Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013

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Summary

Background The contribution of modifiable risk factors to the increasing global and regional burden of stroke is unclear, but knowledge about this contribution is crucial for informing stroke prevention strategies. We used data from the Global Burden of Disease Study 2013 (GBD 2013) to estimate the population-attributable fraction (PAF) of stroke-related disability-adjusted life-years (DALYs) associated with potentially modifiable environmental, occupational, behavioural, physiological, and metabolic risk factors in different age and sex groups worldwide and in high-income countries and low-income and middle-income countries, from 1990 to 2013.

Methods We used data on stroke-related DALYs, risk factors, and PAF from the GBD 2013 Study to estimate the burden of stroke by age and sex (with corresponding 95% uncertainty intervals [UI]) in 188 countries, as measured with stroke-related DALYs in 1990 and 2013. We evaluated attributable DALYs for 17 risk factors (air pollution and environmental, dietary, physical activity, tobacco smoke, and physiological) and six clusters of risk factors by use of three inputs: risk factor exposure, relative risks, and the theoretical minimum risk exposure level. For most risk factors, we synthesised data for exposure with a Bayesian meta-regression method (DisMod-MR) or spatial-temporal Gaussian process regression. We based relative risks on meta-regressions of published cohort and intervention studies. Attributable burden for clusters of risks and all risks combined took into account evidence on the mediation of some risks, such as high body-mass index (BMI), through other risks, such as high systolic blood pressure (SBP) and high total cholesterol.

Findings Globally, 90·5% (95% UI 88·5–92·2) of the stroke burden (as measured in DALYs) was attributable to the modifiable risk factors analysed, including 74·2% (95% UI 70·7–76·7) due to behavioural factors (smoking, poor diet, and low physical activity). Clusters of metabolic factors (high SBP, high BMI, high fasting plasma glucose, high total cholesterol, and low glomerular filtration rate; 72·4%, 95% UI 70·2–73·5) and environmental factors (air pollution and lead exposure; 33·4%, 95% UI 32·4–34·3) were the second and third largest contributors to DALYs. Globally, 29·2% (95% UI 28·2–29·6) of the burden of stroke was attributed to air pollution. Although globally there were no significant differences between sexes in the proportion of stroke burden due to behavioural, environmental, and metabolic risk clusters, in the low-income and middle-income countries, the PAF of behavioural risk clusters in males was greater than in females. The PAF of all risk factors increased from 1990 to 2013 (except for second-hand smoking and household air pollution from solid fuels) and varied significantly between countries.

Interpretation Our results suggest that more than 90% of the stroke burden is attributable to modifiable risk factors, and achieving control of behavioural and metabolic risk factors could avert more than three-quarters of the global stroke burden. Air pollution has emerged as a significant contributor to global stroke burden, especially in low-income and middle-income countries, and therefore reducing exposure to air pollution should be one of the main priorities to reduce stroke burden in these countries.

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Introduction

A comparative assessment of the burden of stroke (in disability-adjusted life-years [DALYs]) attributable to potentially modifiable risk factors between regions and countries is crucial for education campaigns, evidence-based planning, priority setting, and resource allocation in stroke prevention. Understanding of the contribution of each risk factor to changes in stroke burden is important to establish country-specific and region-specific policies for both short-term and long-term population welfare. Documenting how much of the worldwide burden of stroke can be explained by lifestyle, environmental and occupational exposures, and metabolic risk factors allows quantification of the magnitude of stroke burden associated with various risks and prioritisation of preventive strategies at the global, regional, and national levels.

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Research in context

Evidence before this study
Disability-adjusted life-years (DALYs) are the most comprehensive measure of population health, and combine the disability and mortality associated with a disease into one metric. We searched Scopus, MEDLINE, and PubMed for reports published in any language up to Dec 31, 2015, using the search terms "stroke" AND "DALY(s)" AND "population-attributable fraction" (PAF) AND "risk factors". A report from the INTERSTROKE study was based on findings from case-control studies in 22 countries and showed that more than 90% of strokes can be attributed to ten key stroke risk factors. The most recent Global Burden of Disease Study 2013 report provided a global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks factors or clusters of risk factors in 188 countries from 1990 to 2013, but did not analyse in detail the stroke burden attributable to risk factors.

Added value of this study
To our knowledge this study is the first to quantify stroke burden in terms of DALYs and report changes in burden attributable to 17 potentially modifiable behavioural, environmental and occupational, and metabolic risks or clusters of risks at the global, regional, and country levels from 1990 to 2013. The study showed that 90·5% (95% UI 88·5–92·2) of the global burden of stroke was attributable to the modifiable risk factors analysed, including 74·2% (95% UI 70·7–76·7%) to behavioural factors (ie, smoking, poor diet, and low physical activity). Clusters of metabolic factors (high systolic blood pressure, high body-mass index, high fasting plasma glucose, high total cholesterol, and low glomerular filtration rate) and environmental factors (air pollution and

lead exposure) were the second and third largest contributors to DALYs. For the first time, air pollution emerged as one of the leading contributors to stroke burden worldwide, accounting for 29·2% of the stroke-related DALYs. Globally, the PAF of all risk factors to the burden of stroke increased with time (except for second-hand smoking and household air pollution from solid fuels) and varied significantly between countries and regions.

Implications of all the available evidence
These findings are important for education campaigns, evidence-based planning, priority setting (including for stroke research), and resource allocation in stroke prevention. Understanding the contribution of each risk factor and risk cluster to the changes in stroke burden is important to establish country-specific and region-specific policies on stroke prevention strategies. Although the proportion of the stroke burden of risk clusters provides a broad view of investment priorities, stroke burden due to individual risks in different age groups of the population can inform the potential elements of a more specific intervention. For example, reducing exposure to air pollution should be one of the main priorities to reduce stroke burden in low-income and middle-income countries, whereas reduction of behavioural risks should be one of the main priorities in high-income countries. For future research, the next step is to close the knowledge gap on stroke burden. This would include identification of previous health conditions grouped by age, sex, and stroke subtype, in addition to the regular monitoring of stroke incidence, mortality, prevalence, associated disability, and modifiable risk factors.

Previously, we reported on 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks for diseases, including all cardiovascular disease, in 188 countries from 1990 to 2013.[1] In this Article, we report estimates from the Global Burden of Disease Study 2013 (GBD 2013) for population-attributable fraction (PAF) of stroke-related DALYs associated with potentially modifiable environmental and occupational, behavioural, and physiological, and metabolic risk factors by age groups globally, in high-income countries, and in low-income and middle-income countries as defined by the World Bank, from 1990 to 2013. We also report PAF of stroke-related DALYs associated with behavioural, environmental, and metabolic risk clusters by sex, globally, and regions in 2013.

