Diverging temporal trends in stroke incidence in younger versus older people: a systematic review and meta-analysis

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Key Points

Question: What is happening to stroke incidence in younger vs older adults in high-income countries in the 21st century?

Findings: In a systematic review of 50 studies, trends in incidence of young stroke were heterogeneous, but a divergent trend was evident across all studies, with a fall incidence at older ages not being seen at younger ages.

Meaning: The consistently divergent temporal trend in stroke incidence at younger vs. older ages highlights the urgent need to better understand aetiology and prevention of stroke at younger ages.

Abstract

Importance: Overall stroke incidence is falling in high-income countries, but data on time-trends in incidence of 'young stroke' (age<55 years) are conflicting. We hypothesised that an age-specific divergence in incidence, with less favourable trends at younger versus older ages, might be a more consistent underlying finding across studies.

Objective: To do a systematic review to compare temporal trends in incidence of stroke at younger vs older ages in high-income countries.

Data Sources: PubMed and Embase from inception to February 2022 and one unpublished population-based study (Oxford Vascular Study).

Study Selection: Studies reporting age-specific stroke incidence in high-income countries at more than one time point.

Data Extraction and Synthesis: For all retrieved studies, two authors independently reviewed the full text against the inclusion criteria to establish their eligibility. Meta-analysis was performed with the inverse variance weighted random effects model. We reported according to PRISMA guidelines.

Main Outcome(s) and Measure(s): Age-specific divergence (<55 vs ≥55-years) in temporal trends in stroke incidence (relative temporal rate ratio - RTTR) in studies extending to at least the year 2000. RTTR calculated for each study and pooled by random effects meta-analysis, with stratification by administrative vs prospective population-based methodology, sex, stroke subtype (ischaemic vs intracerebral haemorrhage/ICH vs subarachnoid haemorrhage/SAH) and geographical region.

Results: Among 50 studies in 20 countries, 26 (13 prospective population-based; 13 administrative) reported data allowing calculation of the RTTR for stroke incidence at younger vs older ages across two or more periods, the latest extending beyond year 2000. Reported trends in absolute incidence of young stroke were heterogeneous, but all studies showed a less favourable trend in incidence at younger vs. older ages (pooled RTTR=1.57, 95%CI 1.42-1.74). The overall RTTR was consistent by stroke subtype (ischaemic -1.62, 1.44-1.83; ICH - 1.32, 0.91-1.92; SAH-1.54,1.00-2.35) and by sex (men-1.46, 1.34-1.60; women – 1.41, 1.28-1.55), but was greater in studies reporting trends solely after year 2000 (1.51, 1.30-1.70) vs. solely before (1.18, 1.12-1.24), and was highest in population-based studies in which the most recent reported period of ascertainment started after 2010 (1.87, 1.55-2.27).

Conclusions and Relevance: Temporal trends in stroke incidence are diverging by age in high-income countries, with less favourable trends at younger versus older ages, highlighting the urgent need to better understand aetiology and prevention of stroke at younger ages.

Introduction

Stroke incidence has declined by 42% over the last four decades in high-income countries.[1] However, there have been several reports that incidence at younger ages (aged <55 years) appears to be increasing in the USA and some other countries.[2-5] This finding could be an early signal of a reversal in younger generations of the decline in vascular event rates seen over the last 50 years in older generations.

Such a reversal would be consistent with recent trends in colorectal cancer incidence and in overall mortality rates at younger ages in several high-income countries,[6-8] but uncertainty remains over the validity of apparent trends in incidence of young stroke.[2] First, many studies relied only on routinely collected administrative data, often based on hospital admissions or deaths, which are prone to bias as diagnostic coding practices and admission policies change over time.[9] Second, increased use of brain imaging, particularly diffusion-weighted-imaging, has prompted new definitions of strokes,[10] which may have resulted in diagnostic drift between transient ischaemic attack (TIA) and stroke. Third, given that a significant proportion of the strokes at younger ages are minor events,[11,12] studies with less rigorous ascertainment of all events might underestimate trends at younger ages, and studies in which methods of ascertainment improved over time might overestimate trends.[13] Finally, although stable or decreasing incidence of young stroke has been reported in some countries,[14-16] it is uncertain whether such trends might still be less favourable than those at older ages.

