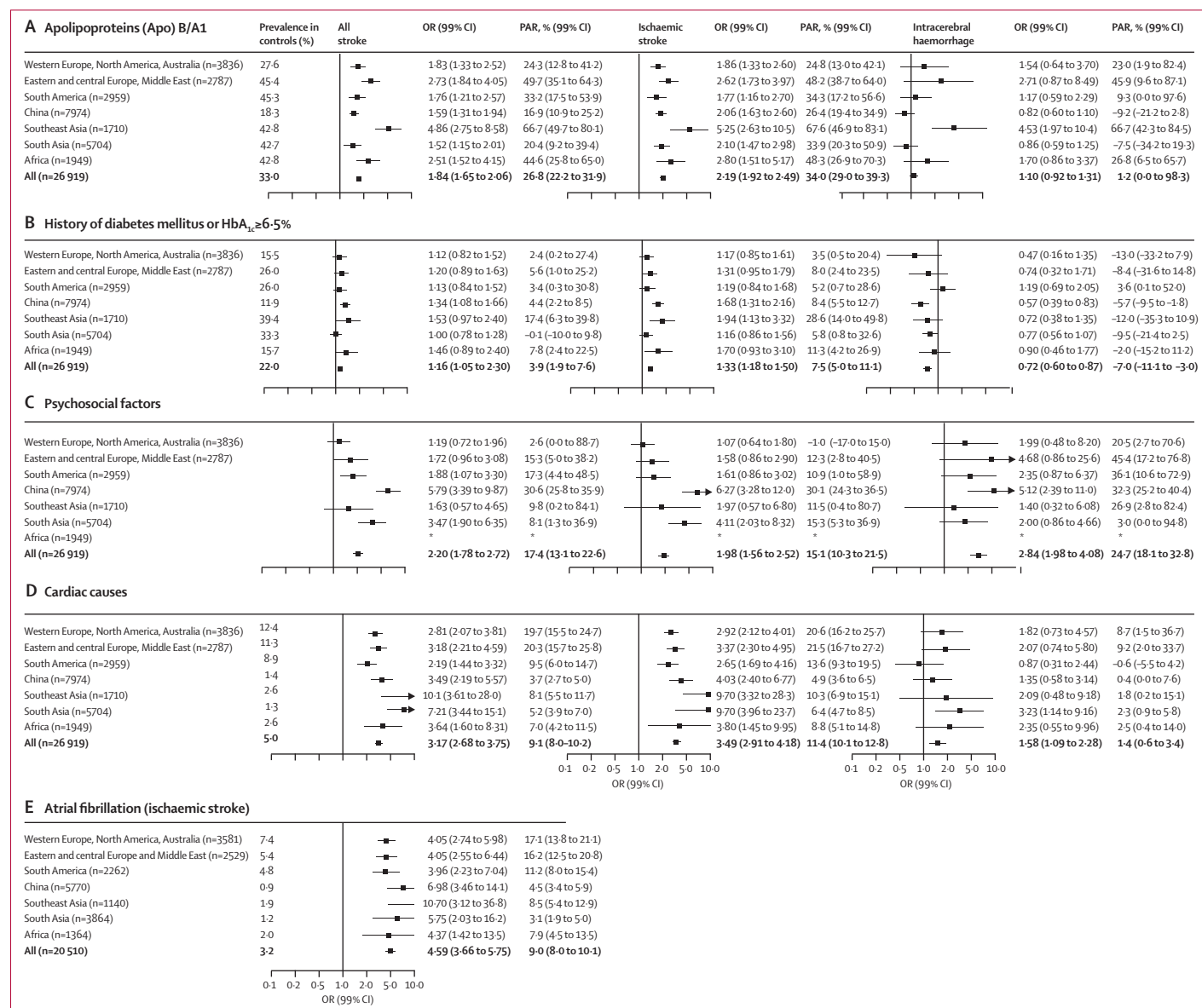


Figure 3: Multivariable analysis by region

Western Europe, North America, Australia: Australia, Canada, Denmark, Germany, Sweden, UK, and Ireland. Eastern and central Europe, Middle East: Croatia, Poland, Russia, Turkey, Iran, Saudi Arabia, Kuwait, and United Arab Emirates. South America: Argentina, Brazil, Chile, Colombia, Ecuador, and Peru. Southeast Asia: Philippines, Thailand, and Malaysia. South Asia: India and Pakistan. Africa: Mozambique, Nigeria, South Africa, Sudan, and Uganda. (A) ApoB/ApoA1 ratio (OR is reported for T3 vs T1, PAR was calculated for T2 + T3 vs T1). (B) History of diabetes mellitus or HbA_{1c} ≥ 6.5%. (C) Psychosocial factors. (D) Cardiac causes. (E) Atrial fibrillation, including atrial flutter (ischaemic stroke only). The variables age, hypertension, smoking, waist-to-hip ratio, diabetes, physical activity, mAHEI, alcohol intake, psychosocial factors, apolipoproteins, and cardiac causes were included in all models. Data were missing in 255 participants in western Europe, North America, Australia, 375 participants in eastern and central Europe, Middle East, 268 participants in South America, 116 participants in China, 90 participants in southeast Asia, 1543 participants in south Asia, and 365 participants in Africa for apolipoproteins; ten participants in South America, four participants in south Asia, and one participant in Africa for diabetes; 25 participants in western Europe, North America, Australia, ten participants in eastern and central Europe, Middle East, 52 participants in South America, 16 participants in China, 120 participants in southeast Asia, 36 participants in south Asia, and 40 participants in Africa for psychosocial factors. A Wald test was used to test for interaction between risk factor × region for all stroke, p_{interaction} was significant (p < 0.01) for ApoB/ApoA1, psychosocial factors, and cardiac causes (and atrial fibrillation) using logistic regression. *High prevalence of psychosocial factors in Africa (93% of controls, 88% of patients who had ischaemic stroke, and 92% of patients who had intracerebral haemorrhage reported at least one of composite outcome) resulted in implausible values for OR and PAR. OR=odds ratio. PAR=population attributable risks. T=tertile.

