Influence of age on the association of vascular risk factors with acute stroke (INTERSTROKE): a case–control study

*Catriona Reddin, Graeme J Hankey, John Ferguson, Peter Langhorne, Shahram Oveisgharan, Michelle Canavan, Helle K Iversen, Annika Rosengren, Danuta Ryglewicz, Anna Czlonkowska, Xingyu Wang, Fernando Lanas, Albertino Damasceno, Denis Xavier, Patricio Lopez-Jaramillo, Andrew Smyth, Salim Yusuf, Martin O'Donnell, on behalf of the INTERSTROKE investigators**

Summary

Background The absolute burden of stroke is increasing due to an ageing population, as well as an increased incidence of stroke in young adults. We aimed to determine whether age modifies the magnitude of association between vascular risk factors and stroke in the INTERSTROKE study.

Methods INTERSTROKE is an international case–control study of risk factors for first acute stroke. Cases and controls (matched by age and sex) were recruited in 32 countries (between Jan 11, 2007, and Aug 8, 2015). Participants completed a clinical assessment and provided blood and urine samples within 72 h of recruitment. Odds ratios (ORs) for vascular risk factors and their population attributable fractions (PAFs) were calculated among age groups. We tested for an interaction of age by each risk factor.

Findings Among 26 950 participants, the mean age of cases was 62·2 years (SD 13·6) and of controls 61·3 years (13·3). Increasing age was associated with a significant increased prevalence for seven vascular risk factors (hypertension, physical inactivity, diabetes, atrial fibrillation, high waist-to-hip ratio, high apolipoprotein B concentration [p<0·0001 for all], and obesity [p=0·016]), reduced prevalence for four vascular risk factors (smoking, alcohol use, psychosocial stress [p<0·0001 for all], and unhealthy diet [p=0·0081]) and unchanged prevalence for one vascular risk factor (depression). Increasing age was associated with a reduced magnitude of OR of stroke for hypertension ($p_{interaction}$<0·0001), high apolipoprotein B concentration ($p_{interaction}$<0·001), high waist-to-hip ratio ($p_{interaction}$ 0·011), alcohol use ($p_{interaction}$<0·0001), and psychosocial stress ($p_{interaction}$=0·033). No vascular risk factor was associated with a higher odds of stroke with increased age. Hypertension, high waist-to-hip ratio, and physical inactivity accounted for the largest PAF among all age groups.

Interpretation Vascular risk factors exhibit different patterns of association with stroke by age, with consequent variations in their relative PAF. This information could be used to prioritise risk factor screening and modification by age group.

Funding Canadian Institutes of Health Research; Heart and Stroke Foundation of Canada; Canadian Stroke Network; AFA Insurance, Health Research Board Ireland; Swedish Research Council; Swedish Heart and Lung Foundation; The Health & Medical Care Committee of the Regional Executive Board, Region Västra Götaland (Sweden); AstraZeneca; Boehringer Ingelheim (Canada); Pfizer (Canada); MSD; Chest, Heart, and Stroke Scotland; and The UK Stroke Association.

Introduction

The incidence of stroke increases with age.[1] Although the age-adjusted incidence of stroke is reducing in some regions, such as high-income regions, the absolute burden of stroke is increasing globally. This increase is due to an ageing population, as well as an increased incidence of stroke in young adults.[1,2] Among people younger than 70 years, stroke incidence rates from 1990 to 2019 have increased by 15·0% (95% CI 12·0–18·0),[1] highlighting the need to better understand the prevalence of risk factors for stroke, and the strength of the association of modifiable risk factors for stroke, in younger and older age groups.[3,4]

There is some evidence that the strength of association of common modifiable vascular risk factors might change with advancing age, but studies are scarce.[5] An analysis of the REGARDS prospective cohort study reported a lower hazard ratio for hypertension and diabetes with increased age, and other studies have reported a diminishing magnitude of risk for other vascular risk factors, such as diet and lipids.[5–7] A meta-analysis of prospective cohort studies reported an attenuated association of blood pressure control with stroke and vascular mortality with advancing age.[8] The annual absolute differences in risk were greater with older age. Further evaluation of whether age modifies the relationship between cardiovascular risk factors and stroke risk is required. If the magnitude of risk associated with individual risk factors differs by age, established public health interventions might need to be tailored for different age groups.

Lancet Healthy Longev 2025; 6: 100709

Published Online July 2, 2025 https://doi.org/10.1016/j.lanhl.2025.100709

*The INTERSTROKE investigators are listed in the appendix (pp 13–15).

HRB Clinical Research Facility Galway, University of Galway–University Hospital, Galway, Ireland (C Reddin MB BCh BAO, J Ferguson PhD, M Canavan, PhD, A Smyth PhD, M O'Donnell PhD); **Wellcome Trust–HRB, Irish Clinical Academic Training, Dublin, Ireland** (C Reddin); **Centre for Neuromuscular and Neurological Disorders, Medical School, The University of Western Australia, Perth, WA, Australia** (G J Hankey MD); **Perron Institute for Neurological and Translational Science, Perth, WA, Australia** (G J Hankey); **Academic Section of Geriatric Medicine, Glasgow Royal Infirmary, University of Glasgow, Glasgow, UK** (P Langhorne PhD); **Rush Alzheimer Disease Research Center, Rush University Medical Center, Chicago, IL, USA** (S Oveisgharan MD); **Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark** (H K Iversen MD); **Sahlgrenska University Hospital and Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden** (A Rosengren PhD); **Military Institute of Aviation Medicine, Warszawa, Poland** (D Ryglewicz PhD, A Czlonkowska PhD); **Beijing Hypertension League Institute, Beijing, China** (X Wang MD); **Faculty of Medicine, Universidad de La Frontera, Temuco, Chile** (F Lanas MD); **Eduardo Mondlane University, Maputo, Mozambique** (A Damasceno MD); **St John's Medical College and Research Institute, Bangalore, India** (D Xavier MD); **Masira Research Institute, Medical School, Universidad**

de Santander, Bucaramanga, Colombia (P Lopez-Jaramillo PhD); Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada (S Yusuf DPhil, M O'Donnell)

Correspondence to: Dr Catriona Reddin, HRB Clinical Research Facility Galway, University of Galway–University Hospital Galway, Galway H91YR71, Ireland
catriona.reddin@universityofgalway.ie

See Online for appendix

Research in context

Evidence before this study

We searched PubMed from database inception to March 15, 2024, for previous studies published in English using the search terms "stroke" AND "ageing" OR "age" AND "global", OR "international" PLUS "risk factors", "hypertension", "smoking", "diet", "alcohol", "diabetes", "atrial fibrillation", "physical inactivity", "apoB", "stress", "depression", "body mass index", OR "waist-to-hip". We identified meta-analyses of epidemiological studies, including the Global Burden of Disease 2019 report of global, regional, and national burden of stroke and its risk factors in 204 countries from 1990 to 2019. Other than INTERSTROKE, we did not identify an international study, which included regions spanning North America, South America, Europe, Africa, Asia, and Australia, including high-income, middle-income, and low-income countries, and reported the association of multiple risk factors with stroke by age.