In light of these uncertainties, and to address the apparent heterogeneity between studies in trends in incidence of young stroke, we aimed to determine if there was an age-specific divergence in trends in stroke incidence in high-income countries. We did a systematic review of all published studies reporting temporal trends in stroke incidence in high-income countries at younger ages and determined the temporal trend in incidence at younger ages relative to that at older ages, with stratification by study and clinical characteristics. We also

included data from an additional population-based study (Oxford Vascular Study) now reported in a companion paper.[17]

Methods

This systematic review followed a pre-specified protocol and is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses[18] (online appendix).

We searched for studies reporting stroke incidence in high income countries at younger ages (usually <45 years; <55 years; or <60 years) over at least time two periods (full search strategy available in e-table-1). We also scrutinised the reference lists of all relevant reviews, and those of the eligible publications. After exclusion of duplicate studies, titles and abstracts were screened by two authors (CS and LL). For all retrieved studies, two authors (CS and LL) independently reviewed the full text against the inclusion criteria to establish their eligibility and where differences arose these were discussed with the third author (PMR).

Our study inclusion and exclusion criteria are detailed in e-table 2. Briefly, eligible studies could be "population-based" (i.e. community based studies with multiple ascertainment methods) or "administrative" (i.e. relying only on routinely collected coding data). Eligible administrative studies must have included stroke incidence data during at least two periods between from 1970 onwards, with the latest period extending to 2000 or beyond. For population-based studies we also included reports if they extended to at least 1990. Studies were included irrespective of their definition of stroke, type of event (first ever, first, and combined first and recurrent), or stroke subtype (ischaemic stroke (IS), intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH) or stroke events combined). Studies reporting stroke hospitalisation rates only (with no population denominator) were excluded.

Data were extracted and entered onto a predesigned electronic form by CS (e-figure 1) and LL checked the extracted data. We contacted three authors[19-21] for clarification of results in published papers of which one responded.[19]

No generic study quality appraisal tool incorporates the important items most relevant to reliable estimation of stroke incidence.[22] We therefore developed a domain based approach to assess the quality of the included studies adapted from that used by van Asch et al. [23]

Domains assessing case finding methods relevant to stroke incidence studies were chosen based on the "ideal stroke incidence study" criteria,[22] and the methods used to ensure ascertainment and adjudication of minor stroke (e-table 5).

For each study we extracted the number of strokes, denominator population, incidence rates and 95% confidence intervals(CI) in a younger age group (ideally <45 and <55 years) and older age group (ideally ≥55 and ≥45) as well as standardised rates for each reported time period. Methods for calculating incidence rates from the data provided in individual studies are detailed in e-methods-2. Where stroke incidence rates or other requisite data were only reported graphically, these were estimated manually where possible. When sufficient data were available 95%CI for incidence rate estimates were calculated using the Poisson distribution. For studies which reported stroke incidence in different age groups, sexes, ethnicities or stroke subgroups, where raw numbers were not available, inverse variance weighted fixed effects meta-analysis were used to generate summary incidence rates. If change in incidence was only reported qualitatively or as numerical trends these were extracted and summarised. In studies where change of TIA incidence was reported alongside changes of stroke, we also summarised the incidence change of TIA at younger ages.

Statistical analysis

Our primary analyses were confined to studies reporting at least one time period after 2000. We first plotted the absolute incidence of young stroke (or ischaemic stroke) during the different time periods reported, with separate plots for population-based vs administrative studies to visually assess trends. We also plotted the incidence of young stroke (at age <55 years where possible) divided by the incidence of stroke at older ages (where possible ≥55 years) at each time point (the incidence ratio). Where two or more studies reported from the same dataset the decision regarding which to include in the plots was based on the following hierarchy: 1.most recent time period, 2.studies reporting <55 years, 3.other reported age cut

off under 55 years. Plots were also produced to visually assess trends in the following pre-specified subgroups: <45 years, <55 years, <60 years.

For studies providing sufficient data, we calculated the ratio of the incidence during the latest vs earliest reported time period (incidence rate ratio – IRR) for the younger age group and for the older age group separately. To minimise any inclusion bias, we also recorded the direction of any temporal trend in incidence in those studies that reported some measure of the trend without reporting sufficient data to calculate the IRR, allowing a qualitative analysis of the direction of the trends by vote counting i.e. we compared the number of positive studies (increase in stroke incidence between the two time periods, regardless of statistical significance) with the number of negative studies (decrease in stroke incidence between the two time periods) in the younger and older age groups respectively. A binomial probability test (sign test) was used to assess the significance of evidence for the existence of an association in either direction.[24] Where two or more studies or papers reported from the same dataset the decision regarding which to include in the vote count and sign test used the following hierarchy:1. most recent time period; 2. age cut-off closest to 55 years; 3. all stroke preferred over ischaemic stroke.