	All stroke, PAR (99% CI)	Ischaemic stroke, PAR (99% CI)	Intracerebral haemorrhage, PAR (99% CI)
Western Europe, North America, Australia	88.6% (82.5–92.8)	89.5% (83.4–93.5)	82.0% (43.6–96.4)
Eastern and central Europe, Middle East	90.5% (83.5–94.7)	90.4% (82.9–94.8)	90.7% (59.5–98.5)
South America	93.2% (86.1–96.8)	91.8% (82.0–96.5)	94.4% (80.2–98.6)
China	94.3% (91.0–96.4)	95.2% (91.8–97.3)	90.7% (83.7–94.9)
Southeast Asia	97.4% (90.2–99.3)	97.8% (89.0–99.6)	97.6% (85.1–99.7)
South Asia*	90.8% (83.6–95.1)	92.9% (85.1–96.7)	80.3% (62.8–90.7)
Africa†	82.7% (65.0–92.5)	83.2% (61.2–93.9)	86.5% (66.9–95.3)

Variables included in the model were age, self-reported hypertension or blood pressure $\geq 140/90$ mm Hg, smoking, waist-to-hip ratio, diabetes or HbA_{1c} of $\geq 6.5\%$, physical activity, mAHEI, alcohol intake, psychosocial factors, apolipoproteins, and cardiac causes. PAR=population attributable risk. mAHEI=modified Alternative Healthy Eating Index. *Composite PAR including mAHEI as T3 + T2 vs T1 for south Asia, consistent with direction of association. Composite PAR including mAHEI as T1 + T2 vs T3 was 85.1% for all stroke, 88.1% for ischaemic stroke, and 78.2% for intracerebral haemorrhage. †Excluding psychosocial factors in Africa because of high prevalence in cases and controls resulting in implausible value for PAR.

Table 2: PAR for all risk factors by region (all stroke, ischaemic stroke, and intracerebral haemorrhage)

pathological subtype of stroke was ischaemic stroke in 10 388 (77.3%) individuals and intracerebral haemorrhage in 3059 (22.7%) individuals. Overall, 1149 (8.5%) patients had died by 1 month of follow-up (modified Rankin score 6) and 1397 (10.4%) had a stroke associated with severe disability (modified Rankin 4–5) at 1 month of follow-up.

Data on lipids were available in 23 907 (88.8%) of participants and data for HbA_{1c} were available in 21 894 (81.3%) of participants. For the entire cohort (cases and controls), data were missing in 14 (0.05%) participants for smoking, 299 (1.1%) participants for psychosocial factors, five (0.02%) participants for self-reported history of diabetes mellitus, 719 (2.67%) participants for waist-to-hip ratio, and 34 (0.13%) participants for alcohol.

Association of risk factors with stroke, ischaemic stroke, and intracerebral haemorrhage is reported in figures 1, 2, and 3. History of hypertension or blood pressure of 140/90 mm Hg or higher, regular physical activity, apolipoprotein (Apo)B/ApoA1 ratio, diet, waist-to-hip ratio, psychosocial factors, current smoking, cardiac causes, alcohol consumption, and diabetes mellitus were associated with all stroke (figure 1). The same risk factors were also associated with ischaemic stroke (figure 1). History of hypertension or blood pressure of 140/90 mm Hg or higher, regular physical activity, diet, waist-to-hip ratio, psychosocial factors, cardiac causes, and alcohol consumption were associated with intracerebral haemorrhage (figure 1). In an analysis that formally compared intracerebral haemorrhage to ischaemic stroke (case-case analyses), hypertension was significantly more strongly associated with intracerebral haemorrhage than ischaemic stroke, whereas smoking, diabetes, cardiac causes, and apolipoproteins were more significantly associated with ischaemic stroke (appendix p 7).

Combining all ten risk factors, PAR was 90.7% (88.7–92.4) for all stroke, 91.5% (89.4–93.2) for

ischaemic stroke, and 87.1% (82.2–90.8) for intracerebral haemorrhage.

