Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study

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Background The contribution of various risk factors to the burden of stroke worldwide is unknown, particularly in countries of low and middle income. We aimed to establish the association of known and emerging risk factors with stroke and its primary subtypes, assess the contribution of these risk factors to the burden of stroke, and explore the differences between risk factors for stroke and myocardial infarction.

Methods We undertook a standardised case-control study in 22 countries worldwide between March 1, 2007, and April 23, 2010. Cases were patients with acute first stroke (within 5 days of symptoms onset and 72 h of hospital admission). Controls had no history of stroke, and were matched with cases for age and sex. All participants completed a structured questionnaire and a physical examination, and most provided blood and urine samples. We calculated odds ratios (ORs) and population-attributable risks (PARs) for the association of all stroke, ischaemic stroke, and intracerebral haemorrhagic stroke with selected risk factors.

Findings In the first 3000 cases (n=2337, 78%, with ischaemic stroke; n=663, 22%, with intracerebral haemorrhagic stroke) and 3000 controls, significant risk factors for all stroke were: history of hypertension (OR 2·64, 99% CI 2·26–3·08; PAR 34·6%, 99% CI 30·4–39·1); current smoking (2·09, 1·75–2·51; 18·9%, 15·3–23·1); waist-to-hip ratio (1·65, 1·36–1·99 for highest *vs* lowest tertile; 26·5%, 18·8–36·0); diet risk score (1·35, 1·11–1·64 for highest *vs* lowest tertile; 18·8%, 11·2–29·7); regular physical activity (0·69, 0·53–0·90; 28·5%, 14·5–48·5); diabetes mellitus (1·36, 1·10–1·68; 5·0%, 2·6–9·5); alcohol intake (1·51, 1·18–1·92 for more than 30 drinks per month or binge drinking; 3·8%, 0·9–14·4); psychosocial stress (1·30, 1·06–1·60; 4·6%, 2·1–9·6) and depression (1·35, 1·10–1·66; 5·2%, 2·7–9·8); cardiac causes (2·38, 1·77–3·20; 6·7%, 4·8–9·1); and ratio of apolipoproteins B to A1 (1·89, 1·49–2·40 for highest *vs* lowest tertile; 24·9%, 15·7–37·1). Collectively, these risk factors accounted for 88·1% (99% CI 82·3–92·2) of the PAR for all stroke. When an alternate definition of hypertension was used (history of hypertension or blood pressure >160/90 mm Hg), the combined PAR was 90·3% (85·3–93·7) for all stroke. These risk factors were all significant for ischaemic stroke, whereas hypertension, smoking, waist-to-hip ratio, diet, and alcohol intake were significant risk factors for intracerebral haemorrhagic stroke.

Interpretation Our findings suggest that ten risk factors are associated with 90% of the risk of stroke. Targeted interventions that reduce blood pressure and smoking, and promote physical activity and a healthy diet, could substantially reduce the burden of stroke.

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Introduction

Stroke is the second leading cause of death worldwide, and the leading cause of acquired disability in adults in most regions.[1,2] Countries of low and middle income have the largest burden of stroke, accounting for more than 85% of stroke mortality worldwide, but few reliable data are available to identify risk factors for stroke in most of these regions, and particularly for haemorrhagic stroke.[1–5]

Findings from the INTERHEART study[6–10] suggested that nine modifiable risk factors explain most of the risk of myocardial infarction worldwide. An equivalent study is needed for stroke because stroke has several pathologies other than large artery atherosclerosis,[11] so risk factors for stroke and its aetiological subtypes could differ from those for myocardial infarction. Furthermore, the independent contribution of each risk factor to the burden of stroke worldwide—the population-attributable risk (PAR)—is unknown in most regions.

The INTERHEART study showed the feasibility, value, and importance of a large standardised international case-control study (29 972 participants) to establish the importance of, and relation between, key risk factors for myocardial infarction in 52 countries of high, middle, and low income, with participation from every inhabited continent.[6–10] However, additional challenges are presented by a similar study for stroke. In particular, routine

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neuroimaging is needed to establish primary stroke subtypes (ischaemic *vs* haemorrhagic), and patients with disabling stroke who are unable to communicate need to be represented in the study.

The INTERSTROKE study is an international, multicentre, case-control study, designed to establish the association of traditional and emerging risk factors with stroke (and primary stroke subtypes) in countries of high, middle, and low income. We report the results of phase 1 of 3000 cases and 3000 controls from 22 countries, showing that an international case-control study is feasible for stroke, and provide estimates of the importance of common risk factors. Phase 2 is underway and is expected to be completed in the next 3 years.

Methods

Participants

The design of the INTERSTROKE study has been reported previously,[12] and we provide a brief summary. Participants were recruited from 84 centres in 22 countries: Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Croatia, Denmark, Ecuador, Germany, India, Iran, Malaysia, Mozambique, Nigeria, Peru, Philippines, Poland, South Africa, Sudan, and Uganda. Phase 1 lasted from March 1, 2007, to April 23, 2010.

Cases were admitted to hospital with first acute stroke, defined as "a clinical syndrome characterised by rapidly developing clinical symptoms and/or signs, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one".[13] Patients were included if they presented within 5 days of symptoms onset or from when they were last seen without deficit, presented within 72 h of hospital admission, and a CT or MRI of the brain was planned for within 1 week of presentation. For patients unable to communicate sufficiently to complete the study questionnaire, proxy respondents were used. We defined a valid proxy respondent as a spouse or first-degree relative who was living in the same home or was aware of the participant's previous medical history and present treatments. Patients were excluded if: they had non-vascular causes of stroke; they were presently in hospital for acute coronary syndrome; or consent could not be obtained from the patient or a valid proxy respondent. Sites were encouraged to keep a screening log of consecutive patients admitted with acute stroke for the first 3 months of recruitment.

Controls were based in hospital or the community, and had no history of stroke. Controls were matched with cases for age (within 5 years) and sex. We attempted to recruit one control per case at each site, as per the STROBE guidelines. In countries with substantial representation from several ethnic groups (eg, South Africa, Canada), controls were also matched to cases on the basis of ethnic origin. Hospital-based sources included patients admitted to hospital or attending outpatient clinics for disorders or procedures unrelated to stroke or transient ischaemic attack, or visitors or relatives of inpatients. Approaches to identify sources of community-based controls were not prespecified because standardised approaches might not be feasible in all settings.

The primary distinction between stroke subtypes—ischaemic, intracerebral haemorrhagic, and subarachnoid haemorrhagic—was based on clinical assessment and neuroimaging (CT or MRI). We excluded patients with subarachnoid haemorrhagic stroke from analyses in this report. Patients with ischaemic stroke were classified according to the Oxfordshire Community Stroke Project (OCSP) classification,[14] and the presumed aetiological subtype (large vessel, small vessel, cardioembolism or unexplained) was defined by the local physician. Neuroimaging and electrocardiography (ECG) had to be done at baseline in all cases, but we did not mandate any additional investigations. We anticipated substantial variation in the availability and use of cardiac and neurovascular imaging between regions,[15] with reduced occurrence of investigations in low-income settings. Data from available diagnostic testing and stroke subtype were recorded in all cases. The modified-Rankin scale[16] was used to measure stroke severity at baseline and 1-month follow-up.

INTERSTROKE was approved by the ethics committees of all participating centres. Every participant, or their proxy respondent, provided informed written consent before taking part in the study.

