Association of younger vs. older ages with changes in incidence of stroke and other vascular events, 2002-2018

Linxin Li*, DPhil, **Catherine A Scott***, BM BCh, **Peter M Rothwell**, MD, PhD

Wolfson Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford, UK

*contributed equally

Corresponding author:
Professor Peter M Rothwell
Wolfson Centre for Prevention of Stroke and Dementia
Nuffield Department of Clinical Neuroscience
University of Oxford
Wolfson Building, John Radcliffe Hospital
OX3, 9DU, Oxford, UK
Tel: (+) 44 (0)1865 231603
Email: peter.rothwell@ndcn.ox.ac.uk

Number of tables: 2

Number of figures: 3

Number of web appendices: eMethods, eTable 1-12; eFigure 1-9

Date of revision: 20/06/2022

Word count text (excluding abstract, references and table/ figure legends): 3858

Number of references: 39

Key Points

Question: Did stroke incidence rates diverge in younger vs older people from 2002 to 2018?

Findings: This cohort study included 94,567 participants in Oxfordshire, UK and compared between 2002-2010 and 2010-2018. Among participants aged <55 years there was a 67% increase in stroke incidence. Among participants age 55 and older, there was a 15% decrease in incidence. No similar divergence was seen for other vascular events.

Meaning: Between 2002-2010 and 2010-2018, there was an increase in stroke incidence in younger persons and a decrease in older persons, without similar divergence for other vascular events.

Abstract

Importance: Some studies reported increasing stroke incidence at younger ages (<55 years), but often relied only on administrative data, and more population-based studies of adjudicated stroke are required. An understanding of the drivers of any increase in incidence of young stroke also requires comparisons with stroke trends at older ages and with trends in incidence of other vascular events at younger ages.

Objective: To determine temporal changes in incidence of stroke vs other major vascular events at younger vs older ages.

Design, Setting and Participants: Prospective population-based incidence study (Oxford Vascular Study –April 2002-March 2018) with a catchment population of 94,567.

Exposures: Calendar time; premorbid vascular risk factors and occupation.

Main outcomes and measures: Changes in incidence of stroke, transient ischaemic attack (TIA) and other major vascular events (myocardial infarction, sudden cardiac death, peripheral vascular events) stratified by age, sex, diagnostic work-up, aetiology, and severity.

Results: From 2002-2010 to 2010-2018, 2429 incident strokes were ascertained (mean/SD age=73.6/14.4; 51.3% female). Stroke incidence increased significantly among participants age<55 (IRR=1.67, 95%CI 1.31-2.14), but fell significantly among participants age≥55y (0.85, 0.78-0.92; difference – p<.001). The significant increase in incidence at age <55y was independent of sex, stroke severity, pathological subtype and changes in investigation, and was also seen for TIA (IRR=1.87, 1.36-2.57), but not for myocardial infarction and other major vascular events (0.73, 0.58-0.93). Although TIA/stroke at age<55y were significantly associated with diabetes (RR=3.47, 95%CI 2.54-4.74), hypertension (2.52, 2.04-3.12), current smoking (2.38, 1.92-2.94), and obesity (1.36, 1.07-1.72), the significant increase in incidence from 2002-2010 to 2010-2018 was still seen in individuals without these risk factors. The increase was greatest in professional/managerial occupations (IRR=2.52,

95%CI 1.75-3.62) and least in partially/unskilled occupations (1.17, 0.79-1.74). The proportion of TIA/strokes aged<55 without known vascular risk factors increased significantly over time (n/% - 45/30.4% vs 115/42.4%; absolute difference +12.0% (2.6-21.5), especially in patients with cryptogenic events (10/18.5% vs 63/49.2%; absolute difference +30.7% (17.2-44.2); p<.001; p_{het}=0.002).

Conclusions and relevance: Comparing persons living in Oxfordshire, UK from 2002-2010 vs 2010-2018, there was a significant increase in stroke incidence in those younger than 55, but a decrease in those 55 and older. Given the absence of this divergence for other vascular events, further research is needed to understand the causes of this difference.

Introduction

Increasing life-expectancy in high-income countries slowed or even reversed since 2010, mostly due to increased mortality between ages 35 to 50, particularly in the UK and USA.[1,2] A similar age-specific divergence was reported in incidence of colorectal cancer, with increasing rates at younger ages,[3] possibly due to increases in obesity, lack of exercise, and poor diet. Given the overlap in risk factors, similar age-specific divergence in incidence of stroke and other vascular events might also be expected.

In contrast to the continued overall decline of stroke incidence in high-income countries in the 21st century,[4] incidence at younger ages (usually defined as <55 years) appeared to be increasing in the USA and some other countries.[5-7] However, many studies relied on routinely collected administrative data on deaths or hospitalisation, which are prone to bias as diagnostic coding practices and admission policies change over time.[8] Furthermore, increased use of diffusion-weighted brain imaging, and changes in public knowledge and behaviours following public health campaigns may have improved the ascertainment of young stroke.

In light of these uncertainties, this population-based study aimed to determine the incidence of transient ischaemic attack (TIA) and stroke and other vascular events in Oxfordshire, UK, from 2002-2018, taking into account changes in diagnostic practices, control of traditional vascular risk factors, other exposures, lifestyle, and sex-specific causes of stroke.[9,10] In light of conflicting findings in previous studies, with stable or decreasing incidence of young stroke in some countries,[11-13] in a linked systematic review,[14] the divergence in stroke incidence at younger vs. older ages was quantified to determine whether a less favourable change in incidence at younger ages was a more consistent finding.

Methods

Written informed consent or assent from relatives was obtained in all participants. The Oxford Vascular Study was approved by the local research ethics committee (OREC A: 05/Q1604/70).