In all regions, hypertension was significantly associated with all stroke (PAR ranging from 38.8% in western Europe, North America, Australia to 59.6% in southeast Asia), ApoB/ApoA1 was significantly associated with ischaemic stroke (PAR ranging from 24.8% in western Europe, North America, Australia to 67.6% in southeast Asia), and atrial fibrillation was significantly associated with ischaemic stroke (PAR ranging from 3.1% in south Asia to 17.1% in western Europe, North America, Australia). For all stroke, the PAR associated with current smoking ranged from 4.5% in Africa to 18.0% in western Europe, North America, and Australia. The PAR for waist-to-hip ratio and all stroke was lowest in eastern and central Europe, Middle East (2.8%), and China (7.8%), and highest in western Europe, North America, Australia (36.7%), south Asia (32.1%), and southeast Asia (37.2%). The PAR for physical inactivity and all stroke ranged from 4.7% in Africa to 59.9% in China. The PAR for alcohol intake and all stroke was lowest in western Europe, North America, Australia and highest in Africa (10.4%) and south Asia (10.7%).

In all regions, other than south Asia, the direction of association between mAHEI score and stroke was consistent, although non-significant for Africa. In south Asia, increasing mAHEI was associated with an increased risk of stroke. We also assessed the association between daily fruit and vegetable intake (using the definition of this variable in the INTERHEART study), which was significantly associated with reduced odds of stroke in all regions apart from south Asia and Africa (appendix, p 8).

The composite PARs for all ten risk factors by region are reported in table 2. The composite PAR for men was 90.6% and for women was 90.6% (table 3). PAR for smoking and alcohol intake was greater among men than in women because of higher prevalence of each activity; waist-to-hip ratio and cardiac causes were associated with a larger OR in women than in men.

The composite PAR for all ten risk factors was 92.2% (99% CI 88.8–94.6) for individuals aged 55 years or younger, and 90.0% (87.3–92.1) for those older than 55 years (table 4). Hypertension, waist-to-hip ratio, and cardiac risk factors were associated with greater ORs for individuals aged 55 years or younger than those who were older than 55 years, whereas diet had a stronger association with stroke in those older than 55 years. The association between risk factors and stroke by self-reported ethnic origin are reported in the appendix (pp 9–10).

Subgroup analysis by source of information for cases is reported in the appendix (p 11). 7369 (54.7%) of controls were community based, and 6093 (45.2%) were hospital based; data were missing for ten participants. Subgroup analyses in both types of controls (community-based vs hospital-based) suggested stronger magnitude of association for waist-to-hip ratio, physical activity,

	Controls		All-stroke cases			
	Men (N=8026)	Women (N=5446)	Men (N=8013)	Women (N=5434)		
			OR (99% CI)	PAR (99% CI)	OR (99% CI)	PAR (99% CI)
Self-reported history of hypertension or blood pressure \geq 140/90 mm Hg	3634/8026 (45.3%)	2745/5446 (50.4%)	2.87 (2.55 to 3.23)	45.2% (41.8 to 48.7)	3.21 (2.74 to 3.76)	52.3% (47.8 to 56.7)
Current smoking	2596/8022 (32.4%)	421/5443 (7.7%)	1.61 (1.42 to 1.83)	16.6% (13.2 to 20.7)	1.87 (1.43 to 2.43)	5.3% (3.7 to 7.6)
Waist-to-hip ratio						
T2 vs T1	2671/7809 (34.2%)	1802/5307 (34.0%)	1.20 (1.03 to 1.39)	..	1.28 (1.08 to 1.53)	..
T3 vs T1	2559/7809 (32.8%)	1751/5307 (33.0%)	1.23 (1.04 to 1.46)	..	1.80 (1.47 to 2.19)	..
T2 + T3 vs T1	12.7% (6.4 to 23.7)	..	25.8% (18.3 to 35.1)
Diet, mAHEI score						
T2 vs T1	2729/8026 (34.0%)	1849/5446 (34.0%)	0.78 (0.68 to 0.89)	..	0.75 (0.63 to 0.89)	..
T3 vs T1	2648/8026 (33.0%)	1797/5446 (33.0%)	0.60 (0.51 to 0.69)	..	0.59 (0.49 to 0.72)	..
T1 + T2 vs T3	23.5% (17.4 to 31.0)	..	22.9% (15.3 to 32.7)
Regular physical activity	1446/8021 (18.0%)	752/5442 (13.8%)	0.58 (0.48 to 0.70)	37.3% (28.1 to 47.5)	0.65 (0.50 to 0.85)	32.4% (18.4 to 50.4)
Self-reported history of diabetes or HbA _{1c} \geq 6.5%	1746/8019 (21.8%)	1211/5443 (22.2%)	1.16 (1.01 to 1.34)	3.7% (1.5 to 8.9)	1.16 (0.98 to 1.38)	4.1% (1.4 to 11.7)
Alcohol intake	10.0% (6.4 to 15.3)	..	-0.7% (-4.5 to 3.1)
Low or moderate	1537/8018 (19.2%)	609/5441 (11.2%)	1.20 (1.05 to 1.37)	..	0.92 (0.70 to 1.21)	..
High or heavy episodic	571/8018 (7.1%)	131/5441 (2.4%)	2.15 (1.67 to 2.77)	..	1.71 (0.72 to 4.07)	..
Psychosocial factors	2.59 (1.96 to 3.43)	18.5% (13.4 to 25.1)	1.77 (1.27 to 2.47)	15.0% (8.5 to 25.2)
Cardiac causes	430/8026 (5.4%)	238/5446 (4.4%)	2.73 (2.21 to 3.37)	7.8% (6.5 to 9.3)	4.06 (3.06 to 5.40)	11.1% (9.4 to 12.9)
ApoB/ApoA1 ratio						
T2 vs T1	2413/7083 (34.1%)	1637/4843 (33.8%)	1.24 (1.08 to 1.42)	..	1.33 (1.11 to 1.59)	..
T3 vs T1	2332/7083 (32.9%)	1598/4843 (33.0%)	1.81 (1.57 to 2.10)	..	1.88 (1.57 to 2.25)	..
T2 + T3 vs T1	25.1% (19.4 to 31.9)	..	29.2% (21.9 to 37.7)
Composite PAR for all ten risk factors	90.6% (88.0 to 92.7)	..	90.6% (87.1 to 93.3)