Methods
Overview
Details about the basic approach for the GBD 2013 estimates of the PAF and burden of stroke have been reported previously.[1–5] Briefly, we used published and unpublished data on the distribution of risks to estimate

the fraction of the population in each country, age group, and year exposed to different levels of risk factors, when evidence of a causal and biologically plausible association between exposure to the risk factor and the incidence of stroke was convincing.[1] GBD 2013 provides the rates of stroke-related mortality, years of life lost, years lost because of disabilities, and DALYs.[3,6,7] Citations for all sources used to estimate risk factor exposure have been reported in GBD 2013[1] and Roth and colleagues[4] provide citations for all sources used to estimate stroke-related DALYs by country. We defined convincing evidence as evidence from epidemiological studies (prospective observational studies and randomised controlled trials of sufficient size, duration, and quality) showing consistent associations between exposure and disease, with little or no evidence to the contrary. For some risks, such as diet and alcohol consumption, we also used administrative record systems. Of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks analysed in GBD 2013,[1] we selected only those for which stroke was included as a relevant outcome, and for which sufficient data were available to estimate risk factor

	Low-income and middle-income countries		High-income countries		Globally	
	Absolute number	Percentage	Absolute number	Percentage	Absolute number	Percentage
Air pollution and environmental risks						
Ambient PM$_{2.5}$ pollution	16845647 (15165719–18842841)	18.4% (18.3–18.6)	2201971 (1993278–2512352)	10.2% (10.1–10.3)	19047618 (17231500–21183987)	16.9% (16.6–17)
Household air pollution from solid fuels	17706560 (15040046–20421169)	19.4% (18.1–20.2)	0 (0–0)	0.0% (0.0–0.0)	17706560 (15040046–20421169)	15.7% (14.5–16.4)
Lead exposure	7161356 (4815973–9905687)	7.8% (5.8–9.8)	293490 (117643–600411)	1.4% (0.6–2.5)	7454846 (4944736–10520544)	6.6% (4.8–8.4)
Dietary risks						
Diet high in sodium	21643231 (11219006–34875317)	23.7% (13.5–34.5)	3827692 (1820117–6508581)	17.8% (9.2–26.6)	25470923 (13008440–41129128)	22.6% (12.5–33.0)
Diet high in sugar-sweetened beverages	242624 (147971–383221)	0.3% (0.2–0.4)	73910 (46030–115022)	0.3% (0.2–0.5)	316534 (196822–490524)	0.3% (0.2–0.4)
Diet low in fruits	34951359 (24447242–45459644)	38.3% (29.4–44.9)	5219622 (3170539–7724321)	24.3% (16.0–29.7)	40170981 (27585572–52362128)	35.6% (26.5–42.0)
Diet low in vegetables	18073861 (13978042–22430200)	19.8% (16.8–22.2)	4494067 (3566041–5521460)	20.9% (18.2–25)	22567928 (17703088–27912462)	20.0% (17.0–22.4)
Diet low in whole grains	13957466 (10740089–17459358)	15.3% (12.9–17.3)	2918948 (2225147–3688528)	13.6% (11.2–15.1)	16876414 (12970479–20998690)	15.0% (12.5–16.9)
Alcohol use	5815055 (3992097–7381357)	6.4% (4.8–7.3)	2068718 (1599907–2623908)	9.6% (8.1–10.7)	7883773 (5815779–9903657)	7.0% (5.6–8)
Physical activity						
Low physical activity	6277859 (4180135–8349895)	6.9% (5.0–8.3)	2409664 (1640598–3218649)	11.2% (8.3–13.1)	8687523 (5866934–11410108)	7.7% (5.6–9.2)
Tobacco smoke						
Smoking	19423256 (15644478–23748368)	21.3% (18.8–23.5)	3895801 (3207200–4662106)	18.1% (16.2–19)	23319057 (18960560–28287027)	20.7% (18.2–22.7)
Second-hand smoke	2114634 (1845065–2387721)	2.3% (2.2–2.4)	314793 (277170–377361)	1.5% (1.4–1.5)	2429427 (2148939–2733194)	2.2% (2.1–2.2)
Physiological factors						
High BMI	20438045 (16251072–25174726)	22.4% (19.6–24.9)	6111329 (5103348–7285359)	28.4% (25.7–29.7)	26549374 (21499328–32496509)	23.5% (20.7–26.1)
High fasting plasma glucose	10809793 (6488512–16180876)	11.8% (7.8–16.0)	2364821 (1382839–3672705)	11.0% (7.0–15.0)	13174613 (7945290–19594944)	11.7% (7.6–15.7)
High systolic blood pressure	59462084 (51726959–67616909)	65.1% (62.3–66.8)	12863716 (11255918–14974628)	59.8% (56.8–61.1)	72325800 (63779849–81982863)	64.1% (61.3–65.8)
High total cholesterol	3592032 (2191684–5441959)	3.9% (2.6–5.4)	1495834 (791489–2769532)	7.0% (4.0–11.3)	5087866 (3074041–8207961)	4.5% (3.0–6.6)
Low glomerular filtration rate	5972287 (4789340–7473775)	6.5% (5.8–7.4)	2052968 (1653848–2519276)	9.5% (8.3–10.3)	8025255 (6641680–9764377)	7.1% (6.4–7.8)
Clusters of risk factors						
Air pollution*	30808521 (27287721–34553668)	33.7% (32.9–34.2)	2201971 (1993278–2512352)	10.2% (10.1–10.3)	33010493 (29350620–36871584)	29.2% (28.2–29.6)
Tobacco smoke†	21537890 (17804893–25921930)	23.6% (21.4–25.6)	4210594 (3515647–4982921)	19.6% (17.7–20.3)	25748484 (21409286–30719271)	22.8% (20.6–24.7)
Dietary risks‡	59687607 (49121641–70396442)	65.3% (59.1–69.6)	11848596 (9276670–14660670)	55.1% (46.8–59.8)	71536203 (58718147–84445531)	63.4% (56.5–67.8)
Behavioural risks§	68849080 (60222263–78508484)	75.4% (72.5–77.6)	14954070 (12872682–17458060)	69.5% (64.9–71.2)	83803150 (73513301–95498883)	74.2% (70.7–76.7)
Environmental and occupational risks¶	35290595 (31372970–39895305)	38.6% (37.8–39.4)	2464471 (2166341–2892607)	11.5% (10.9–11.8)	37755065 (33656530–42692315)	33.4% (32.4–34.3)
Metabolic risks||	66517266 (58670110–74652066)	72.8% (70.6–73.8)	15201684 (13558787–17507409)	70.7% (68.4–71.4)	81718951 (72980744–91563393)	72.4% (70.2–73.5)
Combined risk factors						
All factors	83247931 (81328933–84801405)	91.1% (89.0–92.8)**	18979120 (17332900–21589790)	89.3% (86.6–91.5)**	102227051 (93307813–112079497)**	90.5% (88.5–92.2)**