Participants

The Oxford Vascular Study (OXVASC) is an ongoing prospective population-based study of the incidence and outcome of all acute vascular events in a mixed rural/urban population.[15] The study population comprised all individuals (2002-2018 mean = 94,567), irrespective of age, registered with about 100 general practitioners (GPs) in nine general practices in Oxfordshire, UK. At the mid-study point (2011), the population was 91% white for all age groups and 88% for age<50 years (eMethods). The detailed study methodology and case definitions have been published before.[15] Briefly, multiple overlapping methods of prospective and retrospective ascertainment were used to achieve near complete identification of all individuals with acute vascular events (eMethods).

Exposures

The main exposure of the study is the calendar year of the incident vascular event. All first-ever incident events ascertained between 01/04/2002 and 31/03/2018 were included.

Other exposures included were premorbid vascular risk factors and occupation. To stratify TIA and stroke incidence in the cohort by the presence of risk factors and by occupation in the underlying population, age and sex-specific data for the background population were obtained from the Health Survey for England (using South East England region as a proxy) and the Annual Population Survey (using Oxfordshire as a proxy) (eMethods & eFigure 1).

Ethnicity was ascertained to determine if disease incidence differed by race and ethnicity and was based on pre-defined categories: Bangladeshi, Black African, Black Caribbean, Chinese, Indian, Pakistani, White and Other. Judgement was made by the researcher and confirmed with the patient or relatives during the face-to-face interview. When interview was not possible due to death before assessment, the researcher extracted relevant information recorded in medical notes.

Both for TIA and stroke cases and the underlying population, deprivation was measured by postcode of residence using the English Indices of Multiple Deprivation (IMD; eMethods).

Outcomes

The outcomes of the study included changes in incidence of stroke, TIA and other major vascular events (myocardial infarction, sudden cardiac death, peripheral vascular events),

Patients with TIA or stroke were ascertained and assessed face-to-face by study physicians as soon as possible after the initial presentation in hospital, an emergency clinic or at home. In the UK, more than 70% of the patients with TIA and minor stroke are assessed in emergency clinics with all diagnostic work-up performed in the outpatient setting.[16] If a patient died before assessment, an eyewitness account of the clinical event was obtained and any relevant clinical records reviewed. Baseline demographic data, premorbid use of preventive medication, premorbid blood pressure measurements, traditional vascular risk factors, other potential risk factors and family history of stroke were collected from face-to-face interview and cross-referenced with primary care records (eMethods) Detailed clinical history was recorded in all patients and assessments were made for stroke severity using the National Institute of Health Stroke Scale (NIHSS) on admission to hospital, or at the time of the first assessment either at the emergency department or in the acute TIA/minor stroke clinic for those that were not admitted. Patients routinely had brain imaging, vascular imaging, cardiac investigation and standard blood tests (eMethods). All cases were reviewed by the same senior stroke neurologist (PMR) throughout the study to ensure consistency of diagnosis and ischaemic stroke aetiology was classified according to the modified TOAST criteria.[17]

All TIA and stroke patients were followed up face to face at 1, 6, 12, 60 and 120 months by a study nurse or physician to determine their functional status (modified Rankin Scale, mRS: 0-6 with 0 being the best outcome).[18] Major stroke is defined as new disability or death (mRS>2) using the 1 month mRS, or as progression of disability (one score increase in mRS) in those with premorbid disability (premorbid mRS>2). For patients who had moved out of the study area, follow up was performed by telephone. All patients were flagged for the Office for National Statistics mortality data and all deaths during follow-up were recorded with causes.

Patients with any other incident major acute vascular event (myocardial infarction, peripheral vascular disease and sudden cardiac death) were also ascertained over the same period (eMethods) as reported previously.[15,19]

Three other sources of data on stroke incidence were also studied. First. stroke incidence between 2002-2018 was compared with that in the Oxfordshire Community Stroke Project (OCSP), a previous population-based study of all first-ever strokes over 4 years (1981-1984&1986) covering the same general practice population. The methods have also been published before, and the case diagnosis, assessment, and follow-up were similar to those in the later cohort (2002-2018).[20] To try to ensure consistency in the application of definitions of stroke between the two studies, all potential cases in the first 2 years of the later cohort (2002-2018) were reviewed by the principal investigator of the early cohort (1981-1986).[15] Second, data on hospitalization for strokes at age<55 years in Oxfordshire in 1975-1976 were extracted from an earlier study.[21] Third, data on annual stroke admissions at age<60 years in England between 1998 and 2018 were extracted from Hospital Episode Statistics (HES)[22], based on ICD 10 codes including I60 (nontraumatic subarachnoid haemorrhage - SAH), I61 (nontraumatic intracerebral haemorrhage - ICH), I63 (cerebral infarction) and I64 (unspecified stroke), and stratified by reported subtype (unknown, ischaemic, ICH,SAH).

Statistical Analyses

Crude incidence rates (per population/year) were calculated by age groups (<55 years / ≥55 years), sex, stroke severity (major vs. minor), stroke subtypes (ischaemic stroke (IS), intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH)) and common stroke risk factor status (smoking, obesity, hypertension, diabetes, and deprivation) with 95% confidence intervals (CI) estimated assuming a Poisson distribution. Incidence rates using the England national data on stroke admissions at age<60 years were also calculated. All incidences were standardised to the 2011 population of England and Wales. Poisson regression models, adjusted for the population age/sex structures, were used to calculate the incidence Rate Ratios (IRR) for 2002-2018 vs. 1981-1986 and for 2010-2018 vs. 2002-2010. IRRs for the change of incidence for TIA, TIA and stroke, and other acute vascular events at age<55 years between 2010-2018 vs. 2002-2010 were also calculated and sensitivity analyses stratified by the participating GP practices and by rural vs. urban catchment area were performed. To measure the age-specific divergence in IRR, the relative temporal difference (RTD) was calculated by dividing the IRR at age <55 years by the IRR at age ≥55 years (eMethods).[14]

For all patients with TIA and stroke aged <55 years, the changes of the following factors between the two 8-year periods were also compared using Chi-square test for categorical variables and t-test for continuous variables: demographics (age, sex and occupation), traditional vascular risk factors; other

potential risk factors; family history of stroke; premorbid blood pressure; event territory (anterior vs. posterior circulation); stroke aetiology (TOAST subtypes for IS; haematoma location for ICH and aneurysmal vs. non-aneurysmal for SAH), mode of diagnostic work-up and patient behaviour, and the non-laboratory version of the Framingham General Cardiovascular Risk Score.[23] Sensitivity analysis excluding TIAs were also performed. Given the multiple nature of these comparisons and the potential for type-1 error, these analyses should be interpreted as exploratory.