A Wald test was used to test for interaction between risk factor \times sex for all stroke, and $p_{\text{interaction}}$ was significant ($p < 0.01$) for waist-to-hip ratio, and cardiac causes using logistic regression. Apo=apolipoprotein. mAHEI=modified Alternative Healthy Eating Index. OR=odds ratio. PAR=population attributable risk. T=tertile.

Table 3: Risk factors for all stroke (ischaemic and intracerebral haemorrhage) in men and women

psychosocial factors, and cardiac causes in the subgroup analysis of community-based controls than in the analysis of hospital-based controls. Collectively, the composite PAR for all ten risk factors was 92.1% (99% CI 89.8–93.9) for community-based controls and 87.8% (83.2–91.2) on conditional regression analyses (appendix p 12).

Using adjusted blood pressure at the time of interview for cases, we observed a consistent association between self-reported hypertension or blood pressure of 140/90 mm Hg or higher and all stroke (OR 2.62 [99% CI 2.39–2.87], PAR 43.3% [40.4–46.2]). Additional estimates for alternative definition of hypertension are reported in the appendix (p 4). Replacing mAHEI with daily intake of fruit and vegetables

was associated with an OR of 0.65 (99% CI 0.57–0.72), and a PAR of 26.7% (21.2–32.9) for all stroke. Using the American Heart Association (AHA) recommendation (2.5 h or more of exercise per week), physical activity was associated with a reduction in all stroke (OR 0.41 [0.35–0.48], PAR 53.0% [47.0–59.0]). Body-mass index was associated with a weaker magnitude of association than waist-to-hip ratio (figure 4). When we re-categorised alcohol intake into moderate, high, or heavy episodic intake (seven or more drinks per week), we found an association between alcohol intake and all stroke (OR 1.46 [1.26–1.69], PAR 4.3% [3.0–6.0]). Number of cigarettes smoked per day was associated with a graded increase in risk of stroke (figure 5).