Data are absolute numbers of DALYs (95% UI) or percentages of DALYs (95% UI). Percentages and number of DALYs in the columns exceeds the totals for all risk factors combined because of overlap between various risk factors. The sum of percentages and number of DALYs are not mutually exclusive. Ambient PM$_{2.5}$ pollution was defined as an annual average daily exposure to outdoor air concentrations of PM$_{2.5}$ more than 8·8 μg/m³. Household air pollution was defined as any exposure to indoor concentration of PM$_{2.5}$. Lead exposure was defined as blood lead concentration of more than 20 μg/L. Diet high in sodium was defined as consumption of sodium more than 5 g/day. Diet high in sugar-sweetened beverages was defined as consumption of sugar-sweetened beverages more than 64·3 g/day. Diet low in fruits was defined as consumption of less than 200 g/day. Diet low in vegetables was defined as consumption of less than 350 g/day. Diet low in whole grains was defined as consumption of less than 100 g/day. Alcohol use was defined as any amount. Low physical activity was defined as average weekly work, home, transport-related, and recreational physical activity of less than 8000 metabolic equivalent of task-min. Smoking was defined as any previous or current tobacco smoking. Second-hand smoking was defined as daily indoor exposure to second-hand smoking. High body-mass index was defined as body-mass index greater than 23·0 kg/m². High fasting plasma glucose was defined as serum fasting plasma glucose greater than 5·4 mmol/L. High systolic blood pressure was defined as systolic blood pressure greater than 119 mm Hg. High total cholesterol was defined as total cholesterol more than 4·8 mmol/L. Low glomerular filtration rate was defined as glomerular filtration rate less than 60 mL/min per 1·73m² (excluding end-stage renal disease). DALY=disability-adjusted life-year. PM$_{2.5}$=particulate matter with aerodynamic diameter smaller than 2·5 μm. 95% UI=95% uncertainty interval. *Air pollution cluster includes ambient PM$_{2.5}$ pollution and household air pollution. †Tobacco smoke includes smoking and second-hand smoking. ‡Dietary risks cluster includes diet high in sodium, diet high in sugar-sweetened beverages, diet low in fruits, diet low in vegetables, and diet low in whole grains. §Behavioural risks cluster includes smoking (including second-hand smoking), dietary risks (diet high in sodium, diet high in sugar-sweetened beverages, diet low in fruits, diet low in vegetables, diet low in whole grains, and alcohol use), and low physical activity. ¶Environmental risks cluster includes air pollution cluster and lead exposure. \|\|Metabolic risks cluster includes high fasting plasma glucose, high total cholesterol, high systolic blood pressure, high body-mass index, and low glomerular filtration rate. **Age-standardised total percentage of DALYs due to all risk factors combined.

Table: DALYs due to stroke for selected risk factors and risk factor clusters by country income level for both sexes combined in 2013

exposure. We defined sufficient data as estimates for which the effect sizes increase per unit of exposure, and for which there was evidence that these effects could be applied to a general population. We assessed risk–outcome pairs (17 risks and stroke-related DALYs) that met explicit evidence criteria for 188 countries.

Stroke burden and risk factors

To estimate stroke burden associated with various risks, we included any exposure to risks that exceeded a theoretical minimum risk exposure level (TMREL). TMREL was defined as the level of exposure at which risk from all causes of DALYs combined is at a minimum, and was based on a consultation with risk factor epidemiologists. As explained in detail in GBD 2013,[1] the TMREL should minimise individual (and population level) risk and should, in theory, be possible to achieve, but not necessarily affordable or feasible. For causes such as systolic blood pressure (SBP) of less than 120 mm Hg, the evidence for the selection of the TMREL is convincing.[8] For other causes, such as sodium consumption or body-mass index (BMI), the evidence for the selection of the TMREL is not so certain and, for these causes, we used a uniform distribution of different TMRELs in the uncertainty estimation sampling, as explained in detail previously.[1] Based on the selected TMRELs, we established 17 risks: ambient particulate matter pollution, household air pollution from solid fuels, lead exposure, diet high in sodium, diet high in sugar-sweetened beverages, diet low in fruits, diet low in vegetables, diet low in whole grains, alcohol consumption (any dosage), low physical activity, smoking, second-hand smoking, high BMI, high fasting plasma glucose, high SBP, high total cholesterol, and low glomerular filtration rate (GFR). The criteria used to define these risks are reported in the table. We also assessed clusters of risk factors: behavioural (ie, smoking [including second-hand smoking], dietary [diet high in sodium, diet high in sugar-sweetened beverages, diet low in fruits, diet low in vegetables, diet low in whole grains, and alcohol use], low physical activity), environmental and occupational (ie, ambient particulate matter pollution, household air pollution, and lead exposure), and metabolic (high BMI, high fasting plasma glucose, high SBP, high total cholesterol, high GFR). Tobacco smoke (smoking and second-hand smoking) was considered as a separate cluster but was also included in the behavioural cluster. The PAFs of risk factor clusters took into account interactions between risk factors included in the cluster, as explained elsewhere.[2]

Statistical analysis

For most risks, we synthesised data for exposure with a Bayesian meta-regression method, DisMod-MR 2.0[9] or spatial-temporal Gaussian process regression.[10] Relative risks were based on meta-regressions of published

cohort and intervention studies. Attributable burden for clusters of risks and all risks combined took into account evidence on the mediation of some risks, such as high BMI, through other risks, such as high SBP and high total cholesterol. Justifications for thresholds of the risks have been discussed in the GBD 2013 report.[1] The relative risks were summarised by age and sex for each risk factor and outcome pair.[1] As explained previously,[1] we used relative risks from studies controlled for confounding but not for factors along the causal pathway between exposure and outcome. We used estimates of the size of the association between exposure to a risk factor and stroke (rate ratios)[11] and estimates of stroke-related DALYs from GBD 2013[1,3] to calculate the burden (as measured in DALYs) attributable to each risk factor exposure in view of the TMREL (PAF analysis). This approach brings together data for excess stroke mortality and disability associated with risk factors, data for exposure to risks, and evidence-based assumptions on the desired counter-factual distribution of risk exposure to estimate how much of the stroke burden in a particular year can be attributed to risk exposure in that year and in all previous years. PAF is the estimated proportion of disease burden in a population that would be avoided if exposure to a risk factor were reduced to an alternative theoretical exposure scenario (eg, no tobacco use). The attributable stroke burden was calculated using the equation:[1]

$$AB_{jasct} = \sum^{W} DALY_{oasct} PAF_{joasct}$$

Where AB_{jasct} is the attributable burden for risk factor j in age group a, sex s, country c, and year t. $DALY_{oasct}$ is DALYs for cause o (of w relevant outcomes for risk factors j) in age group a, sex s, country c, and year t. PAF_{joasct} is the PAF for cause o due to risk factor j in age group a, sex s, country c, and year t. Risk factors were assessed individually and then aggregated in multiple hierarchical levels including environmental, behavioural, physiological, and metabolic categories of individual risk factors. We assumed the risks to be independent, but mediators between risks were included if data were available.[1] PAFs of risk factor clusters took into account interactions between risk factors included in the cluster, as explained elsewhere.[2] Reported estimates for risk factors and risk factor clusters are not mutually exclusive or adjusted for other risk factors or risk factor clusters analysed. We stratified countries into two groups (high-income countries and low-income and middle-income countries based on the gross domestic product).[12] Countries included in various GBD regions are listed in the appendix (pp 1–2).