The prevalence of traditional vascular risk factors in patients with TIA and stroke was also compared with the prevalence reported in the background population for each four-year time-periods respectively and then pooled the risk ratio (RR) using random effect meta-analysis. For deprivation, patients were divided into 4 groups according to the English quartiles of the IMD score, with quartile 1 being the most affluent and 4 being the most deprived. The same approach was undertaken for the income subcomponent score. Age-specific incident stroke rates (per 1000 population per year) were calculated and stratified by quartile of deprivation.

Complete analyses without imputation were performed and missing data were reported where applicable. P values were 2-sided with statistical significance set at less than 0.05.

All analyses were done using SPSS version 25 and Stata version 17.0.

Results

Overall, 2429 incident strokes (51.3% female) were ascertained (1166 for 2002-2010 and 1263 for 2010-2018). There was a significant decline in stroke incidence at age ≥55 years in 2010-2018 vs. 2002-2010 (IRR=0.85, 95%CI 0.78-0.92; p<.001; figure 1, eTable 1) but a significant increase at age <55 (1.67, 1.31-2.14, p<.001; table 1, figure 1, eTable 1) with an annual percent change of +5.5 (95%CI 3.4-7.7, p for trend <.001). These divergent changes (RTD=1.96, 95%CI 1.52-2.55, p<.001; eTable 1) were consistent for non AF-related events (eFigure 2) and also by sex, stroke type and stroke severity (eTable 1). The decrease of stroke incidence at age 55-64 years was less prominent than at older ages and was not statistically significant (eTable 1).

Incidence of TIA at age<55 also increased significantly from 2010-2018 to 2002-2010 (table 1), whereas incidence of myocardial infarction and of all major non-stroke vascular events at age<55 declined significantly (IRR=0.73, 95%CI 0.58-0.93, p=0.01; table 1, figure 1).

In contrast to the significant increase in incidence of TIA and stroke at age<55 during 2002-2018, there was no significant difference in incidence rates between 2002-2006 and the earlier cohort (1981-1986) or a hospital based study of young stroke from the same county in 1975-1976 (figure 2).[25] However, incidence of stroke at age ≥55 decreased significantly between 1981-1986 and 2002-2006 (IRR=0.77, 95%CI 0.69-0.87, p<.001). After 2002-2006 incidence of both stroke and TIA at age<55 increased approximately linearly in the cohort (figure 2 and eFigure 3 & eTable 2), consistent with national stroke admission rates (available for 1998 onwards) at age<60 years (figure 2), and with a significant increase in incidence of both ischaemic stroke and ICH (table 1), consistent again with national stroke admission data (eFigure 4).

Of 350 incident TIAs or ischaemic strokes at age <55 years between 2002-2018, 245 (70.0%) were of cryptogenic or small vessel disease subtypes. For each of the main TOAST subtypes the absolute number of events was greater in 2010-2018 than in 2002-2010 (table 2, eTable 3&4), but not for events caused by arterial dissection (9 in 2002-2010 vs. 7 in 2010-2018). The absolute increase in numbers was greatest for cryptogenic and small vessel events (table 2).

Of 270 incident strokes at age <55 years, most were non-disabling (n=213/78.9%), but a significant increase in incidence was seen for disabling or fatal strokes (table 1& eTable 2), with consistent results also using the initial NIHSS as a measure of stroke severity (table 1& eFigure 5). The one-year

risk of recurrent stroke at age <55 years was also similar to that at age ≥55 years (7.4% vs 9.6%, p=0.33; eFigure 6).

Among demographic characteristics of patients with stroke or TIA at age <55 years (table 2 & eTable 5-8) there was a significant increase in the proportion who were in more skilled occupations (table 2), particularly for professional/managerial occupations, which remained after adjustment for age, sex, history of hypertension, diabetes, hyperlipidaemia, myocardial infarction, peripheral vascular disease and current smoking (adjusted OR for the step change towards a more skilled occupation=1.51, 95%CI 1.17-1.96), and after adjustment for occupational status in the underlying study population (professional or managerial occupations - IRR=2.52, 95%CI 1.75-3.62; skilled - 2.10, 1.47-3.00; partially/unskilled occupations - 1.17, 0.79-1.74). The increase in the proportion in professional/managerial occupations was present for analyses of young stroke alone and for events in men and women separately (eTable 5-8). However, there was no significant increase among young patients with myocardial infarction (39/33.1% vs. 28/33.3%, eTable 9).

The absolute prevalence of traditional vascular risk factors in patients with TIA/stroke at age<55 was high (61.8%; table 2), especially for current smoking (38% vs. regional prevalence of 20% in 2011 & 15% in 2018[24]) and obesity (table 2 & eTable 10). Prevalences were broadly similar in men vs women (eTable 10), but the proportion of women having a predicted 10-year risk of cardiovascular events of ≥10% was significantly lower in men (26.2% vs 71.1% respectively; eTables 7,8,10).

Prevalence of traditional vascular risk factors in patients with TIA/stroke at age<55 was significantly higher than in the underlying population (eFigure 7) for diabetes (RR=3.47, 95%CI 2.54-4.74), hypertension (2.52, 2.04-3.12), current smoking (2.38, 1.92-2.94), and obesity (1.36, 1.07-1.72). Only 19.2% (41/214) of patients with TIA/stroke at age<55 had an ideal premorbid blood pressure (mean blood pressure <120/80 mmHg[25]) during the year prior to the index stroke/TIA, compared with 39.3% in the underlying population in 2002-2017. The prevalence of vascular risk factors in patients aged<55 was similar for TIA/stroke vs myocardial infarction, except for current smoking (37.8% vs 54.7% respectively; p<.001).