For studies where IRR was calculable for both younger and older age groups, we estimated the relative temporal change in incidence at younger vs. older ages within each study by deriving the relative temporal trend ratio (RTTR). The RTTR was calculated within each study by dividing the IRR in the younger age group (where possible, <55 years) by the IRR of the older age group (where possible ≥55 years) (see e-methods-3 for further details of the RTTR and the calculation of a 95%CI), thereby providing an estimate that could be meta-analysed across studies and might help to overcome some between-study differences in methodology and within-study changes in ascertainment, diagnosis and investigation.

The RTTRs for each study were pooled with inverse variance weighted random effects meta-analysis to generate a pooled RTTR with 95%CI. We estimated statistical heterogeneity using Cochran's Q test. Our primary analysis included studies reporting all

stroke or ischaemic stroke with an age comparison of <55 vs ≥55 years or <50 vs ≥ 50 years, with stratification by study methodology and by time period (most recent reported period of ascertainment started after vs before 2010). Methods of our secondary analysis are fully detailed in e-methods-4, briefly we stratified by study characteristics (size of study, geographical region, time period, duration, case ascertainment methods) and clinical characteristics (age, sex, and stroke subtype). To further assess the impact of study duration on the RTTR, for each age group we fitted a linear regression model (i.e. assuming a linear trend) to all reported incidence rates at all available time points to estimate the predicted IRR between 2000 and 2010 for each study. We then calculated the predicted RTTR over this 10-year period ($RTTR_{10}$) for each study and also derived pooled estimates by meta-analysis.

The proportion of overall heterogeneity in RTTR across all studies was calculated by an inverse variance weighted linear regression of RTTR against the above study characteristics including study size, age cut-off used, region, study period, duration, and ascertainment quality in univariate and multivariate analyses.[95]

All analyses were done using SPSS version 25 and Stata version 16.1

Results

Our search of databases and other sources (e-figure 2) identified 29,221 records, with 463 potentially relevant full text articles assessed after screening of titles and abstracts. Of these, 49 eligible published studies (e-figure 2 and e-table 3)[3,4,12,14-16,19-21,25-89] reported some data on temporal trend in incidence of stroke at younger ages with ascertainment until at least 1990. Addition of our own concurrently published data,[17] resulted in 50 studies (table 1, e-table 4; 20 prospective population-based; 30 based on routinely collected administrative data). These 50 studies were done in 20 countries, with observation periods ranging from 6 to 37 years. Characteristics and results of individual studies are provided in e-table 4 and study quality in e-table 5. Reports differed in relation to time-periods covered and age cut-offs used for "young stroke".

Two studies reported data on only haemorrhagic stroke.[65,80] Among the 48 studies reporting at least some data on temporal trend in incidence of all young stroke or young ischaemic stroke until at least 1990, incidence rate ratios (latest vs earliest reported time period) were calculable in 36 (e-figure 3) and some other measure of the direction of any temporal trend was reported in 12 (e-tables 6-8). After excluding overlapping studies of administrative data and studies that did not ascertain events after 2000, 36 studies reported unique data on temporal trends in incidence of young stroke (e-figure 4). Comparing the latest vs earliest reported incidence rate in each study (e-table 8), one study stated only that incidence was 'stable',[34] and another reported stable incidence graphically.[61] Among the remaining 34 studies, 24 (71%) reported at least a trend towards an increase in young stroke or young ischaemic stroke incidence and 10 (29%) reported at least a trend towards a decrease (sign test; p=0.02).

Of the 36 studies that reported unique data on temporal trends in incidence of young stroke to at least 2000, 33 also reported at least some data on the temporal trend at older ages (e-figure 4, e-table 8). Of these 33 studies, 29 (88%) reported at least a trend towards

decreasing incidence at older ages and only four (12%) reported a trend towards increasing incidence (sign test; p<0.001).