To estimate the proportion (%) of DALYs associated with the analysed individual risk factors and risk factor clusters, we used stroke-related DALYs from GBD 2013[1,3,7] at global,

regional, and country-specific levels. We used the same methods as used for GBD 2013[1] to calculate uncertainty intervals (UI) based on a Bayesian approach for all PAFs. UIs should be interpreted as given current data and prior assumptions (priors), and the statistics might vary by this interval. Contrary to the frequentist approach commonly used to estimate 95% CIs, our approach does not assume a single true value for 95% CI, but instead has a posterior distribution. For practical purposes, the implications of both UIs and CIs are similar. The inclusion criteria for each risk–outcome (stroke) pair, data sources, and methods of a systematic search to identify relevant scientific literature to estimate risk factor exposure distributions in 1990 and 2013 have been described in detail elsewhere.[14]

Role of the funding source

The funder 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

Globally, 90·5% of the burden of stroke (as measured in DALYs) was attributable to the modifiable risk factors analysed (table). Although, in most countries worldwide, stroke burden from all these risk factors combined varied between 80% and 97%; in most African countries, it varied between 72% and 79% (figure 1). Of the total
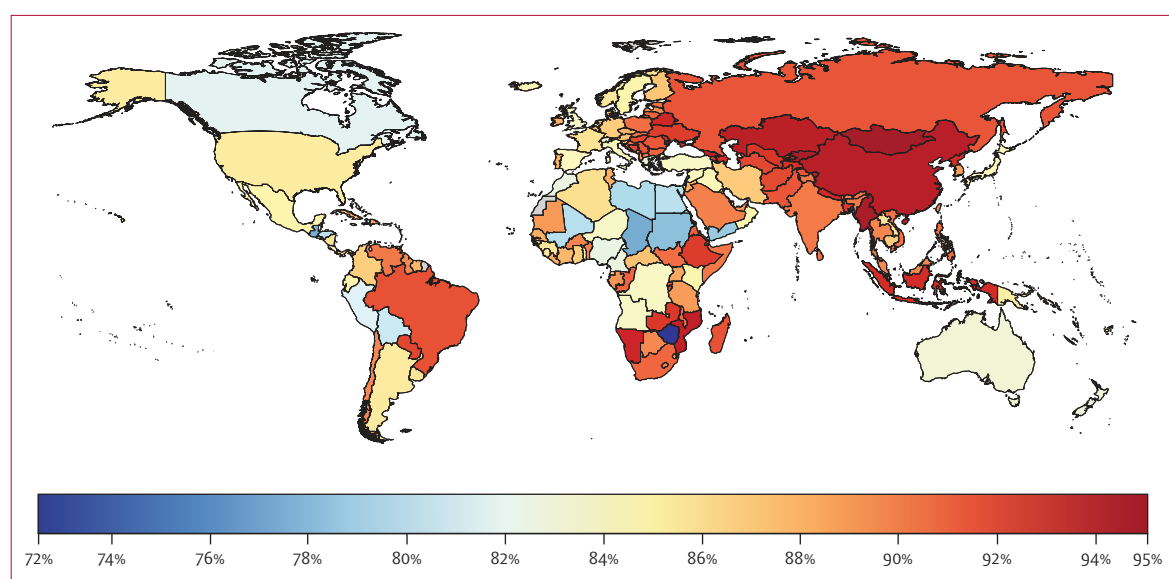
Figure 1: **Stroke-related DALYs attributable to all modifiable risk factors combined for both sexes in 2013**
DALY=disability-adjusted life-year.

| Rank ▪ 1–5 ▫ 11–15 ▪ 6–10 ▫ >15 Risk factor	Global	High-income Asia Pacific	Western Europe	Australasia	High-income North America	Central Europe	Southern Latin America	Eastern Europe	East Asia	Tropical Latin America	Central Latin America	Southeast Asia	Central Asia	Andean Latin America	North Africa and Middle East	Caribbean	South Asia	Oceania	Southern sub-Saharan Africa	Eastern sub-Saharan Africa	Central sub-Saharan Africa	Western sub-Saharan Africa
High systolic blood pressure	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Diet low in fruits	2	2	4	4	3	4	4	3	2	3	4	2	2	3	3	3	2	3	2	2	2	2
High body-mass index	3	6	2	2	2	2	2	6	2	2	2	6	3	2	2	2	8	2	3	5	5	4
Diet high in sodium	4	3	6	10	6	3	8	6	3	4	8	8	4	7	4	12	5	13	7	9	11	8
Smoking	5	4	5	5	5	6	5	5	4	6	6	4	6	6	8	5	7	5	5	8	10	12
Diet low in vegetables	6	5	3	3	4	5	3	4	11	5	3	3	5	4	5	4	4	4	4	4	4	5
Ambient particulate matter (2·5 μm) pollution	7	8	11	14	12	8	12	10	5	9	9	9	8	9	6	11	6	15	11	12	6	6
Household air pollution from solid fuels	8	..	..	..	..	..	15	..	7	14	12	5	12	11	14	7	3	6	8	3	3	3
Diet low in whole grains	9	7	9	8	9	7	6	7	8	7	5	7	7	5	7	6	10	7	10	10	7	9
High fasting plasma glucose	10	10	10	9	7	11	7	9	9	8	7	10	9	10	9	10	9	8	9	11	8	11
Low physical activity	11	9	8	6	8	10	11	11	13	11	13	11	13	12	10	8	12	9	13	14	12	10
Low glomerular filtration rate	12	12	7	7	13	9	10	12	14	10	10	14	10	8	11	9	11	12	6	7	9	7
Alcohol use	13	11	12	11	10	12	9	8	12	12	11	15	11	14	16	15	15	11	12	13	14	14
Lead exposure	14	14	14	13	15	14	16	15	10	15	16	12	14	15	13	13	13	14	14	6	13	13
High total cholesterol	15	13	13	12	11	13	13	13	16	13	14	13	15	13	12	14	14	10	15	15	15	15
Second-hand smoke	16	15	15	15	16	15	14	14	15	16	17	16	16	17	15	17	16	16	16	16	16	16
Diet high in sugar-sweetened beverages	17	16	16	16	14	16	17	16	17	17	15	17	17	16	17	16	17	17	17	17	17	17