Added value of this study

This case–control study explored the importance of vascular risk factors by age and we used a nuanced approach to address this research question by considering prevalence, odds ratios (ORs), and population attributable fractions (PAFs). The INTERSTROKE study involved recruitment of individuals from different regions of the world and individual-level standardised measurements were conducted. Moreover, both cases and controls were recruited from the same communities, permitting paired comparisons. With increasing age, the prevalence of seven risk factors increased (hypertension, physical inactivity, diabetes, atrial fibrillation, higher waist-to-hip ratio, high apolipoprotein B, and obesity) and the prevalence of four risk factors decreased (smoking, alcohol use, psychosocial stress, and low-quality diet). With increasing age, the magnitude of the OR for stroke decreased for five risk factors (hypertension, high apolipoprotein B concentration, high waist-to-hip ratio, alcohol use, and psychosocial stress). Hypertension, high waist-to-hip ratio, and physical inactivity accounted for the largest PAF of stroke among all age groups. Diminution of OR might also have been influenced by differences in risk factor modification by age; for example, the proportion of the population treated with antihypertensive therapy. Although we found evidence of differences in proportion of antihypertensive use, these differences do not account for the overall difference in OR by age subgroup. This finding highlights the importance of considering population-level risk factors in the context of risk factor prevalence. The PAF of other risk factors differed by age group, with alcohol use and psychosocial stress ranked higher in early life (aged <40 years), and atrial fibrillation ranked higher in later life (aged >65 years).

Implications of all the available evidence

The prevalence, relative risk, and absolute risk of several common risk factors for stroke vary with age, which has implications for policy and strategies to reduce the global burden of stroke. Hypertension, high waist-to-hip ratio, and physical inactivity account for the largest population attributable risk and are the most important target for prevention strategies across all age groups. Execution of strategies to target other risk factors might be of more impact if prioritised by age group (eg, strategies to deal with psychosocial stress in early life, and atrial fibrillation detection in later life).

The aim of this analysis of the INTERSTROKE study is to evaluate whether age modifies the association of vascular risk factors with stroke risk.

Methods

Study design and participants

INTERSTROKE is an international case–control study of risk factors for incident stroke from 32 countries. The methods have been described previously.[9] Patients were recruited from 142 centres between Jan 11, 2007, and Aug 8, 2015. Each case was matched for sex and age (±5 years) with a control from the same centre. For the current analysis, we included 13 462 cases and 13 488 controls. Cases were patients who presented with first acute stroke, either ischaemic or haemorrhagic (confirmation by CT or MRI brain imaging), enrolled within 72 h of hospital admission or 5 days of symptom onset. Ischaemic stroke subtype was based on clinical assessment (at baseline and at 1 month), neuroimaging (CT or MRI at baseline), and results of tests (eg, vascular imaging and cardiac monitoring) to determine the cause of stroke. Control participants were either community-based or hospital-based (eg, individuals attending an outpatient clinic for disorders or procedures not related to stroke, or visitors or relatives of other inpatients). The study was approved by the ethics committees in all participating centres (appendix pp 1–7). Written informed consent was obtained from participants or their proxy.

Procedures

Standardised questionnaires were used to collect data on baseline demographics, lifestyle-related risk factors for stroke, and characteristics of acute stroke from all cases and controls. Sex and ethnicity were self-reported by participants. Physical measurements (eg, blood pressure, waist-to-hip ratio, height, and weight) were recorded in a standardised manner. Hypertension was defined as a composite of self-reported hypertension and a blood pressure reading of greater than 140/90 mm Hg at recruitment. Diabetes was defined as a history of diabetes or glycated haemoglobin (HbA_{1c}) of 6·5% or greater. Smoking status was defined as never or former, or current smoker. Alcohol use was categorised as current alcohol use, or formerly used or never used alcohol products. Diet quality was defined by the modified Alternative Healthy Eating Index (mAHEI), with a higher score indicating a healthier cardiovascular

diet. Physical activity (during leisure time) was measured by asking which of the following best reflects the level of activity (with examples of activity levels provided) during leisure time: mainly sedentary, mild exercise, moderate exercise, or strenuous exercise. We measured depressive symptoms by asking whether the participant had felt sad, blue, or depressed for 2 consecutive weeks or more during the previous 12 months. For psychosocial and psychological stress in the preceding year, we used a combined measure of psychosocial stress used in the INTERHEART study,[10] which combines measures of stress (home and work). Cases were instructed to respond as they would have before having the stroke event. Concentrations of apolipoprotein B were measured by non-fasting blood samples, which were collected within 48 h of recruitment.

Outcomes

The primary outcome was all stroke. Secondary outcomes were stroke subtypes; ischaemic and haemorrhagic stroke.