	Controls		All-stroke cases			
	≤55 years (N=4234)	>55 years (N=9238)	≤55 years (N=4216)		>55 years (N=9231)	
			OR (99% CI)	PAR (99% CI)	OR (99% CI)	PAR (99% CI)
Self-reported history of hypertension or blood pressure ≥140/90 mm Hg	1334/4234 (31.5%)	5045/9238 (54.6%)	4.51 (3.77–5.41)	49.7% (46.0–53.4)	2.55 (2.27–2.85)	46.0% (42.2–49.8)
Current smoking	1242/4231 (29.4%)	1775/9234 (19.2%)	1.66 (1.36–2.02)	16.3% (11.6–22.3)	1.70 (1.47–1.97)	10.9% (8.6–13.7)
Waist-to-hip ratio						
T2 vs T1	1386/4133 (33.5%)	3087/8983 (34.4%)	1.42 (1.15–1.75)	..	1.16 (1.01–1.33)	..
T3 vs T1	1203/4133 (29.1%)	3107/8983 (34.6%)	1.56 (1.23–1.98)	..	1.39 (1.20–1.62)	..
T2 + T3 vs T1	23.5% (15.2–34.5)	..	16.0% (9.7–25.2)
Diet, mAHEI score						
T2 vs T1	1460/4234 (34.5%)	3118/9238 (33.8%)	0.78 (0.64–0.95)	..	0.76 (0.67–0.87)	..
T3 vs T1	1313/4234 (31.0%)	3132/9238 (33.9%)	0.68 (0.55–0.86)	..	0.56 (0.48–0.64)	..
T1 + T2 vs T3	16.4% (7.9–30.9)	..	26.5% (20.9–33.0)
Regular physical activity	688/4232 (16.3%)	1510/9231 (16.4%)	0.60 (0.45–0.80)	35.3% (21.0–52.8)	0.60 (0.50–0.72)	35.9% (26.4–46.7)
Self-reported history of diabetes or HbA _{1c} ≥6.5%	727/4229 (17.2%)	2230/9233 (24.2%)	1.29 (1.04–1.61)	5.6% (2.5–12.1)	1.14 (1.01–1.30)	3.6% (1.4–8.8)
Alcohol intake	10.9% (6.1–18.7)	..	4.1% (1.7–9.4)
Low or moderate	797/4229 (18.8%)	1349/9230 (14.6%)	1.27 (1.03–1.56)	..	1.09 (0.94–1.27)	..
High or heavy episodic	231/4229 (5.5%)	471/9230 (5.1%)	2.20 (1.49–3.23)	..	2.14 (1.54–2.96)	..
Psychosocial factors	2.36 (1.60–3.50)	22.8% (14.8–33.3)	2.06 (1.59–2.68)	15.3% (10.5–21.8)
Cardiac causes	73/4234 (1.7%)	595/9238 (6.4%)	4.56 (2.81–7.41)	4.9% (3.8–6.3)	2.94 (2.45–3.53)	10.8% (9.4–12.4)
ApoB/ApoA1 ratio						
T2 vs T1	1219/3702 (32.9%)	2831/8224 (34.4%)	1.30 (1.06–1.60)	..	1.28 (1.13–1.46)	..
T3 vs T1	1275/3702 (34.4%)	2655/8224 (32.3%)	2.01 (1.62–2.49)	..	1.79 (1.56–2.05)	..
T2 + T3 vs T1	30.8% (22.6–40.5)	..	25.6% (20.1–31.9)
Composite PAR for all ten risk factors	92.2% (88.8–94.6)	..	90.0% (87.3–92.1)

A Wald test was used to test for interaction between risk factor × age subgroup for all stroke, and $P_{interaction}$ was significant ($p < 0.01$) for hypertension, waist-to-hip ratio, diet, and cardiac causes using logistic regression. Apo=apolipoprotein. mAHEI=modified Alternative Healthy Eating Index. OR=odds ratio. PAR=population attributable risk. T=tertile.

Table 4: Risk factors for all stroke (ischaemic and intracerebral haemorrhage) by age group

Compared with our primary analysis of PAR estimates, results from the APAR analysis showed a lower estimate for individual risk factors, but a similar estimate for combination of all ten risk factors (APAR 89.1% [99% CI 87.2 to 90.9] for all stroke) and generally preserved the relative importance of individual risk factors (appendix p 13).

Discussion

In the first phase of the INTERSTROKE study (n=6000),³ we reported preliminary estimates of the association of common risk factors with the PAR for stroke in an

international population, but phase 1 was of insufficient scope to report estimates by regions or in key populations. In this full-scale study (which includes phases 1 and 2 of the INTERSTROKE study), we provide more robust and reliable estimates for the contribution of these ten potentially modifiable risk factors in a larger population (n=26 919), with representation from all major regions of the world (32 countries). We report that ten potentially modifiable, and common, risk factors were associated with about 90% of the PAR for stroke in all regions, thereby extending the generalisability of our findings from phase 1. However, we found evidence of regional and

ethnic variations in magnitude of importance of individual risk factors, which was related to variations in the relative magnitude of ORs (rather than direction, which we only observed for diet) and differences in prevalence of risk factors among regions. Similarly, we found variations in importance of individual risk factors in men and women, and in younger and older subgroups. Despite these differences, the collective contribution of these ten risk factors to stroke risk was consistent in all populations, meaning that general approaches to prevention of stroke can be similar worldwide, but population-specific refinement of programmes might be needed.

The GBD study 2013 has reported meta-analytic estimates for population-attributable fraction of 17 risk factors associated with stroke risk, based on a systematic analysis of stroke-related disability-adjusted life years, prevalence of risk factors from studies in 188 countries, and meta-regression estimates of relative risks associated with individual risk factors.⁸ Of risk factors common to both analyses, hypertension was identified as the most important risk factor for stroke in both, although the population-attributable estimate from GBD analyses was higher (64.1%, compared with INTERSTROKE (47.9%), which could in part relate to different cutoff points for systolic blood pressures between studies (≥ 120 mm Hg for GBD, ≥ 140 mm Hg in INTERSTROKE). Estimates for smoking (12.4% for INTERSTROKE vs 20.7% for GBD meta-analysis), diabetes (3.9% vs 11.7%), and diet (23.2% vs 63.4%) were also higher in GBD analyses. For diet, differences in estimates might relate to different approaches to measuring diet, dietary factors included in analyses, and assumptions of no regional variations in magnitude of association in the GBD analyses. However, we report larger magnitudes of association for lipids (PAR 26.8% in INTERSTROKE vs 4.5% in GBD), which probably relates to our use of apolipoprotein ratio rather than total cholesterol, which has been shown to have a weaker association with stroke risk,^{3,21} and we report a larger magnitude of association for physical inactivity (PAR 35.8% vs 7.7%). By contrast with the GBD meta-analysis, estimates from the INTERSTROKE study are based on standardised methods of measuring each risk factor and determination of stroke, which is expected to provide more reliable estimates of association, and comparisons between regions. Crucially, INTERSTROKE includes a large proportion of individuals from low-income and middle-income countries, where to date, there has been insufficient data on the importance of these risk factors for stroke, but where the largest burden of stroke occurs. Ultimately, however, there is considerable commonality between study findings, providing complementary information on the collective importance of key common modifiable risk factors for stroke worldwide.