Figure 2: **Top risk factors ranked by number of DALYs attributable to stroke for both sexes combined in 21 regions in 2013**
For the list of countries included within these regions, please see the appendix (pp 1–2). DALY=disability-adjusted life-year.

stroke-related DALYs, 74·2% (83·8 million DALYs) were due to behavioural factors (ie, smoking, poor diet, and low physical activity) and 72·4% (81·7 million DALYs) were attributable to metabolic risks (ie, high fasting plasma glucose, high total cholesterol, high SBP, high BMI, and low GFR; table). The five leading risk factors for DALYs were high SBP (72·3 million DALYs [64·1%]), diet low in fruits (40·2 million DALYs [35·6%]), high BMI (26·5 million DALYs [23·5%]), diet high in sodium (25·5 million DALYs [22·6%]), and smoking (23·3 million DALYs [20·7%]; figure 2, 3, table). Clusters of metabolic and behavioural risk factors were the leading causes of stroke-related DALYs in low-income and middle-income countries (15·2 million DALYs [70·7%] and 15·0 million DALYs [69·5%]; table).

We noticed geographical variations in the highest and lowest PAFs of risk factors associated with stroke-related DALYs (appendix p 3). For example, stroke burden associated with household air pollution from solid fuels was highest in central, eastern, and western sub-Saharan Africa and south Asia, and lowest in high-income North America, central, eastern, and western Europe, Australasia, and high-income Asia Pacific. Almost half the stroke-related DALYs due to the risk factors and risk factor clusters occurred in people aged 50–69 years (appendix p 7). Although most risk factors accounted for more DALYs in people aged 15–49 years than in people aged 70 years or older, the PAFs of low physical activity, low GFR, and lead exposure were greater in the older age group (appendix pp 4–9). Globally, household air pollution from solid fuels, diet low in vegetables, high BMI, air pollution, and environmental risk clusters accounted for significantly more DALYs in people aged 15–49 years than in the other age groups, but high SBP and metabolic risk clusters were most prominent in people aged 50–69 years globally and in low-income and middle-income countries (appendix pp 4–6).
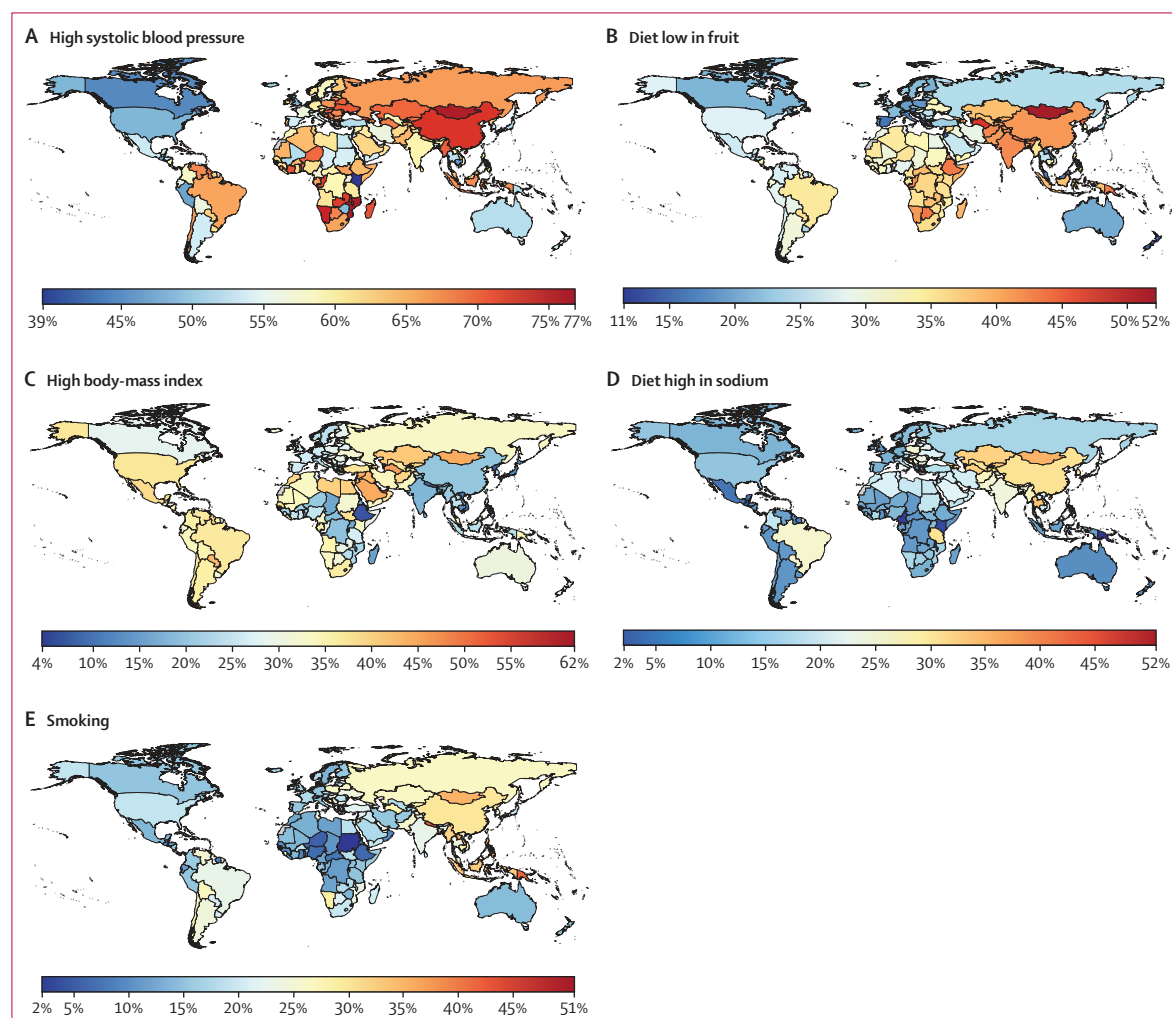
***Figure 3*: Global distribution of leading risk factors for stroke-related DALYs in 2013**
Maps show the five leading risk factors for stroke-related DALYs (as established by PAF) for both sexes combined in 2013: high systolic blood pressure (A), diet low in fruit (B), high body-mass index (C), diet high in sodium (D), and smoking (E). DALY=disability-adjusted life-year. PAF=population-attributable fraction.