Statistical analysis

Descriptive statistics were used to characterise the study population by age group. A trichotomised age group variable was derived; early life (aged <40 years), mid-life (aged 40–65 years), and later life (aged >65 years). Binary variables for risk factors of interest were derived where responses were continuous or more than two categories a dichotomous variable was derived. High waist-to-hip ratio was defined as greater than 0·85 for female individuals and greater than 0·90 for male individuals. Obesity was defined as BMI greater than or equal to 30 kg/m^2. High apolipoprotein B concentration was defined as greater than 1 g/L. Physical inactivity was defined as mainly sedentary or mild exercise during leisure time. Mainly sedentary or mild exercise was defined as physical inactivity. Moderate exercise, and strenuous exercise was defined as physically active. A two-level mAHEI variable was derived: tertile 1 (low-quality diet) and tertile 2 or 3 (high-quality diet). Alcohol use was defined as current alcohol use. Psychosocial stress was defined as several periods or permanent stress at home or work in the preceding year. The correlation between age and individual risk factors was tested using Pearson correlation coefficients. We used multivariable conditional logistic regression with an interaction term for age (continuous variable) to explore the association of the following risk factors with stroke: hypertension, atrial fibrillation, high waist-to-hip ratio, high apolipoprotein B concentration, physical inactivity, unhealthy diet, alcohol use, smoking, stress, and depression. The primary analysis was mutually adjusted for other risk factors (hypertension, diabetes, atrial fibrillation, physical inactivity, smoking, alcohol use, psychosocial stress, depression, high waist-to-hip ratio, obesity, high apolipoprotein B concentration, and unhealthy diet [mAHEI score]). A sensitivity analysis was conducted for hypertension and high apolipoproten B concentration to evaluate the association of these risk factors by treatment status (antihypertensive or statin therapy). We used the Wald test to test for interactions between age (continuous variable) and risk factors. All conditional analyses were stratified on the matching criteria (ie, controls were matched for sex and age (±5 years) with cases; age matching was extended (±10 years) for participants older than 90 years). We used restricted cubic splines to explore the pattern of association. Population attributable fraction (PAF), the proportion of all cases in the population (exposed and unexposed) that may be attributed to the exposure, was calculated using Levin's formula.[11] The PAF was estimated with by age groups (early life, mid-life, and later life) and as a function of age. With regard to PAF as a function of age, risk factor prevalence and odds ratios (ORs) by age (extracted from a multivariate logic model) with 95% CIs were substituted into Levin's formula to estimate age-specific PAF. A p value <0·05 was considered statistically significant. Statistical analyses were performed using R version 4.4.1.

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.

Results

Among 26 950 participants analysed, the mean age of cases was 62·2 years (SD 13·6) and of controls 61·3 years (13·3); 5441 (40·4%) cases and 5453 (40·4%) controls were female individuals and 8021 (59·6%) cases and 8035 (59·6%) controls were male individuals (table 1).

Among controls, the prevalence of seven vascular risk factors significantly increased with increased age: hypertension (46·5% increase in prevalence from early life to later life; p<0·0001), physical inactivity (3·2% increase in prevalence from early life to later life; p<0·0001), diabetes (15·7% increase in prevalence from early life to later life; p<0·0001), atrial fibrillation (3·9% increase in prevalence from early life to later life; p<0·0001), high waist-to-hip ratio (14·2% increase in prevalence from early life to later life; p<0·0001), high apolipoprotein B (11·8% increase in prevalence from early life to later life; p<0·0001) and obesity (3·9% increase in prevalence from early life to later life; p=0·016). The prevalence of four other vascular risk factors significantly reduced with increased age: smoking (13·5% reduction in prevalence from early life to later life; p<0·0001), alcohol use (2·9% reduction in prevalence from early life to later life; p<0·0001), psychosocial stress (15·5% reduction in prevalence from early life to later life; p<0·0001), and unhealthy diet (3·5% reduction in prevalence from early life to later life; p=0·0081). The prevalence of depression was not significantly correlated with age (figure 1).

Increasing age was associated with a diminution of the OR of stroke for five vascular risk factors: hypertension (OR 6·10 [95% CI 4·09–9·09] in early life, 3·74 [3·40–4·12] in mid-life, and 2·36 [2·13–2·62] in later life; $p_{interaction}$<0·0001), apolipoprotein B (1·27 [0·90–1·80] in early life, 1·21 [1·10–1·33] in mid-life, and 0·93 [0·84–1·03] in later life; $p_{interaction}$<0·0001), high waist-to-hip ratio (1·59 [1·14–2·23] in early life,