A total of 25 studies reported unique quantitative data on incidence of young stroke during at least one period beyond 2000 and during previous period(s) before or after 2000 (figure 1). Among 13 population based studies, the trends in young stroke incidence were inconsistent, with a trend towards increased incidence in eight studies and either stable or a trend towards a decrease in five (South London (UK),[14] Porto (Portugal), [15] Orebro (Sweden), [43] Lund (Sweden)[16] and Valley of Aosta (Italy)[35] ; figure 1, top). However, when the incidence of stroke at older ages was taken into account, the relative incidence of stroke at younger versus older ages did increase after 2000 in all 12 studies (figure 1, bottom). Results were also consistent for administrative data (figure 1).

Twenty six studies (e-figure 4) reported incidence during at least one period beyond 2000 and during previous period(s) before or after 2000 and had sufficient data to allow us to derive a quantitative measure (relative temporal trend ratio - RTTR) of the divergence in incidence trend at younger vs. older ages. When these data were used to calculate the temporal trend in incidence at younger vs older ages (RTTR), the divergence of age-specific incidence was consistent across all studies (26 vs 0; p<0.001), with a less favourable trend at age <55 vs ≥55 years (i.e. RTTR>1), and was highly significant on pooled analysis (RTTR=1.57, 95%CI 1.42-1.74, p<0.001; figure 2). In addition, 3[55,61,63] of the 4[55,61,63,85] further similar studies that did not report quantitative data sufficient to calculate an exact RTTR did provide qualitative information indicating that the RTTR would have been greater than one.

There was, however, still heterogeneity between studies in RTTR i.e. in the absolute extent to which the trend in incidence was less favourable at age <55 vs ≥55 years (figure 2; p_{het}<0.001). Standardising the RTTR to a 10-year period reduced between-study differences to some extent, but heterogeneity remained (p_{het}=0.001; e-figure 6). The diverging trend at younger vs. older ages was more pronounced in those population-based studies in which the most recent reported period of ascertainment started after 2010 (1.87, 1.55-2.27). Having

the most recent period starting after 1st January 2010 and differences in ascertainment of minor stroke explained 78% of the heterogeneity in RTTR between population-based studies. There was also heterogeneity in RTTR between administrative studies (pooled RTTR=1.50, 1.32-1.71; p_{het}<0.001), 74% of which was explained by differences in the diagnostic codes used for stroke (e-figure 7). Overall, study size, age cut-offs used, study region, study period, study duration, and quality of ascertainment explained 88% of all of the heterogeneity in RTTR across all included studies.

On combining all 26 studies irrespective of study methods (figure 3, e-figure 7), the lowest age-specific divergence in incidence was seen in three Southern European studies (RTTR=1.02, 0.91-1.15), and the most pronounced divergence in North American studies (1.87, 1.54-2.27, n=6). There was no evidence of higher RTTRs in smaller vs larger studies (figure 3; e-figure 7). Eight studies that reported time trends of stroke incidence (e-table 9) also included data on trends in TIA incidence at younger ages, with trends being broadly consistent in direction between TIA and stroke in each study, helping to exclude confounding of stroke incidence trends by temporal changes in diagnosis, imaging or definition.

In relation to clinical characteristics (figure 3), the RTTR pooled across all 26 studies was consistent by sex (data available from 18 studies), although the RTTR in population-based studies (table 2) tended to be larger and less heterogeneous in men (RTTR=1.73, 1.43-2.11; p_{het}=0.12) than in women (1.44, 1.05-1.97, p_{het}<0.001). Results were unrelated to age cut-off, but there were insufficient studies reporting ethnic specific incidence trends to allow pooled analysis, although age-specific divergence in stroke incidence was consistent within studies where it could be estimated (e-table 10), and were consistent in Whites (e-table 10). Age-specific divergence was also similar for ischaemic strokes (RTTR=1.62, 95% CI 1.44-1.83; n=14) and for haemorrhagic strokes (ICH - 1.32, 0.91-1.92, n=8; SAH - 1.54, 1.00-2.35, n=4; figure 3 & e-figure 7).

With regard to studies covering different time periods, we compared results for studies spanning adjacent decades (figure 3, e-figure 7 & e-table 11). The pooled RTTR was greater

for comparison of incidence trends during 2000-2010 than those during 1990-2000, with consistent results within six of the seven population-based studies that spanned these decades (e-table 11).

Discussion

We showed that age-specific divergence in stroke incidence was present to some extent in all studies in high-income countries in the 21st century that reported quantitative data. Although trends in absolute incidence at younger ages were inconsistent, the trend was always less favourable than at older ages. This age-specific divergence was broadly similar by stroke subtype, sex and ethnic group.