We report variations in the relative importance of some of these risk factors by region, which parallel findings of analyses by self-reported ethnic origin and provide essential information about the tailoring of regional and

country-specific approaches to primary prevention of stroke (figures 2, 3, appendix pp 9–10). Although the overall OR for the association between diet quality and stroke risk is consistent with estimates from systematic reviews,^{22,23} we found a qualitative difference in direction of association between diet score in south Asia compared with other regions. This finding partly relates to lower intake of combined fruit and vegetables in south Asia than in other regions (appendix, p 8). A recent GBD study²⁴ reported that south Asia has one of the lowest intakes of fruit in the world. Additionally, we did not observe a reduction in risk of stroke associated with daily fruit and vegetable intake in south Asia, which might relate to variations in type of fruit and vegetables consumed, method of preparation, or both. A large

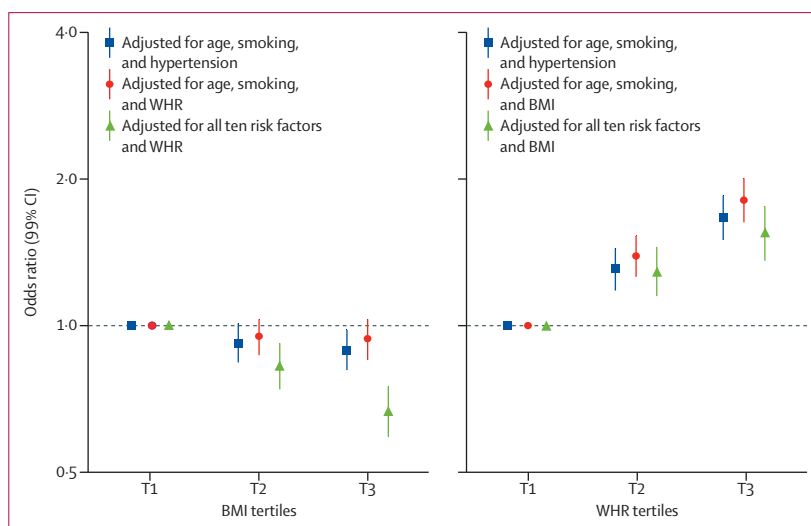


Figure 4: BMI and WHR association with risk of all stroke

BMI=body-mass index. WHR=waist-to-hip ratio.

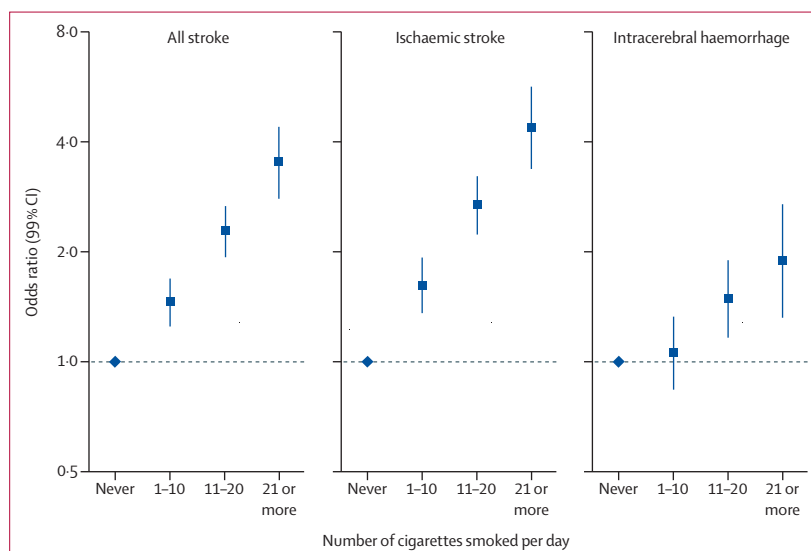


Figure 5: Current smoking and risk of ischaemic stroke and intracerebral haemorrhage