Measurement of risk factors

Our approach to assessment of all key vascular risk factors, history of hypertension and diabetes mellitus, anthropometrical measurements (waist and hip circumference, height, and weight), physical activity, diet and alcohol intake, smoking status, and psychosocial factors was consistent with the INTERHEART study.[6–10] Structured questionnaires were administered and physical examinations were undertaken in the same manner for cases and controls. Waist and hip circumferences were measured in the standing and supine positions; if patients with stroke were unable to stand because of disability, these measurements were completed in the supine position only.

For cases, blood pressure and heart rate were recorded at three timepoints: admission; the morning after admission (from patient's chart); and at interview (done by research personnel). For controls, blood pressure and heart rate were recorded at interview only. Hypertension was defined with two approaches: self-reported history of hypertension; or the composite of self-reported hypertension or blood pressure of higher than 160/90 mm Hg (mean of three measurements for cases).

We assessed both waist-to-hip ratio and body-mass index because findings from INTERHEART showed that waist-to-hip ratio was a stronger risk factor for myocardial infarction than was body-mass index.[9] For waist-to-hip ratio and body-mass index, tertiles (T) were calculated on

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the basis of the overall control data: we used cutoffs of 0·91 and 0·96 in men, and 0·86 and 0·93 in women, to divide participants into thirds. Self-report was used to define diabetes mellitus. Individuals were classified as physically active if they were regularly involved in moderate exercise (walking, cycling, or gardening) or strenuous exercise (jogging, football, and vigorous swimming) for 4 h or more per week. We used a similar approach as that used in the INTERHEART study[17] to generate a diet risk score on the basis of foods that were associated with an increased or reduced risk of stroke (an increasing score indicates an increasingly unhealthy cardiovascular diet). Initial exploration of data suggested a J-shaped association of alcohol intake with all stroke; on this basis, alcohol intake was categorised into never or former drinker, moderate drinker (1–30 drinks per month), drinker of more than 30 drinks per month, or binge drinker (>5 drinks per day at least once per month). Smoking status was defined as never, former, or current smoker. We defined current smokers as individuals who smoked any tobacco in the past 12 months and included those who had quit within the past year. Former smokers were defined as those who had quit more than a year earlier. For psychosocial stress, we used a combined measure of general stress at home and in the workplace (permanent or several periods of stress *vs* no or some periods of stress in the past year). Depression was defined as feeling sad, blue, or depressed for two or more consecutive weeks during the past 12 months. Our approach to psychosocial factors differed from INTERHEART,[10] which included additional measures of psychosocial stress, because of our smaller sample size. Atrial fibrillation or flutter was based on self-reported history, review of baseline ECG, and results of cardiac monitoring. Previous myocardial infarction, rheumatic valvular heart disease, and prosthetic heart valve were based on medical history.

Non-fasting blood samples (20 mL) were drawn from cases (within 72 h of admission) and controls (at the time of interview), separated into six equal volumes, and frozen immediately after processing at –20°C or –70°C.

	All (n=3000)	High-income countries* (n=422)	South America† (n=151)	Southeast Asia‡ (n=1146)	India (n=958)	Africa§ (n=323)
Age (years)	61·1 (12·7)	66·0 (13·3)	65·6 (13·4)	58·5 (11·6)	58·9 (12·0)	57·7 (15·3)
Age ≤45 years	415 (14%)	32 (8%)	13 (9%)	146 (13%)	147 (15%)	77 (24%)
Women	1106 (37%)	169 (40%)	71 (47%)	412 (36%)	313 (33%)	141(44%)
Intracerebral haemorrhagic stroke	663 (22%)	40 (9%)	39 (26%)	257 (22%)	218 (23%)	109 (34%)
Ischaemic stroke	2337 (78%)	382 (91%)	112 (74%)	889 (78%)	740 (77%)	214 (66%)
OCSP classification¶						
Total anterior circulation infarct	177 (8%)	28 (7%)	15 (13%)	51 (6%)	42 (6%)	41 (19%)
Partial anterior circulation infarct	1205 (52%)	166 (43%)	37 (33%)	510 (57%)	391 (53%)	101 (47%)
Posterior circulation infarct	321 (14%)	61 (16%)	18 (16%)	121 (14%)	103 (14%)	18 (8%)
Lacunar infarction	499 (21%)	110 (29%)	15 (13%)	194 (22%)	145 (20%)	35 (16%)
Undetermined	135 (6%)	17 (4%)	27 (24%)	13 (1%)	59 (8%)	19 (9%)
Presumed primary aetiology¶						
Cardioembolism	220 (9%)	100 (26%)	18 (16%)	17 (2%)	32 (4%)	53 (25%)
Large vessel	437 (19%)	70 (18%)	5 (4%)	99 (11%)	232 (31%)	31 (14%)
Small vessel	1039 (44%)	115 (30%)	20 (18%)	474 (53%)	373 (50%)	57 (27%)
Other	124 (5%)	16 (4%)	17 (15%)	23 (3%)	25 (3%)	43 (20%)
Undetermined	517 (22%)	81 (21%)	52 (46%)	276 (31%)	78 (11%)	30 (14%)
Modified-Rankin scale (1-month follow-up)						
0–1	1114 (37%)	192 (45%)	35 (23%)	513 (45%)	329 (34%)	45 (14%)
2–3	1312 (44%)	162 (38%)	79 (52%)	479 (42%)	438 (46%)	154 (48%)
4–5	309 (10%)	50 (12%)	18 (12%)	107 (9%)	84 (9%)	50 (15%)
6 (fatal)	260 (9%)	17 (4%)	19 (13%)	46 (4%)	107 (11%)	71 (22%)
Data missing	5 (<1%)	1 (<1%)	0	1 (1%)	0	3 (1%)
CT or MRI of brain	2997 (99·9%)	422 (100%)	151 (100%)	1146 (100%)	955 (99·7%)	323 (100%)
ECG	2957 (99%)	421 (100%)	140 (93%)	1142 (100%)	953 (99%)	301 (93%)
Vascular imaging¶	657 (28%)	293 (77%)	22 (20%)	297 (33%)	41 (6%)	4 (2%)
Transthoracic echocardiography¶	327 (14%)	145 (38%)	5 (4%)	112 (13%)	13 (2%)	52 (24%)
Holter monitor¶	146 (6%)	118 (31%)	1 (1%)	27 (3%)	0	0

Data are mean (SD) or number (%). OCSP=Oxfordshire Community Stroke Project. ECG=electrocardiogram. *Australia, Canada, Croatia, Denmark, Germany, Iran, and Poland. †Argentina, Brazil, Chile, Colombia, Ecuador, and Peru. ‡China, Malaysia, and Philippines. §Mozambique, Nigeria, South Africa, Sudan, and Uganda. ¶Percentages are proportions of the number of cases with ischaemic stroke.