	Controls			Cases		
	Early life (<40 years) n=749	Mid-life (40–65 years) n=6932	Later life (>65 years) n=5807	Early life (<40 years) n=683	Mid-life (40–65 years) n=6667	Later life (>65 years) n=6112
Age, years	33·01 (5·04)	54·13 (6·64)	73·53 (6·35)	32·76 (5·45)	54·18 (6·59)	74·17 (6·72)
Sex						
Female	267 (35·65%)	2541 (36·66%)	645 (45·55%)	257 (37·63%)	2380 (35·70%)	2804 (45·88%)
Male	482 (64·35%)	4391 (63·34%)	3162 (54·45%)	426 (62·37%)	4287 (64·30%)	3308 (54·12%)
Ethnicity						
European	88 (11·75%)	1702 (29·31%)	1162 (16·76%)	88 (12·88%)	1721 (28·16%)	1128 (16·92%)
Chinese	147 (19·63%)	1588 (27·35%)	2283 (32·93%)	124 (18·16%)	1680 (27·49%)	2212 (33·18%)
South Asian	220 (29·37%)	1045 (18·00%)	1773 (25·58%)	208 (30·45%)	1202 (19·67%)	1622 (24·33%)
Other Asian	86 (11·48%)	179 (3·08%)	428 (6·17%)	69 (10·10%)	168 (2·75%)	467 (7·00%)
Arabic	22 (2·94%)	125 (2·15%)	102 (1·47%)	17 (2·49%)	140 (2·29%)	98 (1·47%)
Latin American	71 (9·48%)	772 (13·29%)	590 (8·51%)	71 (10·40%)	772 (12·63%)	557 (8·35%)
African	61 (8·14%)	147 (2·53%)	331 (4·77%)	57 (8·35%)	166 (2·72%)	337 (5·05%)
Other	54 (7·21%)	249 (4·29%)	263 (3·79%)	49 (7·17%)	263 (4·30%)	246 (3·69%)
History of hypertension or adjusted blood pressure >140/90 mm Hg						
Yes	96 (12·82%)	2846 (41·06%)	3443 (59·29%)	277 (40·56%)	4762 (71·43%)	4736 (77·49%)
No	653 (87·18%)	4086 (58·94%)	2364 (40·71%)	406 (59·44%)	1905 (28·57%)	1376 (22·51%)
History of diabetes or HbA_{1c} ≥6·5%						
Yes	69 (9·21%)	1441 (20·81%)	1447 (24·92%)	80 (11·71%)	1903 (28·56%)	1793 (29·35%)
No	680 (90·79%)	5482 (79·19%)	4359 (75·08%)	603 (88·29%)	4761 (71·44%)	4315 (70·65%)
History of atrial fibrillation or flutter						
Yes	6 (0·80%)	91 (1·31%)	273 (4·70%)	28 (4·10%)	340 (5·10%)	961 (15·72%)
No	743 (99·20%)	6841 (98·69%)	5534 (95·30%)	655 (95·90%)	6327 (94·90%)	5151 (84·28%)
Depression (sad, blue, or depressed in the past 2 or more weeks)						
Yes	132 (17·65%)	969 (13·98%)	805 (13·86%)	151 (22·21%)	1221 (18·44%)	1084 (17·83%)
No	616 (82·35%)	5961 (86·02%)	5002 (86·14%)	529 (77·79%)	5400 (81·56%)	4996 (82·17%)
Global stress (several periods or permanent)						
Yes	191 (25·53%)	1164 (16·81%)	578 (9·98%)	234 (34·56%)	1664 (25·21%)	847 (13·95%)
No	557 (74·47%)	5760 (83·19%)	5212 (90·02%)	443 (65·44%)	4936 (74·79%)	5226 (86·05%)
Modified Alternative Healthy Eating Index tertile						
Tertile 2 or 3 (high-quality diet)	485 (64·75%)	4588 (66·19%)	3963 (68·25%)	440 (64·42%)	4146 (62·19%)	3868 (63·29%)
Tertile 1 (low-quality diet)	264 (35·25%)	2344 (33·81%)	1844 (31·75%)	243 (35·58%)	2521 (37·81%)	2244 (36·71%)
Alcohol use						
Never or former	572 (76·37%)	5285 (76·26%)	4602 (79·25%)	490 (71·74%)	4704 (70·58%)	4830 (79·05%)
Current	177 (23·63%)	1645 (23·74%)	1205 (20·75%)	193 (28·26%)	1961 (29·42%)	1280 (20·95%)
Smoking history						
Never or former smoker	531 (70·89%)	5034 (72·65%)	4899 (84·42%)	443 (64·86%)	4102 (61·57%)	4832 (79·08%)
Current Smoker	218 (29·11%)	1895 (27·35%)	904 (15·58%)	240 (35·14%)	2560 (38·43%)	1278 (20·92%)
Physical inactivity during leisure time						
Yes	607 (81·15%)	5779 (83·39%)	4893 (84·35%)	582 (85·21%)	5970 (89·63%)	5508 (90·16%)
No	141 (18·85%)	1151 (16·61%)	908 (15·65%)	101 (14·79%)	691 (10·37%)	601 (9·84%)
High waist-to-hip ratio (>0·85 for women and >0·90 for men)						
Yes	445 (59·57%)	4918 (71·08%)	4263 (73·72%)	456 (67·76%)	5106 (77·65%)	4729 (78·78%)
No	302 (40·43%)	2001 (28·92%)	1520 (26·28%)	217 (32·24%)	1470 (22·35%)	1274 (21·22%)
Obesity (BMI ≥30 kg, kg/m^2)						
Yes	83 (11·19%)	1023 (14·86%)	872 (15·12%)	98 (14·63%)	1117 (17·07%)	937 (15·61%)
No	659 (88·81%)	5863 (85·14%)	4897 (84·88%)	572 (85·37%)	5425 (82·93%)	5064 (84·39%)
High apolipoprotein B (>1 g/L)						
Yes	215 (33·65%)	2759 (44·85%)	2403 (45·57%)	260 (44·52%)	3053 (51·10%)	2389 (43·17%)
No	424 (66·35%)	3392 (55·15%)	2870 (54·43%)	324 (55·48%)	2922 (48·90%)	3145 (56·83%)

HbA_{1c}=glycated haemoglobin.

Table 1: **Baseline characteristics and risk factors among participants by age group**

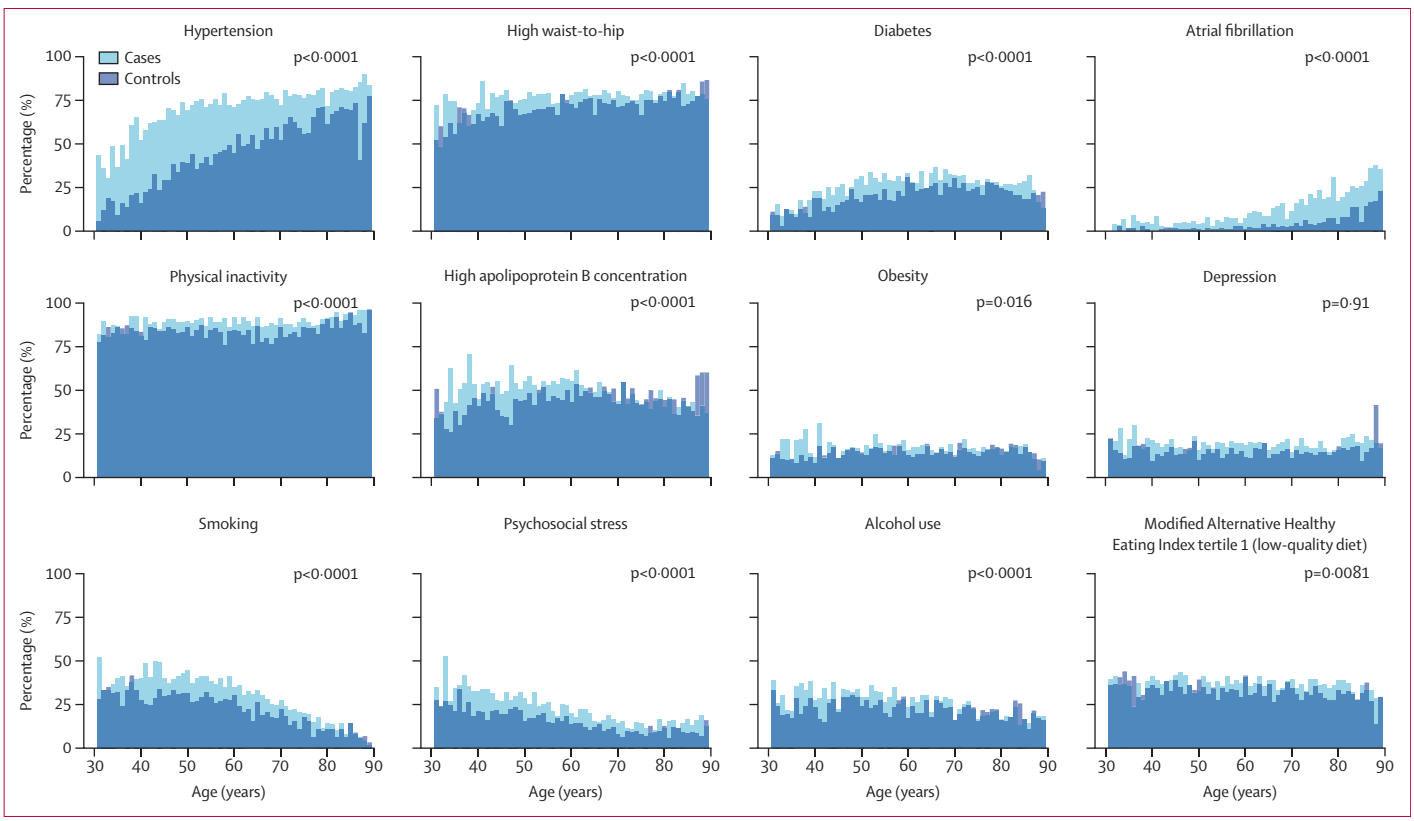

Figure 1: **Prevalence of risk factors among cases and controls**
p value represents p for correlation between individual risk factor and age (continuous) among controls.