The proportion of patients with TIA/stroke at age <55 years without any traditional vascular risk factors was significantly greater in 2010-2018 versus 2002-2010 (table 2), especially among men (16/19.8% vs 65/39.9%; absolute difference +20.1% (8.6-31.6); p=0.002, p_{het}=0.05; eTable 7) and among

patients with cryptogenic events (10/18.5% vs 63/49.2%; absolute difference +30.7% (17.2-44.2); p<.001, p_{het}=0.002; eTable 11). This difference was reversed in patients with myocardial infarction aged <55 years (n/% - 39/29.1% in 2002-2010 vs. 15/14.9% in 2010-2018, p=0.01; eTable 9).

Increased incidence of TIA and stroke at age<55 years during 2002-2018 was present irrespective of any individual traditional vascular risk factor or deprivation (figure 3), and also irrespective of the number of vascular risk factors (eFigure 8).

The frequency of other potential risk factors in patients with TIA/stroke at age <55 years was also high, including for low exercise levels and history of depression or other mental health disorder (table 2 & eTable 5-8), but did not change significantly from 2002-2010 vs 2010-2018, with the possible exception of depression (table 2).

In terms of patients presenting to medical attention after TIA or stroke at age <55 years, proportions calling for medical attention or arriving in hospital within 3 hours after symptom onset did not change significantly from 2002-2010 to 2010-2018 (eTable 3). Of the 270 strokes at age <55 years, the proportion admitted to hospital was also stable over time (n= 60/61.8% vs. 103/59.9%, p=0.83). Although the use of MRI brain imaging for initial investigation increased significantly during the study period for TIA, ischaemic stroke, and stroke mimics at age<55 years, the same pattern was also seen at older ages (eFigure 9).

Discussion

In this population-based study in Oxfordshire, UK, there was a significant increase in stroke incidence from 2002-2010 vs 2010-2018 in those younger than 55, but a decrease in those 55 and older.

This finding of an absolute increase in incidence of young stroke validated UK hospital admission trends and was consistent with findings in the USA.[26-30] The relative divergence in incidence in younger vs. older patients was also consistent with a linked systematic review in which analysis of all stroke incidence studies in the 21st century in high-income countries revealed less favourable trends in stroke incidence at younger ages versus older ages.[14]

The increase in stroke incidence in younger patients from 2002-2010 to 2010-2018 could not be explained by changes in diagnostic work-up, stroke definition and adjudication, patient behaviour, hospital admission policy, or health care coverage (universal in the UK since 1948), lending support to similar changes in other studies in high-income countries which did not address these methodological issues. Moreover, the incidence of TIA also increased significantly at age<55 years in Oxfordshire as well as in USA and Denmark,[29,31] suggesting that the increase in stroke incidence is unlikely to be due to a shift in diagnosis from TIA to stroke. Although MR imaging rates increased at younger ages over time, the same magnitude of increase was also seen at older ages, in keeping with findings in the USA.[6,30]

The prevalence of traditional vascular risk factors in patients with stroke at age <55 years was high in this study, but changes in prevalence in the underlying population did not explain the increase in stroke incidence at younger ages, consistent with the few previous studies that have reported data.[5,6,32] In contrast to patients with myocardial infarction at age<55 years, there was an increase in the proportion of patients with TIA/stroke aged <55 without known traditional vascular risk factors, particularly in cryptogenic events. Taken along with the fall in incidence of myocardial infarction and peripheral vascular events at age<55 years, it seems unlikely that the overall increase in incidence of young stroke is driven by atherosclerosis. Nevertheless, traditional vascular risk factors were still more prevalent among young patients with stroke than among the underlying population, and so their identification and management are still important.

316 Vascular risk factors tend to be under-treated at younger ages, due at least partly to the widespread
317 use of model-based predictions of vascular risk to identify individuals with an apparently sufficient 10-
318 year risk of events.[23] This approach is particularly limiting in terms of primary prevention in women,
319 with 75% of women with TIA/stroke at age <55 in this study having a predicted pre-morbid risk of
320 vascular events below the current treatment threshold, highlighting the need for better prognostication
321 in young women or consideration in the meantime of the possibility of a lower treatment threshold in
322 young women. It is possible that incorporation of early disease markers, such as arterial stiffness, and
323 sex-specific risk factors, such as migraine or use of hormonal treatments, could improve
324 prognostication.

325 In terms of other risk factors for stroke, the similar increase of incidence of young stroke in men and
326 women suggests that endogenous oestrogen or hormone use are unlikely to be the driver, although
327 there was no measure of any exposure to environmental oestrogens. The increase in young stroke
328 was most marked in people doing professional or managerial jobs, which again contrasted with
329 myocardial infarction, possibly suggesting a role for work-related stress, low physical activity, and long
330 working hours, each of which are more strongly associated with risk of stroke than myocardial
331 infarction.[33] A role for atmospheric pollution is also possible,[34] and further analyses in OXVASC are
332 ongoing.

333 The increase of stroke incidence at younger ages might possibly have slowed during 2014-2018 in
334 this study, although interpretation is very difficult given limited statistical power. Similar plateauing
335 after 2010 may also be evident in some studies in North America and in Europe,[35-37] but is not
336 universal.[30] However, there is no evidence of any reversal of the increase in incidence, and no
337 reduction in incidence at ages 55-64 years was found in this study. The Global Burden of Disease
338 Study also reported increasing stroke incidence rates in people aged<70 years in low to middle-
339 income countries.[38]

340 Although a large proportion of strokes at younger ages in this study were minor as measured by
341 NIHSS at baseline, the long-term risks of future vascular events and cognitive decline might be
342 substantial. The focus over recent decades on prevention of vascular events at older ages in light of
343 the ageing population has been successful, but there is an urgent need to better understand the
344 causes and routes to prevention of stroke at younger ages, as well as potential barriers, such as risk-
345 based thresholds for preventative treatment with imperfect models. There is also a need for more

research to determine how best to prevent recurrent strokes in young patients, very few of whom have been included in secondary prevention trials, and there are particular issues relating to the potential durations of treatments required and the time-course of risk of recurrent events.