Table 1: **Demographic and clinical characteristics of cases**

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 (Canada) or at –70°C (national coordinating offices in India and China). Blood samples for total cholesterol, HDL cholesterol, and apolipoproteins B (ApoB) and A1 (ApoA1) were analysed in Hamilton (ON, Canada), Beijing (China), and Super Religare Laboratories, Mumbai (India). We assessed apolipoproteins and lipoproteins because findings from INTERHEART showed that apolipoproteins were stronger risk factors for acute myocardial infarction than were lipoproteins.[7] Cholesterol, HDL cholesterol, and apolipoprotein concentrations were measured in the Canadian core

	Prevalence*			All stroke†		Ischaemic stroke†		Intracerebral haemorrhagic stroke	
	Control (n=3000)	Ischaemic stroke (n=2337)	Intracerebral haemorrhagic stroke (n=663)	Odds ratio (99% CI)	Population-attributable risk (99% CI)	Odds ratio (99% CI)	Population-attributable risk (99% CI)	Odds ratio (99% CI)	Population-attributable risk (99% CI)
Variable 1: hypertension									
A: self-reported history of hypertension	954/2996 (32%)	1277/2335 (55%)	399/662 (60%)	2·64 (2·26–3·08)	34·6% (30·4–39·1)	2·37 (2·00–2·79)	31·5% (26·7–36·7)	3·80 (2·96–4·78)	44·5% (37·2–52·0)
B: self-reported history of hypertension or blood pressure >160/90 mm Hg	1109/3000 (37%)	1550/2337 (66%)	551/663 (83%)	3·89 (3·33–4·54)	51·8% (47·7–55·8)	3·14 (2·67–3·71)	45·2% (40·3–50·0)	9·18 (6·80–12·39)	73·6% (67·0–79·3)
Variable 2: smoking status									
Current smoker‡	732/2994 (24%)	868/2333 (37%)	207/662 (31%)	2·09 (1·75–2·51)	18·9% (15·3–23·1)	2·32 (1·91–2·81)	21·4% (17·5–25·8)	1·45 (1·07–1·96)	9·5% (4·2–20·0)
Variable 3: waist-to-hip ratio									
T2 *vs* T1	989/2960 (33%)	768/2303 (33%)	266/655 (41%)	1·42 (1·18–1·71)	26·5% (18·8–36·0)§	1·34 (1·10–1·64)	26·0% (17·7–36·5)§	1·65 (1·22–2·23)	26·1% (14·1–43·3)§
T3 *vs* T1	984/2960 (33%)	987/2303 (43%)	231/655 (35%)	1·65 (1·36–1·99)	..	1·69 (1·38–2·07)	..	1·41 1·02–1·93)	..
Variable 4: diet risk score									
T2 *vs* T1	1064/2982 (36%)	842/2303 (37%)	271/658 (41%)	1·35 (1·12–1·61)	18·8% (11·2–29·7)§	1·29 (1·06–1·57)	17·3% (9·4–29·6)§	1·53 (1·13–2·08)	24·1% (11·9–42·7)§
T3 *vs* T1	904/2982 (30%)	807/2303 (35%)	221/658 (34%)	1·35 (1·11–1·64)	..	1·34 (1·09–1·65)	..	1·41 (1·01–1·97)	..
Variable 5: regular physical activity¶	362/2994 (12%)	193/2334 (8%)	45/662 (7%)	0·69 (0·53–0·90)	28·5% (14·5–48·5)	0·68 (0·51–0·91)	29·4% (14·5–50·5)	0·70 (0·44–1·13)	27·6% (6·8–66·6)
Variable 6: diabetes mellitus	350/2999 (12%)	495/2336 (21%)	68/662 (10%)	1·36 (1·10–1·68)	5·0% (2·6–9·5)	1·60 (1·29–1·99)	7·9% (5·1–12·3)	||	||
Variable 7: alcohol intake‡									
1–30 drinks per month	524/2989 (18%)	338/2326 (15%)	121/660 (18%)	0·90 (0·72–1·11)	3·8% (0·9–14·4)§	0·79 (0·63–1·00)	1·0% (0·0–83·8)§	1·52 (1·07–2·16)	14·6% (8·5–24·0)§
>30 drinks per month or binge drinker	324/2989 (11%)	383/2326 (16%)	108/660 (16%)	1·51 (1·18–1·92)	..	1·41 (1·09–1·82)	..	2·01 (1·35–2·99)	..
Variable 8: psychosocial factors									
A: psychosocial stress	440/2987 (15%)	465/2324 (20%)	124/654 (19%)	1·30 (1·06–1·60)	4·6% (2·1–9·6)	1·30 (1·04–1·62)	4·7% (2·0–10·2)	1·23 (0·89–1·69)	3·5% (0·7–16·3)
B: depression	424/2995 (14%)	489/2320 (21%)	100/645 (16%)	1·35 (1·10–1·66)	5·2% (2·7–9·8)	1·47 (1·19–1·83)	6·8% (3·9–11·4)	||	||
Variable 9: cardiac causes**	140/3000 (5%)	321/2337 (14%)	28/662 (4%)	2·38 (1·77–3·20)	6·7% (4·8–9·1)	2·74 (2·03–3·72)	8·5% (6·4–11·2)	||	||
Variable 10: ratio of ApoB to ApoA1††									
T2 *vs* T1	695/2091 (33%)	501/1698 (30%)	136/468 (29%)	1·13 (0·90–1·42)	24·9% (15·7–37·1)§	1·30 (1·01–1·67)	35·2% (25·5–46·3)§	||	||
T3 *vs* T1	696/2091 (33%)	825/1698 (49%)	165/468 (35%)	1·89 (1·49–2·40)	..	2·40 (1·86–3·11)	..	||	||

All models were adjusted for age, sex, and region. T=tertile. Apo=apolipoprotein. *Data were missing for some individuals: seven for self-reported history of hypertension, 11 for smoking status, 82 for waist-to-hip ratio, 57 for diet risk score, ten for physical activity, three for diabetes mellitus, 25 for alcohol intake, 35 for psychosocial stress, 40 for depression, one for cardiac causes, and 1743 for apolipoprotein concentrations; these individuals were excluded from the denominator in percentage calculations. †Individual risk-factor estimates for variables 1–9 are derived from the multivariable model, including all variables (1A and 2–9). For intracerebral haemorrhagic stroke, the multivariate model included variables 1A, 2–5, 7, and 8A. ‡Comparator for current smoker and alcohol intake is never or former. §For variables expressed in tertiles, population-attributable risk was calculated from T2 plus T3 versus T1. ¶For the protective factor of physical activity, population-attributable risks are provided for the group without this factor. ||Odds ratio and population-attributable risk was not calculated because the variable was not significant in univariate analyses and so was excluded from multivariate analyses. **Includes atrial fibrillation or flutter, previous myocardial infarction, rheumatic valve disease, or prosthetic heart valve. ††Estimate derived from multivariable model, including all variables (1A and 2–10; n=4257).

Table 2: **Risk of stroke associated with risk factors in the overall population (multivariate analyses)**

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laboratory with the Beckman Coulter Unicel DxC600 Synchron Clinical System and Beckman reagents (Beckman Coulter, Brea, CA, USA), in the Chinese laboratory (Beijing) with the Hitachi 7060 (Roche diagnostics, Mannheim, Germany), and in the Indian laboratory (Mumbai) with the Hitachi 917 (Roche diagnostics, Mannheim, Germany). To standardise results between laboratories, quality-control samples and reference pools that had been analysed in the central core laboratory in Canada were sent to India and China. In India, the data were stored centrally at the national coordinating office. All data were transferred to the Population Health Research Institute, Hamilton Health Sciences and McMaster University, ON, Canada, where quality-control checks and statistical analyses were done.