1·34 [1·20–1·50] in mid-life, and 1·36 [1·20–1·53] in later life; $p_{interaction}$=0·011), psychosocial stress (1·53 [1·08–2·18] in early life, 1·63 [1·44–1·84] in mid-life, and 1·39 [1·19–1·62] in later life; $p_{interaction}$=0·033), and alcohol use (1·64 [1·11–2·44] in early life, 1·39 [1·23–1·57] in mid-life, and 1·09 [0·95–1·25] in later life; $p_{interaction}$<0·0001). The magnitude of association of diabetes and stroke was highest in mid-life (OR 1·42 [95% CI 1·27–1·59]), high in later life (1·13 [1·01–1·28]), and lowest in early life (0·82 [0·46–1·46]; $p_{interaction}$=0·0015). There was no significant difference for other vascular risk factors by age group, and no vascular risk factor was associated with a higher OR with increased age (figure 2; appendix p 9). A sensitivity analysis was conducted for hypertension and high apolipoprotein B concentration by treatment status. A higher proportion of hypertensive participants were prescribed antihypertensive therapy (before hospital admission) in later life than early adulthood (32 [33·8%] of 96 *vs* 2231 [64·8%] of 3443). Increasing age was associated with a diminution of the OR of stroke for treated and untreated hypertension ($p_{interaction}$<0·001), and treated and untreated high apolipoprotein B ($p_{interaction}$<0·001; appendix p 10). The association of vascular risk factors with stroke subtype by age group are reported in the appendix (pp 11–12). Findings were consistent with all stroke outcomes with the exception of the association of diabetes, which was not associated with increased risk of haemorrhagic stroke or significant interaction by age ($p_{interaction}$=0·66).

Figure 3 reports population attributable risk by age. The three risk factors accounting for the highest PAF among all age groups were hypertension, physical inactivity, and high waist-to-hip ratio. The PAF of hypertension was highest in mid-life (PAF 0·52 [95% CI 0·49–0·55] in mid-life *vs* 0·34 [0·30–0·40] in early life and 0·45 [0·40–0·49] in later life). The PAF of physical inactivity was highest in mid-life (PAF 0·42 [95% CI 0·34–0·48] in mid-life, 0·32 [0·05–0·60] in early life, and 0·31 [0·22–0·42] in later life). The PAF of high waist-to-hip ratio was highest in early life (PAF 0·25 [95% CI 0·13–0·40] in early life, 0·19 [0·13–0·26] in mid-life, and 0·21 [0·13–0·28] in later life). The PAF for atrial fibrillation was highest in later life (PAF 0·11 [95% CI, 0·09–0·12] in later life, 0·04 [0·03–0·05] in mid-life, and 0·03 [0·01–0·05] in early life; table 2).

Discussion

In the INTERSTROKE study, we showed a varying effect of age on prevalence of vascular risk factors. Given the rising incidence of stroke in early life and mid-life, and the increase in absolute rates of stroke in later life (in context of an ageing population),[1,2] understanding the differences in the contributions of vascular risk factors by age group is