Limitations

This study has several limitations. First, as stroke is uncommon at age<55 years, there is a trade-off between the smaller sample size in prospective population-based studies of adjudicated strokes and the greater statistical power of large administrative datasets. The numbers in this study were too small to allow reliable determination of trends in incidence in narrower age bands, or of changes in uncommon risk factors over time. Second, the possibility that some unmeasured changes in recognition of stroke symptoms or in care-seeking behaviour accounted for the increase of young stroke in this study cannot be excluded, but the consistency of the age-specific divergence in stroke incidence across all studies in the linked systematic review would indicate that any such bias would have to be very widespread. The finding of similar changes in incidence of minor vs. major strokes also suggests that such recognition/ behaviour bias is unlikely to be a major factor. Third, although the possibility that more minor strokes were identified at younger ages due to the increased use of MRI during the study period cannot be excluded, use of MRI should not bias the time-trends in more major stroke. Time-trends in investigation are more problematic for studies based only on administrative data, and probably explain the apparent decline in strokes coded as unknown subtype in hospital admission data in England. Fourth, the current study results are based on a predominantly white population and might not be generalisable to other ethnic groups where stroke incidence might be higher.[39] However, a similar magnitude of increase in incidence of young stroke was also found in the other population in this study, and no differences between ethnic groups were seen in the linked systematic review.[14] Fifth, the diagnosis and management of acute MI have changed over the last 20 years including more sensitive essays for troponin over time and the introduction of primary percutaneous coronary intervention. However, the same definition for acute myocardial infarction based on symptoms, electrocardiogram changes and consistent threshold for troponin were kept throughout the study.

Conclusions

Comparing persons living in Oxfordshire, UK from 2002-2010 vs 2010-2018, there was a significant increase in stroke incidence in those younger than 55, but a decrease in those 55 and older. Given the absence of this divergence for other vascular events, further research is needed to understand the causes of this difference.

Role of the funding source

The funder of the study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgements: We are grateful to all the staff in the general practices that collaborated in the Oxford Vascular Study: Abingdon Surgery, Stert St, Abingdon; Malthouse Surgery, Abingdon; Marcham Road Family Health Centre, Abingdon; The Health Centre, Berinsfield; Key Medical Practice; Kidlington; 19 Beaumont St, Oxford; East Oxford Health Centre, Oxford; Church Street Practice, Wantage. This work uses data provided by patients and collected by the NHS as part of their care and support and would not have been possible without access to this data. The NIHR recognises and values the role of patient data, securely accessed and stored, both in underpinning and leading to improvements in research and care. LL and PMR 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.

Source of funding: The Oxford Vascular Study is funded by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (IS-BRC-1215-20008), Wellcome Trust 104040/Z/14/Z, Masonic Charitable Foundation, and Wolfson Foundation. Dr Li is in receipt of a fellowship award from the Medical Research Foundation (MRF). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of Interest/Disclosures

The authors have no conflict of interest to disclose.

References

1. PHE (2018a). A review of recent trends in mortality in England. Public Health England, 2018. . Available at:https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/827518/Recent_trends_in_mortality_in_England.pdf. Last checked on 21/03/2022.
2. Woolf SH, Schoomaker H. Life Expectancy and Mortality Rates in the United States, 1959-2017. JAMA. 2019;322(20):1996-2016.
3. Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut. 2019;68(12):2179-2185.
4. Li L, Scott CA, Rothwell PM, Oxford Vascular S. Trends in Stroke Incidence in High-Income Countries in the 21st Century: Population-Based Study and Systematic Review. Stroke. 2020;51(5):1372-1380.
5. Bejot Y, Daubail B, Jacquin A, et al. Trends in the incidence of ischaemic stroke in young adults between 1985 and 2011: The dijon stroke registry. J Neurol Neurosurg Psychiatry. 2014;85(5):509-513.
6. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: Temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79(17):1781-1787.
7. Ekker MS, Boot EM, Singhal AB, et al. Epidemiology, aetiology, and management of ischaemic stroke in young adults. Lancet Neurol. 2018;17(9):790-801.
8. Li L, Binney LE, Luengo-Fernandez R, Silver LE, Rothwell PM, Oxford Vascular S. Temporal trends in the accuracy of hospital diagnostic coding for identifying acute stroke: A population-based study. Eur Stroke J. 2020;5(1):26-35.
9. Bejot Y, Delpont B, Giroud M. Rising Stroke Incidence in Young Adults: More Epidemiological Evidence, More Questions to Be Answered. J Am Heart Assoc. 2016;5(5): e003661
10. George MG. Risk Factors for Ischemic Stroke in Younger Adults: A Focused Update. Stroke. 2020;51(3):729-735.
11. Wafa HA, Wolfe CDA, Rudd A, Wang Y. Long-term trends in incidence and risk factors for ischaemic stroke subtypes: Prospective population study of the South London Stroke Register. PLoS Med. 2018;15 (10): e1002669.
12. Correia M, Magalhaes R, Felgueiras R, Quintas C, Guimaraes L, Silva MC. Changes in stroke incidence, outcome, and associated factors in Porto between 1998 and 2011. Int J Stroke. 2017;12(2):169-179.
13. Aked J, Delavaran H, Norrving B, Lindgren A. Temporal Trends of Stroke Epidemiology in Southern Sweden: A Population-Based Study on Stroke Incidence and Early Case-Fatality. Neuroepidemiology. 2018;50(3-4):174-182.
14. Scott CA, Li L, Rothwell PM. Diverging temporal trends in stroke incidence in younger versus older people: a systematic review and meta-analysis. JAMA Neurology ePub xxx, doi xxx.
15. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004;363(9425):1925-1933.
16. Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attach and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007;370(9596):1432-1442.
17. Li L, Yiin GS, Geraghty OC, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: A population-based study. Lancet Neurol. 2015;14(9):903-913.
18. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19(5):604-607.
19. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet. 2005;366(9499):1773-1783.
20. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 1990;53(1):16-22.
21. Arbuckle DD, Harris RI, Goldacre MJ. Stroke in people under 55 years of age. Public Health. 1982;96(2):96-100.
22. Hospital admitted patient care activity. https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity. Last checked on 21/03/2022.
23. D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-753.
24. Health Survey England . https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england. Last checked on 21/03/2022.
25. Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med. 2001;345(18):1291-1297.
26. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: Temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79(17):1781-1787.
27. Morgenstern LB, Smith MA, Sanchez BN, et al. Persistent ischemic stroke disparities despite declining incidence in Mexican Americans. Ann Neurol. 2013;74(6):778-785.
28. Ramirez L, Kim-Tenser MA, Sanossian N, et al. Trends in Acute Ischemic Stroke Hospitalizations in the United States. J Am Heart Assoc. 2016;5(5): e003233