Globally, during 1990–2013, we noticed increases in the stroke-related burden of almost all individual risk factors (appendix p 10). The only risk factors with a decrease in stroke-related DALYs were second-hand smoke (–31·0%, 95% UI –31·3 to –30·7) and household air pollution from solid fuels (–1·9%, –4·2 to –0·4%). Globally, there was a significant increase in the stroke-related DALYs associated with high BMI (>46% increase), low physical activity (>39% increase), high fasting plasma glucose (~44% increase), high SBP (>39% increase), diet high in sugar-sweetened beverages (>63% increase), high total cholesterol (~24% increase), ambient particulate matter pollution of aerodynamic diameter less than 2·5 µm ($PM_{2.5}$) (>33% increase), alcohol use (>32% increase), low GFR (~25% increase), diet high in sodium (>34% increase), diet low in vegetables (23% increase), and smoking (>10% increase). The only risk factors that were significantly reduced globally were household air pollution from solid fuels (~2% reduction) and second-hand smoke (31% reduction). Changes in other risk factors were not significant on the global scale. In high-income countries, there were significant reductions in stroke-related DALYs due to ambient air pollution, household air pollution from solid fuels, lead exposure, diet high in sodium, diet low in fruits, vegetables, and whole grains, smoking, second-hand smoking, alcohol use, low physical activity, high BMI, high fasting plasma glucose, high SBP, high total cholesterol, and low GFR. However, there was a large (almost 84%) and significant increase in diet high in sugar-sweetened beverages. In low-income and middle-income countries, there were significant increases in stroke-related DALYs due to ambient air pollution, all dietary risks and alcohol use, low physical activity, smoking, high BMI, high fasting plasma glucose, high SBP, high total cholesterol, and low GFR.

Globally, in 2013, the proportions of stroke burden due to behavioural, environmental, and metabolic risk clusters were non-significantly higher in males than in females (figure 4; appendix pp 11–12). However, in 2013, differences between the sexes were significant for the PAF of stroke-related age-standardised DALYs attributable to the behavioural risk cluster in low-income and middle-income countries (1376 per 100 000 person-years and 79·2% in males vs 972 per 100 000 person-years and 70·3% in females), but difference in high-income countries was not significant (1263 per 100 000 person-years and 73·2% in males vs 1014 per 100 000 person-years and 68·1% in females; appendix pp 11–12).

In high-income countries in 2013, the five leading risk factors for DALYs were high SBP, high BMI, diet low in fruits, diet low in vegetables, and smoking (table). Also, in these countries, metabolic and behavioural risk factor clusters were the first and second leading causes of stroke-related DALYs, accounting for 15·2 million DALYs (70·7%) and 15·0 million DALYs (69·5%) (table). Globally, household air pollution from solid fuels, diet low in vegetables, high BMI, and air pollution and

environmental risk clusters accounted for significantly more DALYs in people aged 15–49 years than in other age groups, and high SBP and the metabolic risk cluster were most prominent in people aged 50–69 years in high-income countries (appendix pp 4–5).

The five individual risk factors that contributed most to the stroke-related DALYs in low-income and middle-income countries were high SBP, diet low in fruits, diet high in sodium, high BMI, and smoking (table). The clusters of risk factors that contributed most to DALYs in low-income and middle-income countries were behavioural (68·8 million DALYs [75·4%]; behavioural risks included dietary risks), metabolic (66·5 million DALYs [72·8%]), and environmental risks (35·3 million DALYs [38·6%]), of which ambient $PM_{2.5}$ pollution accounted for 16·9 million DALYs (18·4%) and household air pollution from solid fuels for 17·7 million DALYs (19·4%) (table).

Generally, most risk factors (except low physical activity, high total cholesterol, and low GFR) had the greatest effect on DALYs in low-income and middle-income countries (appendix pp 25–36), and large variations existed between countries in PAFs of the risk factors (figures 2, 3; appendix pp 13–24).
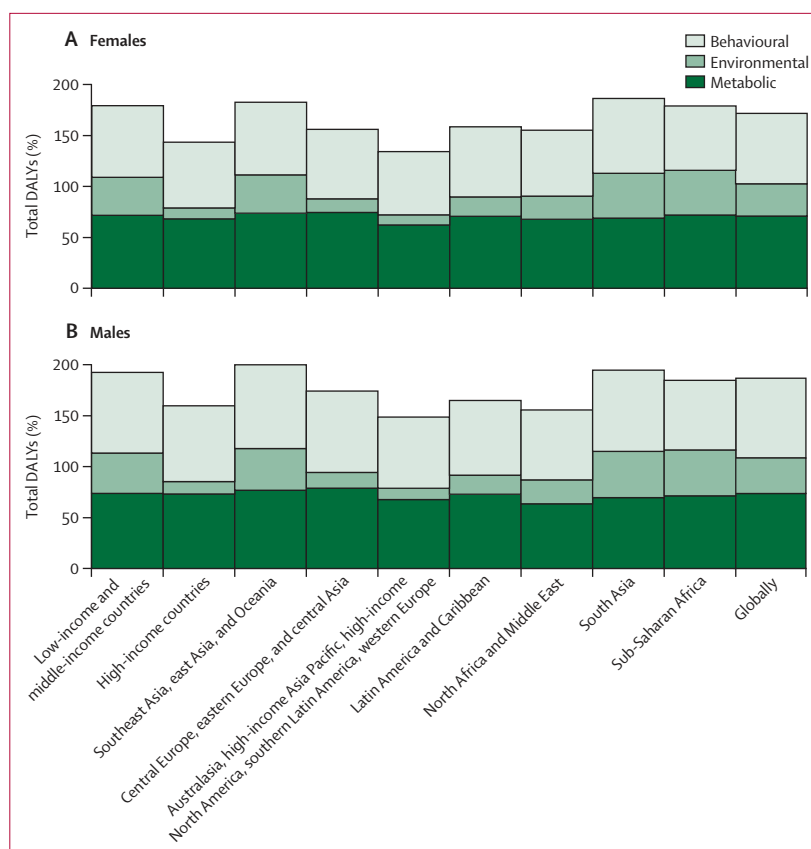
Figure 4: **Stroke-related, age-standardised DALYs attributable to behavioural, environmental, and metabolic risk clusters by sex in 2013**
DALY=disability-adjusted life-year.