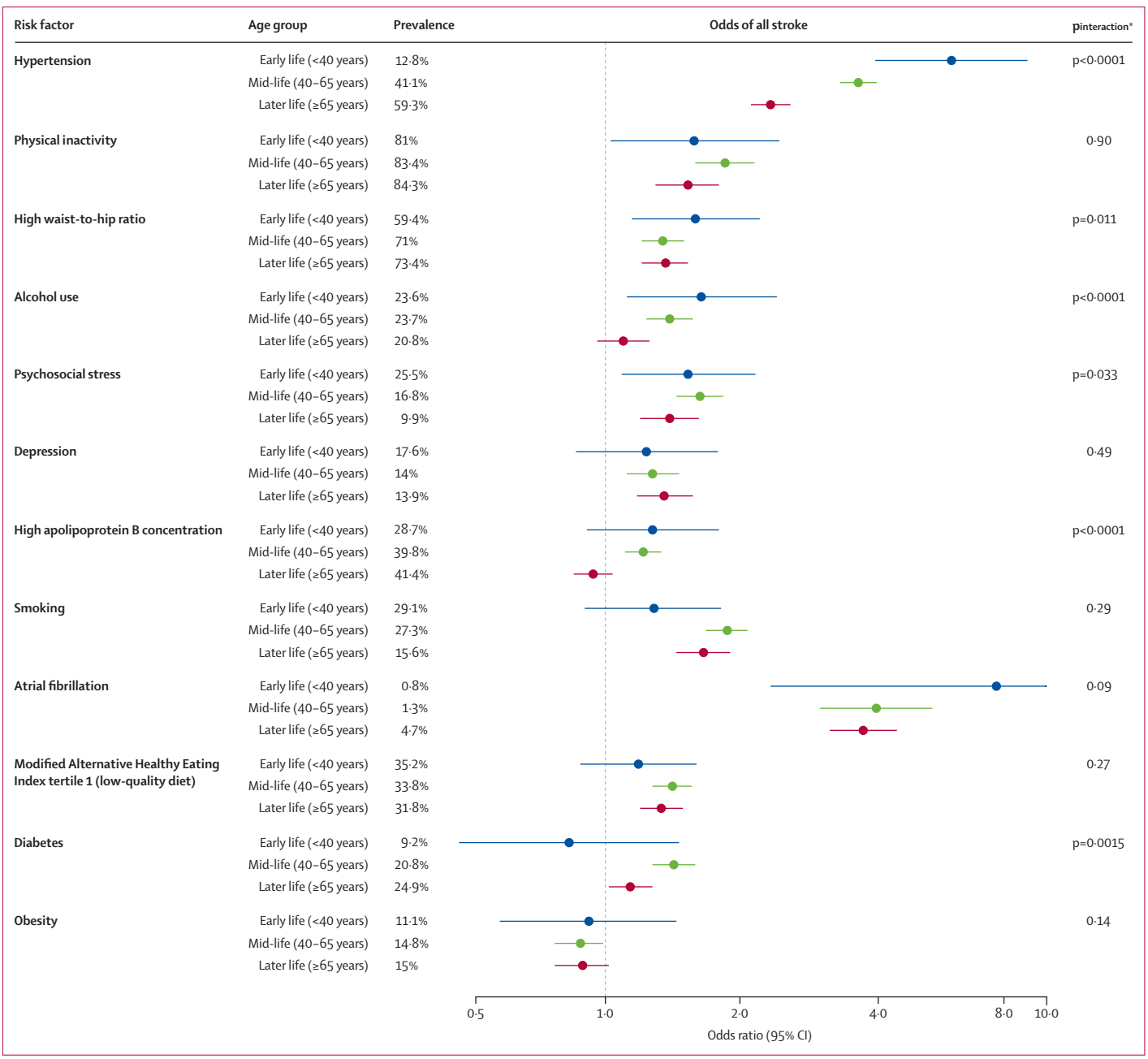

Figure 2: **Association of common risk factors and stroke, by age group**
Each coloured marker (red, green, or blue) represents the odds ratio for a given age group, and the horizontal lines indicate the 95% confidence intervals. The dashed vertical line at an odds ratio of 1·0 denotes no association with stroke. *$p_{interaction}$ calculated between age (continuous variable) and risk factor.

required to guide stroke prevention strategies. We found the highest prevalence of hypertension, diabetes, atrial fibrillation, and waist-to-hip ratio in later life, and the highest prevalence of smoking, alcohol intake, psychosocial stress, and unhealthy diet in early life. Increased age was associated with a reduction in the magnitude of OR of stroke with hypertension, high apolipoprotein B concentration, high waist-to-hip ratio, psychosocial stress, and alcohol use. Although the OR for hypertension and high waist-to-hip ratio diminished with age, there was a counterbalanced increase in prevalence, which resulted in relatively consistent PAFs among age subgroups.

A potential modifying effect of age on the relative importance of known risk factors for stroke has been reported previously.[5] The burden of stroke attributable to risk factors is related to two key determinants, the prevalence of the risk factor and the magnitude of association, represented in our study by the ORs. In the case of hypertension, the prevalence of the risk factor increased with age, but the OR reduced, resulting in a net modest effect on PAF.

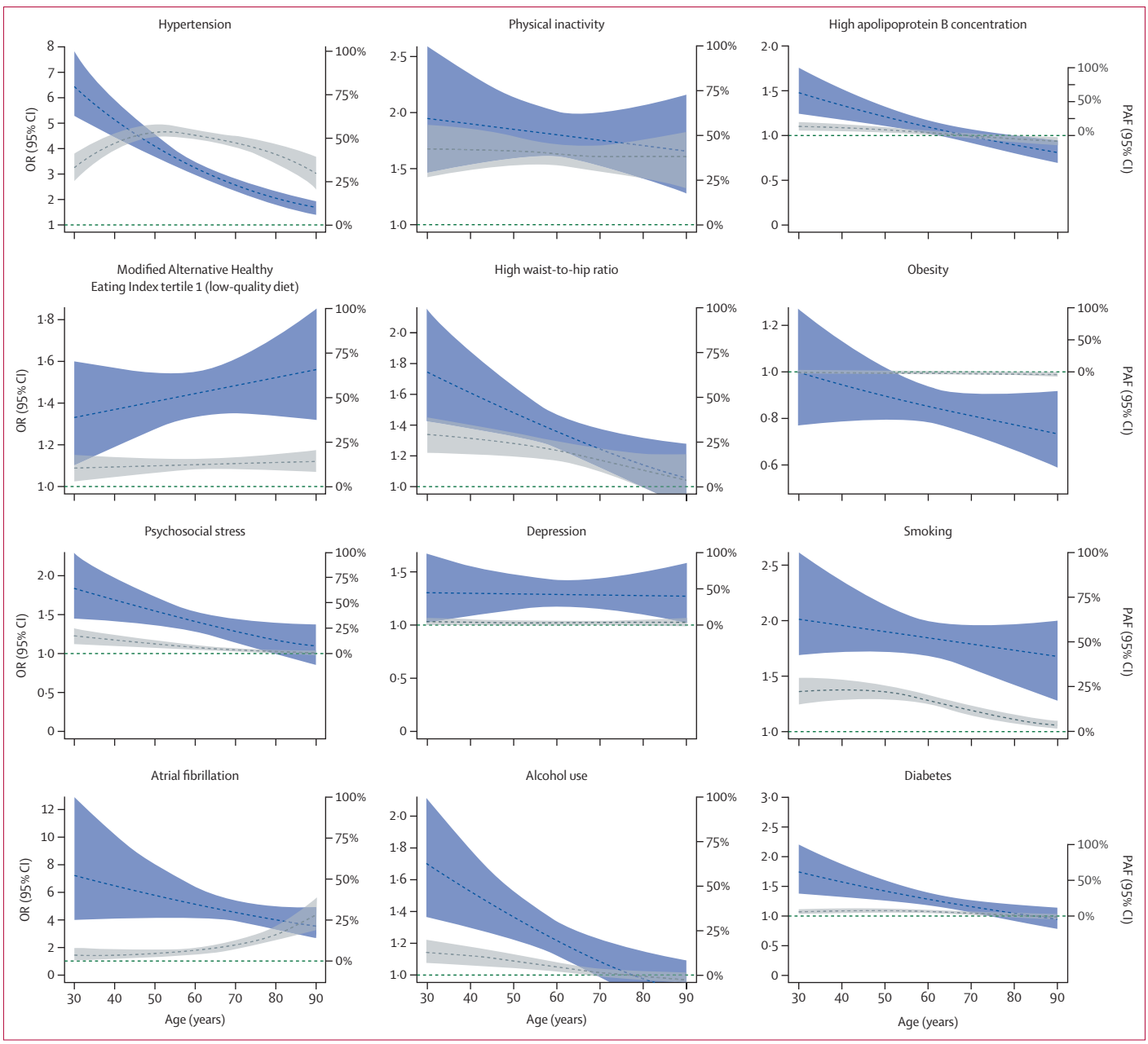

Figure 3: **Association and population attributable risk of risk factors**

The purple lines represent the ORs and the grey lines represent the PAFs. The shaded regions indicate 95% CIs. The dashed horizontal line at OR=1 (for ORs) and PAF=0 (for PAFs) indicates no association between the risk factor and case status. OR=odds ratio. PAF=population attributable fraction.