29. Ramirez L, Kim-Tenser MA, Sanossian N, et al. Trends in Transient Ischemic Attack Hospitalizations in the United States. J Am Heart Assoc. 2016;5(9): e004026
30. Lisabeth LD, Brown DL, Zahuranec DB, et al. Temporal Trends in Ischemic Stroke Rates by Ethnicity, Sex, and Age (2000–2017) The Brain Attack Surveillance in Corpus Christi Project. Neurology 2021; 97 (22): e2164-e2172
31. Tibaek M, Dehlendorff C, Jorgensen HS, Forchhammer HB, Johnsen SP, Kammersgaard LP. Increasing Incidence of Hospitalization for Stroke and Transient Ischemic Attack in Young Adults: A Registry-Based Study. Journal of the American Heart Association. 2016;5 (5): e003158.
32. Harmsen P, Wilhelmsen L, Jacobsson A. Stroke incidence and mortality rates 1987 to 2006 related to secular trends of cardiovascular risk factors in Gothenburg, Sweden. Stroke. 2009;40(8):2691-2697.
33. Kivimaki M, Jokela M, Nyberg ST, et al. Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603,838 individuals. Lancet. 2015;386(10005):1739-1746.
34. Yitshak Sade M, Novack V, Ifergane G, Horev A, Kloog I. Air Pollution and Ischemic Stroke Among Young Adults. Stroke. 2015;46(12):3348-3353.
35. Joundi RA, Smith EE, Yu AYX, Rashid M, Fang J, Kapral MK. Temporal and Age-Specific Trends in Acute Stroke Incidence: A 15-Year Population-Based Study of Administrative Data in Ontario, Canada. Can J Neurol Sci. 2020:1-5.
36. Bejot Y, Duloquin G, Thomas Q, et al. Temporal Trends in the Incidence of Ischemic Stroke in Young Adults: Dijon Stroke Registry. Neuroepidemiology. 2021;55(3):239-244.
37. Madsen TE, Khoury JC, Leppert M, et al. Temporal Trends in Stroke Incidence Over Time by Sex and Age in the GCNKSS. Stroke. 2020;51(4):1070-1076.
38. GBD 2019 Stroke Collaborators. 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 (10):795-820.
39. Howard G, Moy CS, Howard VJ, et al. Where to Focus Efforts to Reduce the Black–White Disparity in Stroke Mortality. Incidence Versus Case Fatality?. Stroke. 2016; 47(7): 1893-1898.

Table 1 Standardised incidence per 10,000 per year (95%CI) for all acute vascular events at age<55 years in Oxfordshire from 1981 to 2018 stratified by sex, stroke subtypes and severity