Discussion

Our results show the global, regional, and country-specific burden of stroke (as measured with DALYs) associated with potentially modifiable risk factors and risk factor clusters from 1990 to 2013. For the first time, air pollution has emerged as one of the leading contributors to stroke burden worldwide, accounting for almost a third of stroke-related DALYs. Our findings suggest that more than 90% of the global burden of stroke in 2013 was attributable to the combined effect of all modifiable risk factors analysed, and that most of the burden of stroke is attributable to behavioural factors and metabolic factors. However, the PAF of stroke risk factors and risk factor clusters differed between countries and regions. For example, the extent of stroke burden attributable to air pollution and environmental risks, tobacco smoke, dietary risks, and high SBP in low-income and middle-income countries was significantly greater (except for dietary risks) than in high-income countries, whereas the contribution of low physical activity and low GFR was significantly greater in high-income countries. Because many of the behavioural risk factors we analysed mediate their effects through metabolic risk factors,[13] efforts to reduce exposure to behavioural risk factors will enhance the control of metabolic risk factors. Other studies[14–16] have also reported an increasing role of some environmental and behavioural risk factors for stroke and geographical variations in mediating the effects of cardiovascular risk factors. Our results showing the key contributions of high SBP, diet low in fruits, high BMI, and smoking to stroke burden are in line with those of other studies.[17–20] Furthermore, for the first time, our analyses showed diverging trends in the proportions of DALYs attributable to most modifiable risk factors from 1990 to 2013, with significant increases in low-income and middle-income countries and significant decreases in high-income countries. If these trends continue, the large disparities that exist in stroke burden between high-income and low-income and middle-income countries[3] will be further increased. Our finding that, globally and in low-income and middle-income countries, diet high in sodium is one of the five leading risk factors for DALYs, with a contribution similar to that of tobacco smoking, represents a new way of looking at the ranking of risk factors in global stroke burden and can be explained by its causal role in elevated blood pressure.[21] Our findings of the large effect of poor diet (especially diet low in fruits) on stroke burden are consistent with previous studies.[22] Although a diet low in vegetables was ranked in the five most common risk factors for DALYs in every region except east Asia, it ranked sixth globally, showing that east Asia (especially China) has a large effect on the overall ranking of risk factors (figure 2). Changes in the PAF of smoking (decreases in tobacco smoking and second-hand smoking in high-income countries, decreases in second-hand smoking in low-income and middle-income countries, and increases in tobacco smoking in low-income and middle-income countries) during 1990–2013 could reflect corresponding changes in smoking prevalence and tobacco banning policies in high-income and low-income and middle-income countries.[23–26] The paradox in low-income and middle-income countries of decreased second-hand smoking and increased tobacco smoking warrants further investigation. Although the contribution of high total cholesterol to DALYs was low (4·5% globally), it was consistent with the range of effects (0–15%) in other studies.[27]

Our data show that, globally, differences between sexes in the proportion of stroke burden due to behavioural, environmental, and metabolic risks were not significant. In low-income and middle-income countries (especially in east Asia) the PAF of the behavioural risk cluster was greater in males than in females. These findings suggest that although preventive interventions to reduce exposure to behavioural, environmental, and metabolic risks will have about the same effect on reducing stroke burden in both males and females in low-income and middle-income countries (especially in east Asia), preventive interventions to reduce exposure to behavioural risks are likely to produce greater reductions in stroke burden in males than in females. Sex differences in stroke burden were also shown in another GBD 2013.[28]

Our results are consistent with those of the INTERSTROKE study,[18] in which roughly 86% of strokes could be attributed to nine potentially modifiable metabolic and behavioural risk factors, emphasising their importance for defining global and regional priorities in reducing stroke burden. Although the noticeable global epidemiological transition happening in low-income and middle-income countries[1] (especially increasing exposure to western lifestyle) might largely be accountable for the greater contribution of behavioural risk factors to stroke burden in these countries, a striking finding of our study was an unexpectedly high proportion of stroke burden attributable to air pollution (29·2% globally), especially in low-income and middle-income countries (33·7% vs 10·2% in high-income countries). In 2013, air pollution contributed to about 33 million stroke-related DALYs, including almost 31 million DALYs in low-income and middle-income countries (table). For example, in south Asia and eastern and central sub-Saharan Africa, based on PAFs, air pollution was the third highest contributor to stroke-related DALYs, accounting for almost 40% of the DALYs (data not shown). In China and India, almost 22% of stroke-related DALYs in 2013 were attributed to ambient $PM_{2.5}$ air pollution. Although household air pollution from solid fuels did not contribute to stroke burden in high-income countries, almost a fifth of stroke burden in low-income and middle-income countries was attributed to household air pollution in 2013 (especially in Asia and sub-Saharan Africa; appendix p 27). These findings are in line with reports[29,30] concluding that ambient and

household air pollution is now the world's largest combined environmental health risk, although these reports were based on observational studies. Possible mechanisms of the association between stroke and air pollution include adverse effects of air pollution on the vascular endothelium, increases in blood pressure, and increased risk of thrombosis.[29] Additionally, evidence suggests that not all $PM_{2.5}$ pollution has the same cardiovascular implications, with fossil fuel emissions regarded as more damaging (especially coal burning) than other types.[31] Consequently, we might be underestimating the effect of $PM_{2.5}$ pollution on stroke in countries with greater contributions of such fossil fuel burning to the total $PM_{2.5}$.[31] The contribution of lead exposure to stroke burden might be due to an interaction with hypertension[32] and other cardiovascular risk factors.[32]

The proportion of DALYs attributable to the analysed risk factors and risk factor clusters varied substantially by age group, country economic status, and geographical region. The lower percentage of DALYs attributable to all risk factors combined in African countries compared with other countries might be related to infectious and rheumatic diseases having a greater role as causes of stroke in Africa than in other countries (these risk factors were not analysed in the present manuscript).[33] For example, in sub-Saharan Africa low GFR might be a consequence of fairly high prevalence of HIV infection.[34] Globally and in high-income countries, the PAF of all risk factors combined to DALYs was largest in people aged 50–69 years, followed by people aged 15–49 years. In low-income and middle-income countries, the proportion of PAF of all risk factors combined was also largest for people aged 50–69 years, but was almost the same in people aged 15–49 years and older than 70 years. The high number of DALYs attributable to modifiable risk factors in people aged 15–49 years and 50–69 years in high-income countries shows an opportunity to halt the burden of stroke in high-income countries. The risk factor that was most increased from 1990 to 2013 was diet high in sugar-sweetened beverages (63·1% increase in stroke-related DALYs), with the greatest increase noted in high-income countries. Although the contribution of this risk factor to stroke burden is currently relatively low (about 0·3%), given its association with overweight and type 2 diabetes mellitus, continuing exposure to diet high in sugar-sweetened beverages could, in a couple of decades, result in a huge increase in stroke burden associated with this risk factor. The differences in rankings between low-income and middle-income and high-income countries by age could represent changes in behaviours in more recent birth cohorts (eg, changes in the proportions of diet low in vegetables in each age group) in these countries and might help in prediction of the future burden. For example, in low-income and middle-income countries, high BMI was ranked ninth in people aged 70 years or older, but was third and fourth in the younger age groups (appendix p 9). The large percentage increase in DALYs

due to some behavioural, dietary, and metabolic risk factors could be a reflection of the negative convergence of these risk factors on cardiovascular disease that has been noted in some countries.[35]