Statistical analysis

A study size of 3000 case-control pairs was chosen arbitrarily. Simple associations were assessed with Pearson's tests for two independent proportions. Means and medians were calculated to summarise continuous variables and were compared with *t* tests or appropriate non-parametric tests when distributional assumptions were in doubt. Categorisation of data by tertiles was based on data for controls. We used unconditional logistic regression adjusted for the matching criteria, similar to the INTERHEART study, rather than a conditional approach. Therefore, all findings presented are adjusted for region, sex, age, and potential confounders, and probably give a slight underestimation of effect sizes for most comparisons. In the multivariate models, we sought to establish the association of common risk factors, identified in the INTERHEART study, with all stroke, ischaemic stroke, and intracerebral haemorrhagic stroke (hypertension, smoking status, diabetes mellitus, physical activity, diet, psychosocial factors, abdominal obesity, alcohol intake, and apolipoprotein concentrations). For all stroke and ischaemic stroke, we also included a variable for cardiac causes. For analyses, we collapsed several cardiac causes into a single variable of cardiac cause because of the low prevalence of each disorder in the entire cohort and a consistent association with ischaemic stroke for each factor (atrial fibrillation or flutter, previous myocardial infarction, rheumatic valvular disease, or prosthetic heart valve). Only risk factors identified as significant in univariate analyses were included in the final multivariate models, which included all risk factors for all stroke and ischaemic stroke, and seven risk factors for intracerebral haemorrhagic stroke. To achieve optimum power to detect associations, we used all controls for analyses of stroke subgroups (ischaemic and intracerebral haemorrhagic).

Adjusted odds ratios (ORs) for risk factors were derived from their respective model coefficients in the multivariate logistic regression model. Estimates of ORs and accompanying 99% CIs are presented for every risk factor. Multivariate estimates for hypertension, smoking status, diabetes mellitus, physical activity, diet, psychosocial factors, abdominal obesity, and alcohol intake were derived from a model that did not include apolipoprotein concentrations because these data were not available for 1743 participants (29%). Statistical analyses and graphics were produced with SAS (version 9.1) and S-Plus (version 8.1). All statistical tests of hypotheses are two-sided. PARs and 99% CIs were calculated for various risk factors in the study by a method based on unconditional logistic regression. The PARs presented are adjusted for confounders in a similar manner to the corresponding logistic regression models for OR estimates, and, where indicated, are stratified by subgroups of interest. PAR estimates were calculated by the interactive risk-attributable program software (US National Cancer Institute, 2002). We used the same approach as that used in INTERHEART[6] for univariate and multivariate estimation of PAR for each risk factor, and combination of risk factors (described by Benichou and Gail[18]). We based calculations of CIs on this method with a logit transformation approach, apart from for negative PAR estimates, in which case conventional Wald-type CIs were used.

	Self-reported hypertension or blood pressure >160/90 mm Hg	Current smoker	Waist-to-hip ratio (T3 *vs* T1)
Region			
High-income countries (n=422)*	2·79 (1·83–4·25)	2·68 (1·64–4·37)	3·34 (1·96–5·68)
South America (n=151)†	3·52 (1·63–7·60)	3·01 (1·00–9·06)	3·82 (1·26–11·55)
Southeast Asia (n=1146)‡	4·49 (3·54–5·70)	2·17 (1·62–2·90)	1·36 (0·99–1·85)
India (n=958)	4·36 (3·34–5·69)	2·22 (1·65–2·97)	1·35(0·96–1·89)
Africa (n=323)§	4·96 (3·11–7·91)	2·18 (1·07–4·43)	1·73 (0·99–3·02)
Sex			
Men (n=1894)	3·88 (3·22–4·68)	2·46 (2·02–3·01)	1·25 (0·99–1·59)
Women (n=1106)	4·89 (3·79–6·32)	1·56 (1·03–2·36)	2·70 (1·95–3·74)
Age (years)			
≤45 (n=415)	8·53 (5·39–13·49)	2·77 (1·72–4·47)	1·38 (0·83–2·28)
>45 (n=2585)	3·89 (3·31–4·56)	2·17 (1·79–2·62)	1·71 (1·39–2·09)
Modified-Rankin scale			
0–2 (n=1899)	4·06 (3·43–4·82)	2·05 (1·69–2·49)	1·55 (1·26–1·91)
3–6 (n=1096)	4·48 (3·62–5·55)	2·51 (1·97–3·20)	1·76 (1·35–2·30)

Data are odds ratio (99% CI). Models are adjusted for age, sex, region, hypertension, smoking status, and waist-to-hip ratio. T=tertile. *Australia, Canada, Croatia, Denmark, Germany, Iran, and Poland. †Argentina, Brazil, Chile, Colombia, Ecuador, and Peru. ‡China, Malaysia, and Philippines. §Mozambique, Nigeria, South Africa, Sudan, and Uganda.

Table 3: **Risk of stroke associated with key risk factors by region, sex, age, and stroke severity**

For **detailed justification of the approach to statistical analyses see the INTERHEART study (webtable 2)** at http://image.thelancet.com/extras/04art8001webtable2.pdf

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

A screening log was maintained for about 3 months in 42 centres from 14 countries. Of 5668 patients in the screening log, 762 (13%) were eligible to be included in phase 1. The most common reasons for ineligibility were: patient had had a previous stroke (n=1199, 24%); stroke did not meet the clinical definition (n=871, 18%); time window for symptom duration was exceeded (n=1294, 26%); and patient was unable to communicate because of severe stroke, aphasia, or dementia, and did not have a valid proxy respondent (n=691, 14%).

Phase 1 included 3000 cases and 3000 controls. 2337 cases (78%) had ischaemic stroke and 663 (22%) had intracerebral haemorrhagic stroke (table 1). About a seventh of cases were aged 45 years or younger, with the lowest proportion in high-income countries and the highest proportion in Africa. In all regions, ischaemic stroke was more common than was intracerebral haemorrhagic stroke, with some regional variation in the proportion with intracerebral haemorrhagic stroke (table 1). Neuroimaging was completed in 2997 cases (99·9%). Questionnaires were completed by patients (n=1131, 38%), proxy respondents (n=1044, 35%), or both together (n=822, 27%); the type of respondent was not known for three cases (<1%). The proportion of patients undergoing diagnostic testing to identify a source of thromboembolism varied between regions (table 1). 260 patients (9%) had died and 569 (19%) had had a stroke which was associated with severe disability or death at 1 month. The OCSP ischaemic stroke subtype and presumed ischaemic stroke aetiology are reported in table 1. Additional ischaemic stroke aetiologies included arterial dissection (n=13, 1%), vasculitis (n=7, <1%), and cerebral venous sinus thrombosis (n=5, <1%).

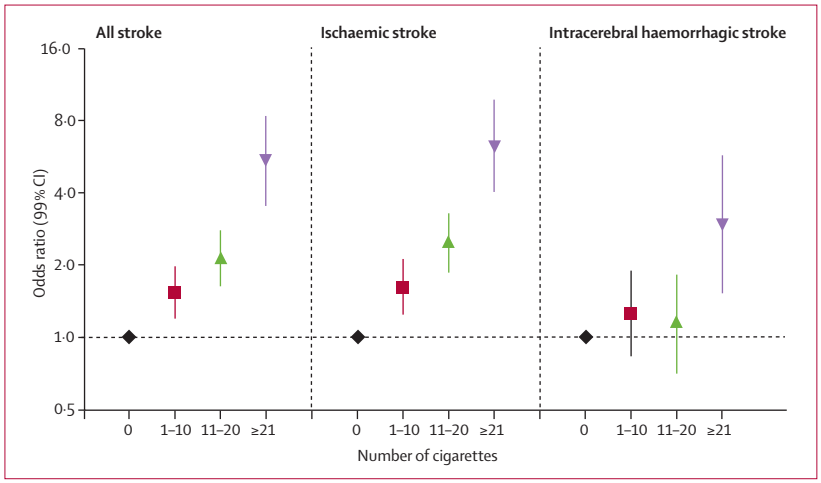

Figure 1: **Risk of stroke associated with number of cigarettes smoked for all stroke, ischaemic stroke, and intracerebral haemorrhagic stroke**
Data are adjusted for age, sex, and region.