	OCSP 1981-1986	OXVASC 2002-2006	Absolute difference	Relative difference	p[e]	OXVASC: 2002-2010	2010-2018	Absolute difference	Relative difference	p[e]
Stroke	1.96 (1.37-2.55)	1.68 (1.18-2.18)	-0.29 (-1.41, 0.57)	0.85 (0.56-1.31)	0.47	1.88 (1.51-2.25)	3.14 (2.67-3.61)	1.27 (0.67,1.86)	1.67 (1.31-2.14)	<.001
TIA	0.74 (0.40-1.07)	0.69 (0.37-1.01)	-0.04 (-0.51, 0.42)	0.94 (0.49-1.80)	0.85	1.04 (0.76-1.32)	1.95 (1.58-2.32)	0.91 (0.44, 1.37)	1.87 (1.36-2.57)	<.001
Other acute vascular events[a]	-	-				3.01 (2.54-3.48)	2.21 (1.81-2.60)	-0.80 (-1.42, -0.18)	0.73 (0.58-0.93)	0.01
MI and SCD	-	-				2.60 (2.16-3.04)	1.94 (1.57-2.31)	-0.67 (-1.24, -0.09)	0.74 (0.58-0.96)	0.02
Peripheral vascular events	-	-				0.43 (0.25-0.61)	0.33 (0.18-0.48)	-0.10 (-0.34, 0.13)	0.77 (0.41-1.43)	0.40
For strokes only:										
Sex										
Men	2.25 (1.36-3.15)	1.86 (1.13-2.59)	-0.39 (-1.55,0.76)	0.83 (0.47-1.45)		2.07 (1.53-2.62)	3.71 (3.00-4.42)	1.64 (0.74,2.53)	1.79 (1.30-2.46)	
Women	1.66 (0.90-2.42)	1.48 (0.79-2.16)	-0.18 (-1.20,0.84)	0.89 (0.46-1.71)		1.67 (1.17-2.18)	2.53 (1.92-3.13)	0.86 (0.07,1.65)	1.51 (1.03-2.22)	
Stroke subtype										
Ischaemic stroke	1.33 (0.85-1.82)	1.00 (0.62-1.39)	-0.33 (-0.95,0.29)	0.75 (0.44-1.29)		1.26 (0.96-1.57)	2.43 (2.02-2.85)	1.17 (0.65,1.68)	1.92 (1.44-2.57)	
ICH	0.25 (0.03-0.48)	0.12 (0.00-0.26)	-0.13 (-0.39, 0.13)	0.49 (0.11-2.08)		0.23 (0.10-0.36)	0.45 (0.28-0.63)	0.23 (0.01, 0.45)	2.00 (1.02-3.91)	
SAH	0.38 (0.13-0.63)	0.55 (0.26-0.84)	0.17 (-0.21, 0.55)	1.46 (0.63-3.35)		0.39 (0.22-0.56)	0.26 (0.12-0.39)	-0.13 (-0.35, 0.09)	0.66 (0.33-1.31)	
Stroke severity (NIHSS at presentation)[bc]										
Minor stroke (NIHSS<3)	-	-				0.94 (0.68-1.20)	1.79 (1.44-2.14)	0.85 (0.41, 1.29)	1.90 (1.36-2.66)	<.001
Ischaemic stroke	-	-				0.88 (0.62-1.14)	1.63 (1.29-1.97)	0.75 (0.32, 1.17)	1.85 (1.30-2.61)	
ICH	-	-				0.06 (0.00-0.12)	0.16 (0.06-0.27)	0.10 (-0.02, 0.23)	2.80 (0.82-9.59)	
Major stroke (NIHSS≥3)	-	-				0.55 (0.35-0.75)	1.10 (0.82-1.38)	0.54 (0.20, 0.89)	2.00 (1.30-3.08)	0.002
Ischaemic stroke	-	-				0.38 (0.21-0.55)	0.80 (0.56-1.04)	0.42 (0.13, 0.71)	2.11 (1.26-3.52)	
ICH	-	-				0.17 (0.06-0.28)	0.29 (0.15-0.44)	0.12 (-0.06, 0.31)	1.73 (0.77-3.87)	
Stroke outcome (mRS change at 1 month)[bd]										
Non-disabling stroke	0.98 (0.56-1.40)	0.93 (0.56-1.30)	-0.05 (-0.61, 0.51)	0.95 (0.53-1.70)		1.19 (0.89-1.49)	2.34 (1.94-2.75)	1.15 (0.65, 1.65)	1.97 (1.46-2.64)	
Ischaemic stroke	0.89 (0.49-1.29)	0.89 (0.52-1.25)	0.00 (-0.54,0.54)	1.00 (0.55-1.83)		1.13 (0.84-1.42)	2.14 (1.75-2.53)	1.01 (0.52,1.49)	1.89 (1.39-2.57)	
ICH	0.09 (0.00-0.23)	0.04 (0.00-0.12)	-0.05 (-0.21, 0.10)	0.43 (0.04-4.83)		0.06 (0.00-0.12)	0.20 (0.08-0.32)	0.14 (0.01, 0.28)	3.45 (1.06-11.22)	
Disabling or fatal stroke	0.60 (0.27-0.94)	0.20 (0.02-0.37)	-0.40 (-0.78, -0.03)	0.33 (0.12-0.93)		0.30 (0.15-0.45)	0.55 (0.35-0.74)	0.24 (0.00, 0.49)	1.81 (1.00-3.29)	
Ischaemic stroke	0.44 (0.16-0.72)	0.12 (0.00-0.25)	-0.33 (-0.64,-0.02)	0.26 (0.07-0.93)		0.13 (0.03-0.23)	0.29 (0.15-0.43)	0.16 (-0.01, 0.33)	2.21 (0.94-5.24)	
ICH	0.16 (0.00-0.34)	0.08 (0.00-0.20)	-0.08 (-0.29, 0.14)	0.52 (0.08-3.22)		0.17 (0.06-0.28)	0.25 (0.12-0.39)	0.09 (-0.09, 0.26)	1.50 (0.66-3.45)	

TIA=transient ischaemic attack; MI=myocardial infarction; SCD=sudden cardiac death; ICH=intracerebral haemorrhage; SAH=subarachnoid haemorrhage. mRS=modified rankin scale. a.including acute myocardial infarction, peripheral vascular event and sudden cardiac death; b. analysis excluding SAH. c. NIHSS calculates the NIH Stroke Scale for quantifying stroke severity. Scores range from 0 to 42, with higher scores indicating greater severity. d. the modified ranking scale ranges from 0-6, with higher scores indicating greater disability. Disabling or fatal stroke is defined as new disability or death (mRS>2) using the 1 month mRS, or as progression of disability (one score increase in mRS) in those with premorbid disability (premorbid mRS>2). e. p values were referring to relevant difference in stroke incidence.

Table 2 Demographics, risk factors, medication at baseline and premorbid blood pressure in young patients (age<55) with incident TIA or stroke