We report that PAF for hypertension is highest in mid-life, which has been reported in other studies;[12] however, hypertension remains the most important modifiable risk factor throughout the age range.

A reduction in OR with increasing age might relate to different underlying factors. First, it might relate to a true reduction in the causative role of a risk factor. For example, the attenuation of association of high apolipoprotein B concentration and risk of myocardial infarction with increasing age been reported previously.[13] Moreover, evidence from a meta-analysis of randomised controlled trials of statin therapy reported a smaller proportional risk reduction in older cohorts, compared with mid-life, and serves as an argument for a different emphasis on use of statin therapy for primary prevention among older individuals.[14] By contrast, meta-analyses of blood pressure-lowering therapy have not reported a differing risk reduction in stroke with increased age.[15,16] Subgroup analyses by age must be interpreted with caution, given the poor representation of older adults in clinical trials.[17]

	Early life (aged <40 years)		Mid-life (aged 40–65 years)		Later life (aged ≥65 years)	
	PAF (95% CI)	Rank	PAF (95% CI)	Rank	PAF (95% CI)	Rank
Hypertension	0·34 (0·30 to 0·40)	1	0·52 (0·49 to 0·55)	1	0·45 (0·40 to 0·49)	1
Physical inactivity	0·32 (0·05 to 0·60)	2	0·42 (0·34 to 0·48)	2	0·31 (0·22 to 0·42)	2
High waist-to-hip ratio (>0·85 for women and >0·90 for men)	0·25 (0·13 to 0·40)	3	0·19 (0·13 to 0·26)	3	0·21 (0·13 to 0·28)	3
Alcohol use	0·11 (0·03 to 0·19)	4	0·08 (0·05 to 0·11)	9	0·02 (–0·008 to 0·05)	7
Psychosocial stress	0·12 (0·04 to 0·23)	5	0·09 (0·07 to 0·11)	6	0·04 (0·02 to 0·06)	10
HIgh apolipoprotein B (>1 g/L)	0·09 (–0·02 to 0·20)	6	0·09 (0·05 to 0·13)	7	–0·03 (–0·08 to 0·15)	12
Depression	0·06 (–0·01 to 0·13)	7	0·03 (0·008 to 0·06)	11	0·05 (0·03 to 0·07)	8
Smoking	0·06 (–0·08 to 0·20)	8	0·18 (0·16 to 0·20)	4	0·09 (0·07 to 0·11)	6
Atrial fibrillation	0·03 (0·01 to 0·05)	9	0·04 (0·03 to 0·05)	10	0·11 (0·09 to 0·12)	4
Modified Alternative Healthy Eating Index tertile 1 (low-quality diet)	0·03 (–0·07 to 0·14)	10	0·13 (0·10 to 0·16)	5	0·11 (0·08 to 0·14)	5
Diabetes	–0·01 (–0·09 to 0·07)	11	0·08 (0·05 to 0·11)	8	0·04 (0·003 to 0·07)	9
Obesity (BMI ≥30 kg, kg/m^2)	–0·06 (–0·15 to 0·04)	12	–0·03 (–0·06- to -0·003)	12	–0·03 (–0·05 to –0·003)	11

Rank indicates highest to lowest PAF within each age group. PAF=population attributable fraction.

Table 2: **PAF by age group**

The INTERSTROKE study included a relatively large proportion of older adults (5160 participants were aged 75 years or older). Second, the age-related increased prevalence of some risk factors—most notable for hypertension, diabetes, and atrial fibrillation—will diminish the individual contribution of risk factors, with a greater magnitude of adjustment of OR on multivariable analysis. Third, the lower OR might relate to an analytic ceiling effect in OR estimate for common risk factors, resulting from increased prevalence. For example, a prevalence of 50% in the control group will limit the OR to less than around 2·0 whereas a prevalence of 5% permits a wider range of possible OR values. The large sample size included in our analysis increases our ability to detect statistically significant p value interactions, which does not instruct on the magnitude or pattern (linear or stepwise) of the interaction between risk factor and age.

In our analysis, risk factors associated with a larger PAF with increasing age were related to an increase in prevalence rather than an increase in OR. The most marked relative change in PAF was atrial fibrillation, which went from 3–4% (early life and mid-life) to 11% (later life) and from 10th to 4th in ranked magnitude of PAF. This finding is consistent with evidence from previous studies,[18,19] reporting a curvilinear increase in prevalence of atrial fibrillation with ageing but consistent risk ratio. In addition, the efficacy of direct oral anticoagulants for stroke prevention in atrial fibrillation populations did not differ by age group, although an interaction between age and major bleeding has been reported.[20] We also observed an increased PAF with age for an unhealthy diet, which has not been reported previously. By contrast, the main determinant of a lower PAF of psychosocial stress with increasing age was a lower prevalence from early to later life age groups, which has been reported previously.[21] We have previously reported that the association of psychosocial stress (measured as combined home and work stress) with stroke was consistent across age groups.[22] Similarly, the PAF for alcohol use declined with increased age in the current study, which might reflect differences in consumption patterns of a younger cohort compared with an older cohort, and potentially differences in the importance of a triggering effect of excess alcohol intake (versus chronic exposure).

Our study has some potential limitations. One limitation was the case–control design, specifically with regard to selection bias, recall bias, or social desirability bias of self-reported risk factors. The INTERSTROKE study aimed to recruit a representative sample of patients across the stroke spectrum, but those with severe stroke syndromes might have been less likely to enrol. Proxy consent was permitted to mitigate communication barriers to enrolment. Knowledge of personal history of risk factors might be higher in later life due to increased health-care contact and, therefore, ascertainment of self-reported risk factors might be more likely in older adults. Although a case–control design is considered inferior to prospective cohort studies, it has advantages in addressing the current research question. The INTERSTROKE study used a case–control design, matched for age and sex. Prospective cohort studies are more suited for the determination of causal inference, and the inception cohort is usually restricted to a narrow age range, making these designs less suited to evaluating the influence of age. In addition, the measurement of exposures (risk factors) is usually completed at baseline and might underestimate the prevalence of risk factors during follow-up, or at the time of the event. Although a limitation of the matched design is the inability to determine the contribution of age to risk of stroke, it does allow us to study the change in the role of risk factors between cases and controls within age subgroups. Case–control studies also allow for accruing a larger number of cases in subgroups with lower disease incidence, such as younger individuals, and overall provide better power for subgroup analyses. For example, the large PURE study of nearly 200 000 people accrued about 5000 strokes over a mean follow-up of 14 years

(unpublished data) and so would have less power compared with INTERSTROKE, to examine variations in the effects of a risk factor by age.