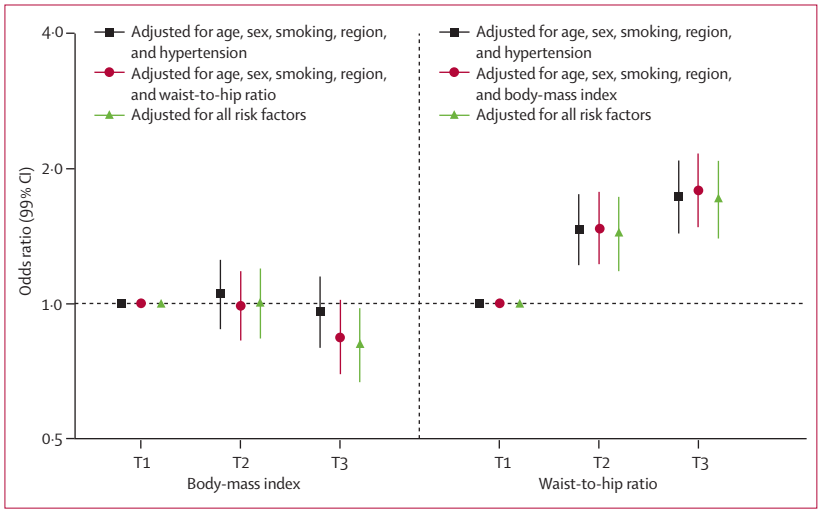

Figure 2: **Risk of all stroke associated with body-mass index and waist-to-hip ratio**
T=tertile.

Table 2 shows data for individual risk factors; data were missing in seven individuals (<1%) for self-reported history of hypertension, 11 (<1%) for smoking status, 82 (3%) for waist-to-hip ratio, 57 (2%) for diet risk score, ten (<1%) for physical activity, three (<1%) for diabetes mellitus, 25 (<1%) for alcohol intake, 35 (1%) for psychosocial stress, 40 (1%) for depression, and one (<1%) for cardiac causes.

Self-reported history of hypertension was the strongest risk factor for stroke, and was stronger for intracerebral haemorrhagic stroke than for ischaemic stroke. Use of the alternative definition for hypertension (self-reported hypertension or blood pressure >160/90 mm Hg), increased the strength of the associations for all stroke and for both stroke subtypes (table 2). With use of this alternative definition, hypertension was more strongly associated with stroke in individuals younger than 45 years than in those aged 45 years or older (table 3).

Current smoking status (*vs* never or former) was associated with an increased risk of stroke, which seemed to be stronger for ischaemic stroke than for intracerebral haemorrhagic stroke (table 2). Risk of stroke increased with the number of cigarettes smoked per day (figure 1). We recorded a reduced risk associated with former smoking (OR 0·74, 99% CI 0·57–0·95) compared with never smoking in multivariate analyses.

Assessment of anthropometrical factors showed that body-mass index was not associated with stroke (figure 2). Conversely, waist-to-hip ratio was associated with increased risk of all stroke, and both ischaemic and intracerebral haemorrhagic stroke (table 2, figure 2). In participants who completed both supine and standing measurements for waist-to-hip ratio (n=2723, 45%), we recorded a strong correlation between sitting and standing measurements (r=0·98 for waist, and r=0·97 for hip).

The diet risk score was associated with an increase in the risk of all stroke, with a consistent association for ischaemic and intracerebral haemorrhagic stroke (table 2). Within food groupings (adjusted for age, sex,

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and region; T3 *vs* T1), increased consumption of fruit (0·61, 0·50–0·73) and fish (0·78, 0·66–0·91), but not vegetables (0·91, 0·75–1·10), was associated with reduced risk. Increased risk of stroke was associated with: increased consumption of red meat, organ meats, or eggs (1·35, 1·10–1·65); increased consumption of fried foods, pizza, or salty snacks (1·16, 0·99–1·37); and cooking with lard (1·66, 1·06–2·60). Regular physical activity was associated with a reduced risk of all stroke (table 2). Self-reported history of diabetes mellitus was associated with an increased risk of all stroke and ischaemic stroke (table 2), but not intracerebral haemorrhagic stroke (0·87, 0·60–1·24).

A history of alcohol intake of 1–30 drinks per month was associated with a reduced risk of ischaemic stroke, whereas consumption of more than 30 drinks per month or binge drinking were associated with increased risk compared with never or former alcohol intake (table 2). For intracerebral haemorrhagic stroke, risk increased with alcohol intake (table 2).

Psychosocial stress was associated with an increased risk of all stroke, with consistent estimates for ischaemic and intracerebral haemorrhagic stroke (table 2). Depression was associated with an increased risk of all stroke and ischaemic stroke (table 2), but not intracerebral haemorrhagic stroke (1·11, 0·82–1·52).

Atrial fibrillation was the most common cardiac source of thromboembolism in cases with ischaemic stroke (203, 9%), with regional variation in prevalence: 86 (23%) in high-income countries, 14 (13%) in South America, 16 (7%) in Africa, 41 (6%) in India, and 46 (5%) in southeast Asia. Cardiac aetiology was associated with an increased risk of ischaemic stroke (table 2), but not intracerebral haemorrhagic stroke (0·90, 0·52–1·56).

Blood analyses were completed in 4317 participants (72%; 2190 cases and 2127 controls). Increased concentration of total cholesterol was not associated with risk of ischaemic stroke, but was associated with reduced risk of intracerebral haemorrhagic stroke (T3 *vs* T1; figure 3). Increased concentration of HDL cholesterol was associated with a reduced risk of ischaemic stroke, but an increased risk of intracerebral haemorrhagic stroke, whereas increased concentration of ApoA1 was associated with a reduced risk of ischaemic stroke, but was not associated with risk of intracerebral haemorrhagic stroke. Increased concentration of non-HDL cholesterol was not associated with risk of ischaemic stroke, but was associated with reduced risk of intracerebral haemorrhagic stroke, whereas increased concentration of ApoB was associated with increased risk of ischaemic stroke, but was not associated with risk of intracerebral haemorrhagic stroke. Ratio of non-HDL to HDL cholesterol was associated with increased risk of ischaemic stroke (T3 *vs* T1) but reduced risk of intracerebral haemorrhagic stroke (T3 *vs* T1). Ratio of ApoB to ApoA1 was a stronger predictor of ischaemic stroke (T3 *vs* T1) than was ratio of non-HDL to HDL cholesterol (figure 3).