	2002-2010 (n=148)	2010-2018 (n=273)	Absolute difference (95%CI)
Event type			
Ischaemic events	n=116	n=234	
Cardioembolic	18 (15.5)	25 (10.7)	-4.8 (-12.5, 2.9)
Large artery disease	8 (6.9)	14 (6.0)	-0.9 (-6.4, 4.6)
Small vessel disease	20 (17.2)	43 (18.4)	+1.2 (-7.3, 9.7)
Cryptogenic	54 (46.6)	128 (54.7)	+8.1 (-3.0, 19.2)
Unknown/Multiple/Other	16 (13.8)	24 (10.3)	-3.5 (-10.9, 3.9)
Intracerebral haemorrhage	n=12	n=25	
Lobar haemorrhage	5 (41.7)	11 (44.0)	+2.3 (-31.7, 36.3)
Deep/posterior haemorrhage/intraventricular	7 (58.3)	14 (56.0)	-2.3 (-36.3, 31.7)
Subarachnoid haemorrhage	n=20	n=14	
Demographics			
Mean age, y (SD)	45.8 (7.5)	45.2 (9.1)	-0.6 (-2.3, 1.1)
Male	81 (54.7)	165 (60.4)	+5.7 (-4.2, 15.6)
Female	67 (45.3)	108 (39.6)	-5.7 (-15.6, 4.2)
Occupation[a]	(n=135)	(n=249)	
Professional/managerial	33 (24.4)	103 (41.4)	+17.0 (7.5, 26.5)
Skilled	47 (34.8)	87 (34.9)	+0.1 (-9.9, 10.1)
Partially/non-skilled	50 (37.0)	51 (20.5)	-16.5 (-26.1, -6.9)
Unemployed	5 (3.7)	8 (3.2)	-0.5 (-4.4, 3.4)
Traditional risk factors			
Current smoker	63 (42.6)	95/270 (35.2)	-7.4 (-17.2, 2.4)
Ex-smoker	27 (18.2)	65/270 (24.1)	+5.8 (-2.2, 13.9)
Known hypertension	43 (29.1)	61 (22.3)	-6.7 (-15.5, 2.1)
Known hyperlipidaemia	37 (25.0)	36 (13.2)	-11.8 (-19.9, -3.8)
Known diabetes	12 (8.1)	25 (9.2)	+1.0 (-4.5, 6.6)
Known atrial fibrillation	3 (2.0)	5 (1.8)	-0.2 (-3.0, 2.6)
None of the above risk factors	45 (30.4)	115/271 (42.4)	+12.0 (2.6, 21.5)
Previous atherosclerotic disease	11 (7.4)	11 (4.0)	-3.4 (-8.2, 1.4)
Overweight or obese	83/144 (57.6)	158/262 (60.3)	+2.7 (-7.3, 12.7)
Obese	37 (25.7)	74 (28.4)	+2.7 (-6.3, 11.6)
Regular alcohol use	36 (24.3)	62/266 (23.3)	-1.0 (-9.6, 7.6)
10-year risk of cardiovascular event[b]	(n=146)	(n=257)	
<10%	69 (47.3)	121 (47.1)	-0.2 (-10.3, 9.9)
10-29%	66 (45.2)	124 (48.2)	+3.0 (-7.1, 13.1)
≥30%	11 (7.5)	12 (4.7)	-2.8 (-7.8, 2.2)
Other potential risk factors			
Exercise (none/below average)	40/124 (32.3)	77/233 (33.0)	+0.8 (-9.4, 11.0)
Previous migraine	45 (30.4)	71/272 (26.1)	-4.3 (-13.4, 4.8)
Depression	31 (20.9)	82/272 (30.1)	+9.2 (0.7, 17.7)
Previous autoimmune disease	16 (10.8)	47 (17.2)	+6.4 (-0.3, 13.1)
Previous cancer	8 (5.4)	11 (4.0)	-1.4 (-5.7, 2.9)
Previous venous thrombosis	4 (2.7)	6 (2.2)	-0.5 (-3.6, 2.6)
Family history of young stroke in parents	8/118 (6.8)	14/229 (6.1)	-0.7 (-6.2, 4.8)
Family history of young stroke in siblings	1/111 (0.9)	10/216 (4.6)	+3.7 (0.4, 7.0)
Premorbid medication			
Currently on OCP or HRT[c]	16 (23.9)	22 (20.4)	-3.5 (-16.2, 9.2)
Antihypertensive	34 (23.0)	47 (17.2)	-5.8 (-13.9, 2.4)
Antidepressants	16 (10.8)	32 (11.7)	+0.9 (-5.3, 7.2)
Statin	14 (9.5)	31 (11.4)	+1.9 (-4.1, 7.9)
Antiplatelet	9 (6.1)	17 (6.2)	+0.1 (-4.7, 4.9)
Anticoagulant	4 (2.7)	9 (3.3)	+0.6 (-2.8, 4.0)
Premorbid blood pressure (mmHg)[d]	(n=146)	(n=249)	
Mean (SD) SBP	131.7 (17.7)	127.9 (13.9)	-3.8 (-7.0, -0.6)
Mean (SD) DBP	80.8 (10.7)	79.0 (9.9)	-1.8 (-3.9, 0.3)
Mean BP≥140/90	46 (31.5)	54 (21.7)	-9.8 (-18.9, -0.7)
Any BP≥140/90	86 (58.9)	144 (57.8)	-1.1 (-11.2, 9.0)

Comparisons of additional factors in eTable 5.BMI=body mass index; OCP=oral contraceptive pills; HRT=hormone replacement therapy; SBP=systolic blood pressure; DBP=diastolic blood pressure; BP=blood pressure. a. Examples of the occupation categories are detailed in eMethods; b. based on the non-laboratory version of the Framingham General Cardiovascular risk score; c. only for female; d. Median of most recent blood pressure to baseline=322 days.

Figure legends

Figure 1 Temporal change in standardised stroke incidence at age<55 years (A) vs. age≥55 years (B) and at age<55 years for stroke vs. all other incident major vascular events (C)

Other major vascular event included acute myocardial infarction, peripheral vascular event and sudden cardiac death. The study year started from 1st April and ended on 31st March the next year.

Figure 2 Temporal changes of standardised stroke incidence in those aged <60 years in England (hospital admission data of any stroke; 1998-2018) and in those aged<55 years in Oxfordshire (stroke incidence studies; 1975-1976;[21] 1981-1986; 2002-2018)

Number of events and population at risk for each study reported in eTable 12. For the population-based study between 2002-2018, the study year started from 1st April and ended on 31st March the next year.

Figure 3 Temporal changes of TIA/stroke incidence at age<55 years stratified by presence of individual risk factors.

A. Smoking; B. Obesity (body mass index ≥30); C. Blood pressure (hypertension=blood pressure≥140/90mmHg); D. Diabetes (fasting glucose 126mg/dl or higher on two separate tests); E. Sex; F. Deprivation. The study year started from 1st April and ended on 31st March the next year. Populations at risk were based on the prevalence of each risk factor in the underlying population during that time-period. Prevalence of smoking, obesity, hypertension, diabetes were determined from the data reported for South East England in the Health Survey for England. Distributions of sex and deprivation were determined for the underlying population by data extraction from study GP practices and IMD stands for Indices of multiple deprivation. Standardised relative incidence rates (IRR) for each strata were presented with 95% confidence intervals