proportion of the population in south Asia are vegetarian (about 40%), and there is evidence of high use of hydrogenated vegetable oil-based ghee in cooking and transition away from whole plant foods, which might contribute to this finding.²⁵ Although additional research is needed to confirm these findings, the results from this study raise caution about the generalisability of diet risk scores developed in North America and Europe to other regions. Other than diet, the direction of association for all other risk factors was generally consistent across regions, although the magnitude of OR varied by region for many risk factors. For example, we found evidence of regional variations in the association between alcohol consumption and stroke, which was also observed in the PURE study,¹⁷ and for acute myocardial infarction in the INTERHEART study,²⁶ which might relate to variations in patterns and types of alcohol consumed. We also observed a graded reduction in OR for hypertension from high-income regions to low-income regions, which could relate to known differences in detection and management of hypertension,²⁷ but perhaps also to differences in magnitude of association by ethnic origin.^{28,29} Other examples include a higher OR for apolipoproteins in southeast Asia and psychosocial factors in China than in other regions. Inter-regional variations in PAR were also related to differences in risk-factor prevalence. Atrial fibrillation was associated with an OR of more than 3.0 for ischaemic stroke in all regions, but PAR ranged from 3.1% in south Asia to 17.1% in western Europe, North America, and Australia. The range of PARs noted were mostly due to variations in the prevalence of atrial fibrillation, and there is some evidence to support regional variations in prevalence of atrial fibrillation in patients with acute ischaemic stroke, based on indirect comparisons of studies.^{30–33} Some variations in the prevalence of atrial fibrillation relate to differences in mean age of participants by region (eg, mean age in western Europe, North America, and Australia is 7–10 years higher than south Asia, southeast Asia, and Africa), but might also relate to reported differences in prevalence of atrial fibrillation by geographic region and ethnic origin.^{34,35} High alcohol intake and smoking were more prevalent in men than women, but had a similar OR, resulting in a different PAR for men and women, which has been reported in other studies.^{17,36} Therefore, targeted interventions to screen and manage these risk factors are expected to have consistent relative reductions in risk across populations, but different effects on incidence of stroke across regions and in men and women. Overall, however, our findings show more consistency than differences among regions and subgroup populations. Hypertension is the most important target for stroke prevention worldwide, associated with PARs ranging from 38.8% to 59.6% in all regions, which is generally consistent with estimates from other studies.^{8,37–39} Hypertension is similarly important in people aged

55 years or younger (PAR 49.7%) and people older than 55 years (PAR 46.0%), and in men (PAR 45.2%) and women (PAR 52.3%), suggesting that a large proportion of the global burden of stroke might be preventable through control of blood pressure, with population-level interventions.⁴⁰

Our study provides further information that clarifies differences in association of risk factors with ischaemic stroke and intracerebral haemorrhage (figure 1, appendix p 7).⁴¹ Seven risk factors were common to both ischaemic stroke and intracerebral haemorrhage, of which hypertension was significantly more strongly associated with intracerebral haemorrhage than with ischaemic stroke. Smoking, diabetes mellitus, and apolipoproteins were significant risk factors for ischaemic stroke, but not for intracerebral haemorrhage. Therefore, although a broader array of targets exists for prevention of ischaemic stroke than for intracerebral haemorrhage, a more marked reduction in intracerebral haemorrhage is expected by the reduction of blood pressure alone.⁴² Our study suggests that the mix of stroke subtypes in a population is probably influenced by variations in the prevalence of vascular risk factors, which could account for some of the worldwide variations in pattern of stroke subtypes.^{1,2,6}

Investigators of the PURE study⁴³ found regional variations in the pattern of cardiovascular disease events. Stroke accounts for a larger proportion of all cardiovascular disease events in Asia than in North America or Europe. Although an indirect comparison of our findings with INTERHEART¹³ shows commonality of risk factors for acute stroke and acute myocardial infarction, the relative magnitude of association for each risk factor seems to be different, which might contribute to worldwide variations in patterns of cardiovascular disease.

In our primary analysis, the sum of PARs for each individual risk factor exceeded the PAR reported for composite risk factors (90.7% for all stroke), which is a characteristic of the PAR metric. Like myocardial infarction, stroke is a consequence of numerous causal risk factors, rather than a single cause, with the arguable exception of severe hypertension for intracerebral haemorrhage. Generally, multiple risk factors are needed to act together to be sufficient to cause an acute stroke. Therefore, the proportion of disease that can be attributed to each of the causal mechanisms of stroke disease can add up to more than 100%,⁴⁴ as observed in our analyses. We explored an alternative method to estimate PAR, average PAR, which requires the sum of individual PARs to equal the overall PAR for the composite of risk factors.^{19,20} In that analysis, we found a lower APAR, compared with PAR, for all individual risk factors, which is expected, with preservation of the relative ranking of importance (appendix p 13). PAR and APAR do not provide conflicting information, but a different perspective on the contribution of common risk factors.

PAR provides a better estimate of the potential effect of complete removal of an individual risk factor on disease burden than APAR, whereas APAR might better reflect anticipated effects when multiple risk factors are modified simultaneously.