Table 4 summarises PARs for various combinations of risk factors. In combination of the five risk factors with the largest PAR for both ischaemic and intracerebral haemorrhagic stroke (ie, hypertension or blood pressure >160/90 mm Hg, smoking status, waist-to-hip ratio, diet risk score, and physical activity; model 2), the multivariate PAR was higher for intracerebral haemorrhagic stroke than for all stroke or ischaemic stroke. For nine risk factors (addition of diabetes mellitus, alcohol, psychosocial factors, and cardiac causes; model 3), PAR

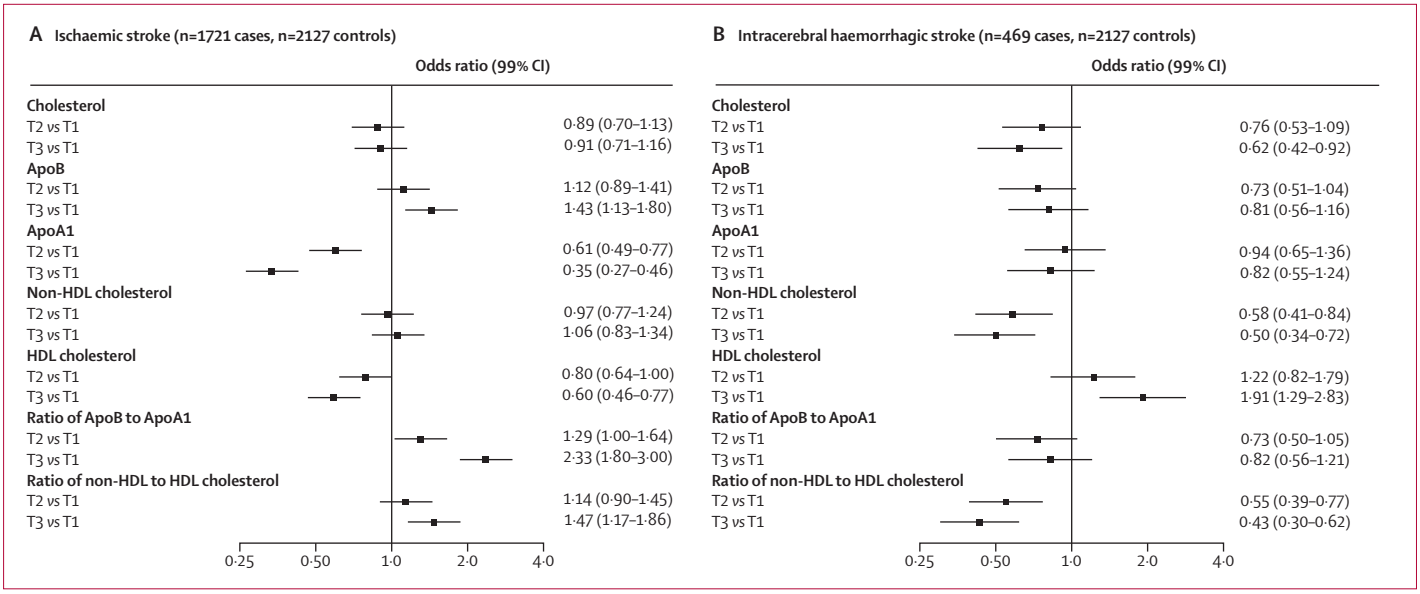

Figure 3: **Risk of ischaemic stroke (A) and intracerebral haemorrhagic stroke (B) associated with lipoproteins and apolipoproteins**
Data are adjusted for age, sex, region, hypertension, alcohol intake, smoking status, physical activity, diet, diabetes mellitus, and waist-to-hip ratio. T=tertile. Apo=apolipoprotein.

	All stroke (n=3000 cases, n=3000 controls)	Ischaemic stroke (n=2337 cases, n=3000 controls)	Intracerebral haemorrhagic stroke (n=663 cases, n=3000 controls)
Model 1: self-reported hypertension, smoking status, waist-to-hip ratio, diet risk score, regular physical activity, diabetes mellitus, alcohol intake, psychosocial factors, and cardiac causes	82·4% (76·2–87·3)	82·7% (76·0–87·8)	83·0% (70·7–90·7)*
Model 2: self-reported hypertension or blood pressure >160/90 mm Hg, smoking status, waist-to-hip ratio, diet risk score, and regular physical activity	83·4% (77·7–87·8)	81·8% (72·5–86·9)	89·6% (81·4–94·4)
Model 3: model 2 plus diabetes mellitus, alcohol intake, psychosocial factors, and cardiac causes	86·1% (80·8–90·0)	85·2% (79·3–89·6)	90·8% (83·1–95·2)*
Model 4: model 1 plus ratio of ApoB to ApoA1 (n=4257)	88·1% (82·3–92·2)	89·7% (84·1–93·4)	†
Model 5: model 3 plus ratio of ApoB to ApoA1 (n=4257)	90·3% (85·3–93·7)	90·9% (85·8–94·3)	†

Data are population-attributable risk (99% CI). Apo=apolipoprotein. *Intracerebral haemorrhagic stroke: estimate derived from multivariable model excluding diabetes mellitus, depression, and cardiac causes because these variables were not significant in the univariate analysis. †Data not presented because the ratio of ApoB to ApoA1 was not significantly associated with intracerebral haemorrhagic stroke.

Table 4: **Population-attributable risk for various risk factor combinations**

	Total anterior circulation infarct (n=177)	Partial anterior circulation infarct (n=1205)	Posterior circulation infarct (n=321)	Lacunar infarct (n=499)
Self-reported hypertension or blood pressure >160/90 mm Hg	3·16 (2·02–4·96)	3·19 (2·62–3·87)	4·09 (2·90–5·79)	4·20 (3·16–5·58)
Current smoker	2·42 (1·44–4·04)	2·43 (1·95–3·03)	2·51 (1·74–3·62)	2·24 (1·65–3·04)
Waist-to-hip ratio				
T2 *vs* T1	1·15 (0·65–2·04)	1·23 (0·97–1·57)	1·56 (1·01–2·43)	1·56 (1·11–2·21)
T3 *vs* T1	1·87 (1·09–3·19)	1·50 (1·18–1·90)	2·29 (1·49–3·50)	1·87 (1·32–2·65)

Data are odds ratio (99% CI). Stroke subtype was undetermined for 135 cases. Models are adjusted for age, sex, region, hypertension, smoking status, and waist-to-hip ratio. T=tertile. *Classified according to Oxfordshire Community Stroke Project.

Table 5: **Risk of ischaemic stroke subtypes* associated with risk factors**

increased for all stroke and ischaemic stroke, and PAR increased even further when the ratio of ApoB to ApoA1 was included in the model (model 5; table 4).

For key risk factors, subgroup analyses were completed by region, age, sex, and stroke severity (table 3), and by OCSP classification of stroke subtype (table 5). For hypertension and smoking, we recorded consistent associations by region and OCSP classification of ischaemic stroke subtypes. We recorded a suggestion of differences in risk-factor association by sex and by region for waist-to-hip ratio, and by age for self-reported hypertension or blood pressure of more than 160/90 mm Hg. Subgroup analyses are reported in table 6 for patient versus proxy respondent, and table 7 for community versus hospital-based control.

Discussion

The INTERSTROKE study is the first large standardised case-control study of risk factors for stroke in which countries of low and middle income were included, and all cases completed routine neuroimaging. Our findings showed that five risk factors accounted for more than 80% of the global risk of all stroke (ischaemic and intracerebral haemorrhagic): hypertension, current smoking, abdominal obesity, diet, and physical activity. With the addition of five other risk factors, including apolipoproteins, the PAR for all stroke rose to 90%.