Although globally the ten most important risk factors were high SBP, diet low in fruits, high BMI, diet high in sodium, smoking, diet low in vegetables, ambient $PM_{2.5}$ pollution, household air pollution from solid fuels, diet low in whole grains, and high fasting plasma glucose, there was much heterogeneity in the PAF of these risk factors for stroke-related DALYs between countries, which is in line with previous findings about cardiovascular disease risk factors.[16] For example, although globally only 7·0% of stroke-related DALYs were associated with alcohol use, in Belarus and Russia the PAF of alcohol use was more than double this proportion (14·9%, 10·3–19·2 in Belarus and 14·2%, 9·3–19·4 in Russia; appendix pp 20, 23). Alcohol use has previously been reported to have a significant role in cardiovascular disease burden in Russia.[36] The between-country differences (including differences between high-income and low-income and middle-income countries) in the PAFs of various stroke risk factors might represent differences in sociodemographic factors (eg, population development, migration, or life expectancy), epidemiological factors (eg, variations in the prevalence and management of risk factors), and access to health, social, and community services. Such differences emphasise the need for region-specific approaches to interventions for the reduction of stroke burden.

Our GBD study has several limitations, as described and discussed in detail elsewhere.[1] For this study, because of the lack of relevant epidemiological data from most countries, we were unable to include some important stroke risk factors (eg, atrial fibrillation and substance abuse) and predisposition to illnesses in the analyses. Inclusion of these and other risk factors might have resulted in an even greater proportion of stroke burden attributable to risk factors and risk factor clusters, because the missing factors are known to have a role in stroke. Also, because of lack of available epidemiological data, we were not able to model different patterns of some risk factors (eg, different dose or types of alcohol drinking; pack-years of smoking; different levels of BMI; elevated blood pressure; or birthweight; genetic factors; socioeconomic status; and public health and medical care interventions) and percentage change in DALYs due to risk factor clusters. Quantification of these other categories of risks or causes is beyond the scope of this study. Additionally, evidence for the selection of TMRELs was uncertain for some risks and based on observational studies that might have had confounders. However, all of our TMREL estimates were discussed and approved by a team of risk epidemiologists and stroke experts. Notably, some risk factors (eg, BMI and diet) have a role in the pathway of stroke rather than being the cause. We did not analyse risk factors for ischaemic and haemorrhagic strokes separately, although another GBD 2013 analysis of

stroke burden showed great variations in the prevalence of ischaemic and haemorrhagic strokes.[3] Some risk factors are common for both ischaemic stroke and haemorrhagic stroke, but the contribution of some risk factors differs for different types of stroke.[18] Although knowledge of risk factors for specific types and causes of stroke is important for the development and implementation of individualised primary prevention strategies, global and regional health-care policy tends to plan and prioritise stroke prevention based on risk factors for ischaemic and haemorrhagic strokes combined. To address the knowledge gap in GBD, the next step would be to include previous health conditions by age, sex, and stroke subtypes in analyses, in addition to at least some of the broader causes of stroke. Continued regular monitoring of stroke incidence, mortality, prevalence, disability, and modifiable risk factors is important. We also aim to update such crucial evidence for stroke prevention at all levels every 2 years, including geographical regions, type of stroke, and further risk factors.

Our results show that more than 90% of stroke burden is attributable to modifiable risk factors and that control of behavioural and metabolic risk factors could avert about three-quarters of the global stroke burden. Our data for the global, regional, and country-specific burden of stroke associated with potentially modifiable risk factors and risk factor clusters are important for evidence-based planning, priority setting (including for research), and resource allocation for stroke prevention. Furthermore, these strategies might have similar effects in the prevention of stroke in both males and females, and contribute to the mission of sex equality in health by governments, WHO, and the UN. Our findings about the magnitudes and trends in stroke burden attributable to various modifiable risks and risk clusters suggest that preventive programmes aimed at risk factor modification could lead to major reductions in stroke burden. The age-specific and country-specific differences in the magnitude of the contributions of various risk factors could inform priorities for stroke prevention from the global level to the national level. For example, reducing exposure to air pollution should be one of the main priorities to reduce stroke burden in low-income and middle-income countries, whereas reduction of behavioural risks should be the main priority in high-income countries. Also, findings from a systematic review suggest that small increases in fruit and vegetable intake can be achieved effectively in population subgroups.[37] About half of all strokes could be prevented with effective interventions tackling common lifestyle factors.[38] Our results have also shown that the contribution of various risk factors to stroke burden varies with time and between countries and continents, thus necessitating regular monitoring of PAFs and country-specific and region-specific strategies for stroke prevention. In view of the variety of risk factors contributing to stroke burden, preventive strategies should include government policies, health-care providers, non-government organisations, communities, and individuals. Although governments have the power and responsibility to influence environmental, social, medical, and lifestyle factors through legislation and taxation (eg, of tobacco, alcohol, and salt, sugar, or saturated fat content), health service providers have the responsibility to identify risk factors that require medical detection and treatment (eg, elevated blood pressure, atrial fibrillation, dyslipidaemia, or symptomatic carotid artery stenosis) to reduce these risk factors for a substantial proportion of the population. Since many lifestyle habits are set early in life, culturally appropriate education about healthy lifestyles should be incorporated into standardised educational curricula and started early with reinforcement throughout the lifetime.[39] Multidrug regimens of highly effective and cheap drugs could lead to cost-effective prevention of stroke in low-income and middle-income regions, potentially halving the risk of death from cardiovascular disease and increasing life expectancy.[40] Use of far-reaching and affordable technological advances, such as the Stroke Riskometer app—which helps individuals to identify their own risk factors and calculate their future risk of stroke, and provides targeted advice on how to reduce the risk—is another promising approach for stroke prevention worldwide.[39,41,42] Integrated national health-care systems would need to change to bring patients, health professionals, and carers together to understand the context of the illness and select the best prevention, treatment, and rehabilitation. When cost-effective, individual-level, health-care interventions are complemented by population-wide prevention strategies, a sustainable effect on the global burden of stroke can be achieved.[43,44] In particular, streamlining of stroke prevention guidelines to take account of the identified behavioural, environmental and occupational, and metabolic risks will help to set out national and international priorities at all levels that can be easily renewed following our global study with updates every 2 years.

Global Burden of Diseases, Injuries, and Risk Factors Study 2013 and Stroke Experts Writing Group

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