To conclude, increased age appears to modify the association of vascular risk factors and stroke risk, with a lower magnitude of association for hypertension, high apolipoprotein B concentration, high waist-to-hip ratio, and psychosocial stress with stroke risk in older adults. Atrial fibrillation is associated with an increased PAF with advanced age, due to increased prevalence rather than higher OR.

Contributors

CR, SY, and MO contributed to conceptualisation. CR, SY, and MO contributed to the study design and methodology. GJH, JF, PL, SO, HKI, AR, DR, AC, XW, FL, AD, DX, PL-J, SY, and MO contributed to data collection. CR and JF contributed to statistical analysis. CR, MC, AS, and MO contributed to writing the original draft. All authors contributed to manuscript review and editing. CR and MO had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

DX reports payment to institutions (Population Health Research Institute, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Indian Council of Medical Research, Pfizer, United Kingdom Medical Research Council, and the Wellcome Trust), speaker fees (Eli Lilly and Sanofi), and support for attending meetings or travel (Indian Council of Medical Research, Eli Lilly, and Sanofi) outside of the submitted work. DX also reports an honorary leadership role with Society for Community Health Awareness Research and Action and Indian Society for Clinical Research. CR, GJH, MC, PL, SO, JF, FL, XW, AR, AC, AD, DR, HKI, PL-J, AS, SY, and MO declare no competing interests.

Data sharing

Additional data is available on reasonable request. Qualifying researchers who wish to access data should submit a proposal outlining the research question and proposed statistical analysis plan to Martin O'Donnell (martin.odonnell@universityofgalway.ie). Proposals will be assessed by a committee formed from the study management group. Available data for analysis at the Population Health Research Institute include de-identified individual participant data (baseline demographics, cardiovascular risk factors, presenting symptoms, and stroke severity).

Acknowledgments

The INTERSTROKE study was funded by the Canadian Institutes of Health Research; Heart and Stroke Foundation of Canada; Canadian Stroke Network; Swedish Research Council; Swedish Heart and Lung Foundation; AFA Insurance; The Health & Medical Care Committee of the Regional Executive Board, Region Västra Götaland (Sweden); and through unrestricted grants from several pharmaceutical companies, with major contributions from AstraZeneca; Boehringer Ingelheim (Canada); Pfizer (Canada); MSD; Chest, Heart and Stroke Scotland; and the UK Stroke Association. CR was supported by the Irish Clinical Academic Training Programme, the Wellcome Trust, and the Health Research Board (grant number 203930/B/16/Z), as well as the Health Service Executive, National Doctors Training and Planning, and the Health and Social Care, Research, and Development Division of Northern Ireland. The sponsors had no role in data collection, analyses or the decision to submit for publication.

References

1 Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021; **20:** 795–820.

2 Owolabi MO, Thrift AG, Mahal A, et al. Primary stroke prevention worldwide: translating evidence into action. *Lancet Public Health* 2022; **7:** e74–85.

3 Scott CA, Li L, Rothwell PM. Diverging temporal trends in stroke incidence in younger *vs* older people: a systematic review and meta-analysis. *JAMA Neurol* 2022; **79:** 1036–48.

4 Li L, Scott CA, Rothwell PM. Association of younger *vs* older ages with changes in incidence of stroke and other vascular events, 2002–2018. *JAMA* 2022; **328:** 563–74.

5 Howard G, Banach M, Kissela B, et al. Age-related differences in the role of risk factors for ischemic stroke. *Neurology* 2023; **100:** e1444–53.

6 Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360:** 1903–13.

7 Hankey GJ. The role of nutrition in the risk and burden of stroke: an update of the evidence. *Stroke* 2017; **48:** 3168–74.

8 Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360:** 1903–13.

9 O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; **376:** 112–23.

10 Rosengren A, Hawken S, Ôunpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364:** 953–62.

11 Lin C-K, Chen S-T. Estimation and application of population attributable fraction in ecological studies. *Environ Health* 2019; **18:** 52.

12 Seshadri S, Wolf PA, Beiser A, et al. Elevated midlife blood pressure increases stroke risk in elderly persons: the Framingham Study. *Arch Intern Med* 2001; **161:** 2343–50.

13 McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet* 2008; **372:** 224–33.

14 Armitage J, Collins R, Bowman L, et al. The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: a randomised placebo-controlled trial [ISRCTN48489393]. *BMC Med* 2005; **3:** 6.

15 Tharmaratnam D, Karayiannis CC, Collyer TA, et al. Is Blood pressure lowering in the very elderly with previous stroke associated with a higher risk of adverse events? *J Am Heart Assoc* 2021; **10:** e022240.

16 Rahimi K, Bidel Z, Nazarzadeh M, et al. Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual participant-level data meta-analysis. *Lancet* 2021; **398:** 1053–64.

17 Nanna MG, Chen ST, Nelson AJ, Navar AM, Peterson ED. representation of older adults in cardiovascular disease trials since the inclusion across the lifespan policy. *JAMA Intern Med* 2020; **180:** 1531–33.

18 Murphy R, Damasceno A, Reddin C, et al. Variations in the prevalence of atrial fibrillation, and in the strength of its association with ischemic stroke, in countries with different income levels: INTERSTROKE case-control study. *Int J Stroke* 2024; **19:** 559–68.

19 Morseth B, Geelhoed B, Linneberg A, et al. Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM Consortium. *Open Heart* 2021; **8:** e001624.

20 Carnicelli AP, Hong H, Connolly SJ, et al. Direct oral anticoagulants versus warfarin in patients with atrial fibrillation: patient-level network meta-analyses of randomized clinical trials with interaction testing by age and sex. *Circulation* 2022; **145:** 242–55.

21 Stone AA, Schneider S, Broderick JE. Psychological stress declines rapidly from age 50 in the United States: yet another well-being paradox. *J Psychosom Res* 2017; **103:** 22–28.

22 Reddin C, Murphy R, Hankey GJ, et al. Association of psychosocial stress with risk of acute stroke. *JAMA Netw Open* 2022; **5:** e2244836.