Our study provides essential information on the importance of common, potentially modifiable vascular risk factors, and builds on previous epidemiological studies.[1,2,4,19–25] For ischaemic stroke, we recorded a significant association with all nine risk factors identified in the INTERHEART study, which were hypertension, smoking, abdominal obesity, diet, physical activity, diabetes mellitus, alcohol intake, psychosocial factors, and apolipoproteins, and collectively, these risk factors accounted for about 90% of the PAR. Although the overall PAR estimate is consistent with INTERHEART, the relative importance of some risk factors for stroke seem to be different compared with myocardial infarction. On the basis of an indirect comparison between the studies, these differences are most notable for hypertension, apolipoproteins, physical activity, and alcohol intake. Although data for intracerebral haemorrhagic stroke were based on fewer cases with wider 99% CIs than for ischaemic stroke, six of these risk factors were important, and accounted for a high proportion of PAR. These findings are important to help guide optimum selection of risk-factor targets for population-based programmes to prevent all cardiovascular diseases. The recorded differences in risk-factor profile could, in part, explain the global variations in incidence of ischaemic stroke, intracerebral haemorrhagic stroke, and myocardial infarction.[22,23]

Consistent with previous studies,[24] our findings showed that hypertension was the most important risk factor for all stroke subtypes, and a more potent risk factor for intracerebral haemorrhagic stroke than for

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ischaemic stroke and especially important in people of 45 years or younger. From the most conservative measure of hypertension, patient-reported history, PAR was 35% for all stroke types. However, a definition of hypertension as patient-reported history or blood pressure of higher than 160/90 mm Hg increased PAR to 52%, an estimate that is consistent with a previous systematic review.[25] Use of history of hypertension probably underestimates the association, but inclusion of actual blood pressure is also problematic in a case-control design: blood pressure might be raised in the acute stroke phase, whereas subsequent readings might be lower than usual blood pressure because of use of antihypertensive drugs and dietary changes. We used the mean of three blood pressure measurements in cases in an effort to keep these competing biases to a minimum. This method might overestimate the importance of raised blood pressure, although we used a high cutpoint for blood pressure of 160/90 mm Hg. However, both approaches suggest that blood pressure is the most important risk factor for stroke, and more important than other objectively measured risk factors (ie, lipids and glucose). Of these three risk factors, blood pressure is arguably the most amenable to change in low-income settings because screening programmes need modest equipment and little specialised expertise. Additionally, blood pressure is readily reduced by inexpensive generic drugs[26] and non-pharmacological approaches (eg, salt reduction).[27]

Similar to INTERHEART,[6] we also noted a much stronger association of stroke risk with waist-to-hip ratio than with body-mass index. Previous studies have reported similar findings for ischaemic stroke. Further, we recorded a consistent association between physical activity and risk of ischaemic and haemorrhagic stroke, with a larger PAR (about 29%) than was reported in INTERHEART[6] for acute myocardial infarction (12%).

We found a dose-response association for number of cigarettes smoked per day, which was more marked for ischaemic stroke than for intracerebral haemorrhagic stroke. Smoking was a strong risk factor in all regions and in all patient subgroups. By contrast with the INTERHEART study,[8] we noted that former smoking conferred no hazard, but instead was associated with reduced risk compared with never smoking; this finding has also been reported by another large study.[28] Even if this apparent reduced risk is not real, the finding suggests that risk rapidly reduces after stopping smoking, indicating that smoking cessation is an essential component for any stroke prevention programme.

Within food groups, intake of fish and fruits—components of a Mediterranean diet[29]—was associated with the greatest risk reduction. Unlike for myocardial infarction, we did not note an association between reduced risk of stroke and vegetable intake; this lack of association has also been suggested by some studies[30] and needs further exploration. The relation between alcohol intake and stroke seems complex: our data suggest that alcohol intake has a J-shaped relation with ischaemic stroke, but is associated with a graded increased risk of intracerebral haemorrhagic stroke. As a result, PAR for alcohol intake was greater for intracerebral haemorrhagic stroke than for ischaemic stroke. These findings are mostly consistent with previous epidemiological studies.[31,32,33] Types of alcohol consumed

	Patient (n=1131)	Proxy respondent (n=1044)	Both (n=822)*
Self-reported hypertension	2·73 (2·19–3·41)	2·22 (1·71–2·88)	2·16 (1·68–2·79)
Current smoker	2·35 (1·83–3·02)	2·40 (1·76–3·26)	2·11 (1·58–2·80)
Diabetes mellitus	1·69 (1·28–2·23)	1·50 (1·08–2·08)	1·50 (1·09–2·07)
Waist-to-hip ratio			
T2 *vs* T1	1·38 (1·05–1·81)	1·26 (0·91–1·74)	1·31 (0·97–1·77)
T3 *vs* T1	1·92 (1·47–2·52)	1·47 (1·07–2·03)	1·44 (1·06–1·96)
Psychosocial stress	1·32 (0·99–1·75)	1·16 (0·82–1·64)	1·30 (0·94–1·82)
Depression	1·86 (1·41–2·46)	1·25 (0·89–1·75)	1·31 (0·94–1·85)
Diet risk score			
T2 *vs* T1	1·18 (0·90–1·54)	1·43 (1·05–1·95)	1·24 (0·92–1·68)
T3 *vs* T1	1·12 (0·85–1·47)	1·77 (1·26–2·48)	1·32 (0·96–1·82)
Regular physical activity	0·74 (0·52–1·05)	0·65 (0·38–1·11)	0·51 (0·30–0·86)
Alcohol intake			
1–30 drinks per month	0·76 (0·56–1·04)	0·82 (0·55–1·22)	0·87 (0·60–1·26)
>30 drinks per month or binge drinker	1·45 (1·06–1·99)	1·20 (0·76–1·87)	1·40 (0·96–2·06)

Data are odds ratio (99% CI). Models are adjusted for age, sex, region, hypertension, alcohol intake, smoking status, physical activity, diet, diabetes mellitus, cardiac causes, depression and psychosocial stress, and waist-to-hip ratio. Information about the type of respondent was missing for three cases (<1%). T=tertile. *Data from questionnaires completed by the patient and proxy respondent together.

Table 6: **Risk of ischaemic stroke associated with risk factors by type of respondent for cases**

	Community (n=1602)	Hospital (n=1379)
Self-reported hypertension	2·86 (2·33–3·51)	2·01 (1·64–2·46)
Current smoker	2·09 (1·65–2·64)	2·53 (1·98–3·24)
Diabetes mellitus	2·26 (1·68–3·06)	1·24 (0·96–1·60)
Waist-to-hip ratio		
T2 *vs* T1	1·41 (1·12–1·79)	1·26 (0·98–1·62)
T3 *vs* T1	1·99 (1·56–2·54)	1·46 (1·14–1·87)
Psychosocial stress	1·98 (1·46–2·68)	0·98 (0·76–1·26)
Depression	1·67 (1·25–2·22)	1·27 (0·98–1·64)
Diet risk score		
T2 *vs* T1	1·10 (0·86–1·40)	1·53 (1·21–1·93)
T3 *vs* T1	1·32 (1·03–1·71)	1·38 (1·08–1·78)
Regular physical activity	0·63 (0·44–0·88)	0·78 (0·55–1·11)
Alcohol intake		
1–30 drinks per month	0·75 (0·57–1·00)	0·89 (0·66–1·18)
>30 drinks per month or binge drinker	1·36 (1·00–1·86)	1·59 (1·13–2·23)
Cardiac causes	3·32 (2·21–5·01)	2·53 (1·74–3·69)

Data are odds ratio (99% CI). Models are adjusted for age, sex, region, hypertension, alcohol intake, smoking status, physical activity, diet, diabetes mellitus, cardiac causes, depression and psychosocial stress, and waist-to-hip ratio. Information about the source of the data was missing for 19 controls (1%).