Our study has a few limitations, some of which have been previously reported in the phase 1 study report.³ A case-control study design is potentially open to bias if the method of ascertaining risk factors is different between cases and controls. Measurement of some risk factors in cases could be misclassified if an acute stroke changes the level of a risk factor. This can be particularly problematic for blood pressure after stroke, and can be a greater source of error for intracerebral haemorrhage than ischaemic stroke. We gave this issue careful consideration, because blood pressure was the most important risk factor for stroke. A study of a population-based cohort in Oxfordshire, UK, evaluated the relationship between premorbid blood pressure and acute post-stroke blood pressure, and we used this study's findings to estimate expected preadmission blood pressure for patients.¹⁴ We chose adjusted blood pressure at the time of hospital admission to estimate blood pressure because it represents a single, consistent timepoint in all patients, is not affected by use of in-hospital blood pressure drugs (which might have regional variability in use), and is not influenced by medical complications after stroke. We used a single measurement in cases, rather than mean of three measurements, because blood pressure in controls was measured on one occasion. However, we did several sensitivity analyses, using different approaches to define hypertension by blood pressure measurement in cases (appendix p 4). Our primary estimate of PAR association with hypertension is generally consistent with estimates derived from previous studies, and lower than that reported by the GBD analyses.⁷ For atrial fibrillation (and other cardiac causes), more measurements were taken in cases than controls, although use of cardiac diagnostics was low in the entire cohort, with marked regional variations, meaning that the true prevalence of atrial fibrillation is expected to be higher than reported, particularly in low-income and middle-income countries. We chose apolipoproteins and HbA_{1c}, because these measurements are less affected by non-fasting status than lipoproteins and glucose, respectively.^{45,46}

Choice of controls might also affect the prevalence of risk factors in the control group. We recruited both community-based and hospital-based controls, which allowed us to assess whether the results depended on how controls were selected, and observe some modest difference in magnitude of association for some risk factors (appendix p 12), but this did not materially alter our overall findings. Any such bias might also influence apparent regional variations in relative magnitude of association because some regions had larger proportions of hospital-based controls than others. For example, inclusion of hospital controls could increase the prevalence of diseases that have independent associations

with vascular risk factors (eg, smoking and chronic obstructive pulmonary disease). However, the prevalence of measured comorbidities was similar in cases and controls (appendix p 14). Inclusion of some hospital controls could have increased the prevalence of diabetes in controls, which might have contributed to the lower PAR reported in our study compared with other studies,^{8,37} although estimates for Asia are similar to those reported by Huxley and colleagues.³⁶ Overall, the prevalence of most risk factors in controls seems consistent with estimates of these risk factors from the PURE study;^{27,43} for example, the prevalence of hypertension was 47·4% in INTERSTROKE versus 40·8% in PURE and, for current smoking, 22·4% versus 20·9%.

Finally, a causal association between risk factors and disease cannot definitively be concluded from a case-control design. However, our objective was to quantify the effect of known risk factors on burden of disease, rather than to establish new causal relationships, which has already been done for most of the risk factors we assessed in prospective cohort studies and randomised controlled trials.

Our study has several strengths, particularly the large representative sample of individuals with stroke from all major regions of the world, which has not been used in any other study. A case-control design provides a practical approach to measuring the importance of risk factors for stroke worldwide. Although prospective cohort studies, such as in the PURE study, provide a more methodologically rigorous design than case-control studies, they need a considerably larger number of participants, greater resources, logistics, and duration of follow-up. Extended follow-up of large prospective cohort studies (eg, PURE,⁴³ Kadoorie,⁴⁷ and UK Biobank⁴⁸) will provide additional insights and clarification with prospective assessment of the importance of these risk factors for stroke risk, and other cardiovascular diseases. Additionally, further research is needed for niche populations not included in INTERSTROKE (eg, specific indigenous groups from around the world).

In conclusion, ten potentially modifiable risk factors are collectively associated with about 90% of the PAR of stroke in each major region of the world, in ethnic groups, in men and women, and in different age groups. However, we found important regional variations in the relative importance of most individual risk factors for stroke, which could contribute to worldwide variations in frequency and case-mix of stroke and support the development of both global and region-specific programmes to prevent stroke.

Contributors

MJO'D and SY designed the study, planned analyses, and wrote the first draft of the report. PR-M and XZ did statistical analyses. All authors contributed to the collection of data, discussions and interpretation of the data, and to the writing of the report. All authors had full access to data and reviewed and approved the drafts of the report.

Declaration of interests

GJH reports personal fees from Bayer and Medscape, outside of the submitted work. H-CD has received honoraria for participation in

clinical trials, contribution to advisory boards, or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth, and Yamanouchi; financial support for research projects provided by AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis, and Talecris; served as editor of *Aktuelle Neurologie*, *Arzneimitteltherapie*, *Kopfschmerznews*, *Stroke News*, and the Treatment Guidelines of the German Neurological Society within the past year; and served as co-editor of *Cephalalgia*, and on the editorial board of *Lancet Neurology*, *Stroke*, *European Neurology*, and *Cerebrovascular Disorders* in the past year. MJO'D, SLC, SR, DX, LL, HZ, PR-M, XZ, PP, SA, PL-J, AD, PL, MJM, AR, MD, ALD, AE, AA, CM, DR, AC, NP, CW, RI, RD, KY, AY, AO, XW, EP, FL, OSO, AO, HKI, GM, ZR, SO, FAH, DM, YN, JF, GP, and SY declare no competing interests.

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