Table 7: **Risk of ischaemic stroke associated with risk factors by source of controls (community-based or hospital-based)**

could be important, and will be analysed in phase 2 of INTERSTROKE when increased numbers of cases and controls have been accrued.

Our study provides important and new information on the association of lipoproteins and apolipoproteins with stroke risk. Findings of epidemiological studies have been inconsistent, with most studies failing to identify an association between cholesterol and ischaemic stroke.[34] Further, for intracerebral haemorrhagic stroke, an inverse association has been reported in some studies.[34] For ischaemic stroke, we recorded no association with total or non-HDL cholesterol, but we did record strong associations with apolipoproteins and HDL cholesterol. Apolipoproteins, which are known to be stable in acute stroke,[35] were stronger risk factors for ischaemic stroke than were lipoproteins; this finding was not reported for ischaemic stroke in the AMORIS study,[36] but was reported for carotid artery disease in NOMASS,[37] and for myocardial infarction in the INTERHEART study.[7] Our study provides convincing evidence that apolipoproteins are associated with risk of ischaemic stroke. A particularly striking finding in our study was that the reduction in risk of ischaemic stroke associated with increased ApoA1 and HDL cholesterol was larger than the increase in risk associated with increased ApoB or non-HDL cholesterol; this relation has been suggested in some previous studies,[38] but not by a recent meta-analysis.[39] For intracerebral haemorrhagic stroke, cholesterol and non-HDL cholesterol were associated with reduced risk, which has been reported in previous studies,[34] but this relation is poorly understood and will be further explored in phase 2 of our study. Conversely, HDL cholesterol was associated with an increased risk of intracerebral haemorrhagic stroke, and apolipoproteins had no association.

We expected that cardiac disorders would account for a greater proportion of PAR for ischaemic stroke than was recorded.[3] Although atrial fibrillation was diagnosed in more than a fifth of cases in high-income regions, the prevalence was much lower in southeast Asia and India. We had also suspected that rheumatic heart disease would be a more common cause of stroke in some regions, especially Africa and India, than was actually recorded. An obvious limitation of our study is the low proportion of patients undergoing cardiac investigations. Therefore, we are unable to comment on the true proportion of patients with underlying, asymptomatic rheumatic heart disease.

Our study has several potential limitations, including those inherent to a case-control design (eg, selection bias, recall bias), but we made a concerted effort to overcome such anticipated biases by obtaining information in a standardised manner, with objective measures of risk factors where possible (eg, lipids, blood pressure), and proxy respondents for patients unable to communicate. First, although use of proxy respondents allowed inclusion of patients with aphasia and severe stroke, this might have led to reporting bias. However, for almost all risk factors that relied on past medical history, we recorded consistent results when patients, proxy respondents, or both provided the information. For subjective risk factors, we noted more consistency between patients and proxy respondents for psychosocial stress than for depression, which might indicate that stress is more easily identified by a close relative than is depression. Second, we used controls from both community-based and hospital-based sources. Ideally, controls would be drawn from the general population without the disease and come from community sources in the same catchment areas. In some settings, however, community-based controls were impractical. Although our overall findings are consistent, hospital-based controls could underestimate the true association for some risk factors. Third, our study recruited patients who were presently in hospital for stroke, introducing a selection bias whereby stroke severity extremes might not be included (ie, very minor or rapidly fatal). However, we recruited patients across a wide range of stroke severities, and we did not note convincing differences in key risk factor associations by stroke severity. Fourth, our study was confined to centres in which CT or MRI scanning was available, possibly introducing a selection bias, especially in countries of middle and low income in which neuroimaging facilities might be confined to larger centres.

Fifth, we relied on investigations done as part of routine clinical practice to establish ischaemic stroke aetiology. Clinicians provided a presumed aetiology for most cases of ischaemic stroke, but the vast majority of cases did not undergo vascular imaging or cardiac testing, which is needed for valid determination of ischaemic stroke subtype. Although we recorded marked regional variations in aetiological subtypes, this finding might be due to differences in diagnostic work-up, rather than true variation in subtypes. In particular, low occurrence of diagnostic testing could increase the proportion of patients reported to have presumed small vessel aetiology in some regions. Differences between regions in proportions of cases with the ischaemic stroke subtype, for aetiology and OCSP classification, could also be due to lack of uniform application of subtype definitions. For this reason, we have not reported completed analyses by aetiological ischaemic stroke subtypes. In most regions, the cost of diagnostic investigations precludes their routine clinical use. However, in phase 2, we will attempt to increase the routine use of diagnostic testing in all sites, especially large vessel imaging, in all sites.

Sixth, phase 1 of INTERSTROKE is the largest international case-control study to assess the importance of risk factors for stroke, but our present sample size might be inadequate to provide reliable information about the importance of each risk factor in different geographical regions, ethnic groups, and validly defined stroke subtypes. Phase 2 is expected to include an additional 10 000 case-controls pairs, which will be

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sufficient to provide reliable information in each region and in other subgroups. Such large samples sizes are also needed to establish the independent contribution of genetics, which are likely to be modest, to stroke risk. Importantly, phase 1 has shown that such an undertaking is achievable.

In conclusion, a large international epidemiological study of stroke that requires routine neuroimaging is feasible in countries of low and middle income. Our findings suggest that ten simple risk factors are associated with 90% of the risk of ischaemic and intracerebral haemorrhagic stroke worldwide. Targeted interventions that reduce blood pressure and smoking, and promote physical activity and a healthy diet, could substantially reduce the global burden of stroke.

Contributors

MO'D and SY designed the study, planned analyses, and wrote the first draft of the report. PRM and SI 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. No medical writer or other people participated in the study design, data analysis, or writing of this report.

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Conflicts of interest

H-CD has received board membership fees, consulting fees, honoraria, payment for manuscript preparation, payment for development of educational presentations, or travel expenses, or a combination, from Abbott, AstraZeneca, Bayer Vital, Bristol Myers Squibb, Boehringer Ingelheim, CoAxia, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Knoll, Merck Sharpe and Dohme, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Sankyo, Schering Plough, Servier, Solvay, Thrombogenics, Wyeth, and Yamaguchi; and his institution has received grants from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Janssen-Cilag, Sanofi-Aventis, German Research Council (DFG), Gernam Ministry of Education and Research (BMBF), European Union, US National Institutes of Health, Bertelsmann Foundation, and Heinz Nixdorf Foundation. MJM has received honoraria from Merck and Pfizer for presentations. RLS has received consultancy fees from Boehringer Ingelheim (none in the past 16 months); is president-elect and serves on the board of the American Heart Association; and his institution has received consultancy fees from the National Institute of Neurological Disorders and Stroke, and committee membership fees from the Population Health Research Institute, Canada. All other authors declare that they have no conflicts of interest, apart from distribution of funds received from sources listed in the Acknowledgments to cover recruitment costs, research staff, study materials and equipment, funds for CT scans, and travel to investigator meetings for the INTERSTROKE study.

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