Although this age-specific divergence in incidence might seem surprising, similar divergence has been reported in high income countries for other conditions that share risk factors with stroke, such as colorectal cancer, for which the increasing incidence only at younger ages has been attributed to age-specific trends in obesity, lack of exercise, and poor diet.[8] Indeed, there is a tendency for vascular risk factors to be under-treated at younger ages, due at least partly to the widespread use treatment thresholds based on model-based predictors of vascular risk, such that a large proportion of young stroke patients, especially women, have predicted premorbid vascular risks below the current treatment threshold.[17] However, although we showed that traditional vascular risk factors were highly prevalent and poorly controlled among young stroke patients compared to the age-matched underlying population in our population,[17] they did not appear to explain the increase of stroke incidence, particularly as incidence of myocardial infarction at younger ages is continuing to fall.[17]

The impact of other emerging vascular risk factors, such as air pollution appear to be age-specific,[90] and long working hours is more strongly associated with risk of stroke than myocardial infarction.[96] We showed that the age-specific divergence in stroke incidence was consistent for men and women, suggesting that sex-specific factors, such as pregnancy and oral contraceptive use, are unlikely to be major drivers, although we could not rule out an effect of possible increases in exposure to environmental oestrogen over time. There was some suggestion that trends were more heterogeneous in women, which might reflect regional and temporal variation in the decline in use of hormone replacement therapy in the early 2000s, and which could have also offset an otherwise greater increase in stroke

incidence in women.[92] On the other hand, there was also a higher proportion of women with stroke at older ages, especially with atrial-fibrillation related strokes,[93] and increased use of direct oral anticoagulants (DOACs) in primary prevention may change the incidence of stroke at older ages in the future.

Irrespective of potential mechanisms, could the apparent age-specific divergence in stroke incidence be artefact? In relation to potential biases in our analyses, we attempted several mitigations. First, to limit any potential inclusion bias we included studies that reported only qualitative data on trends in incidence, with a simple but fully inclusive analysis of the qualitative direction of incidence trends (sign test). Second, our within-study measure of age-specific divergence in stroke incidence (RTTR) would tend to underestimate divergence. The estimates of RTTR were based only on the crude incidence of stroke in each of the two age groups and would not therefore fully adjust for the ageing of the underlying study population over time. Any fall in age-specific stroke incidence in the older age group would be underestimated by the crude incidence rate due to the continuing population aging that will have occurred during these studies in high-income countries. Since this same bias would not be seen in the younger age group, the RTTR will have tended to underestimate divergence.

In relation to biases due to methods of the original studies, the most important problem in interpreting temporal trends in incidence of stroke at younger ages is the preponderance of more minor events in this age group,[11-12] increasing the potential for bias due to trends in coding practice, hospital admission policy, or patient behaviour that might result in increasing diagnosis and/or ascertainment of minor strokes over time. However, age-specific divergence was most pronounced in population-based incidence studies that had consistent methods of ascertainment over time and that used methods that were likely to have minimised under-ascertainment of minor strokes irrespective of age or study period. We were also reassured by the same directional change of incidence of TIA and stroke at younger ages in studies that reported both, and by the observation in our own study that the incidence of disabling stroke at younger ages is increasing.[17]

In relation to other potential biases, the relative increase in MR brain imaging use over time in TIA/stroke referrals has been similar at younger versus older ages in our own study and where it has been reported elsewhere.[4,17,49] Moreover, the similar increase in incidence of TIA and stroke at younger ages does not suggest diagnostic drift from TIA to stroke due to increased use of MRI. Furthermore, we found similar age-specific divergence for ischaemic and haemorrhagic strokes, with the latter being less likely influenced by the use of MRI. In relation to patient behaviour, we did not find any temporal change in initial perception or behaviour after stroke symptom onset in younger patients in Oxfordshire, UK.[17]

Our analysis does nevertheless have several limitations. First, although we derived the RTTR to illustrate the extent to which the temporal trend incidence was less favourable at younger vs. older ages irrespective of the absolute direction of the overall trend in incidence, and to pool estimates of age-specific divergence across studies and quantify heterogeneity, it is a crude summary statistic with several limitations (e-methods 3). Second, overall heterogeneity between studies in RTTR was highly statistically significant, although much of the variation was explained by study methodology, and there was qualitative consistency in direction of effect. Moreover, the statistical significance of heterogeneity across administrative studies also mainly reflects the very large sample sizes and narrow confidence intervals. Third, we included only studies published in English, and restricted our review to high-income countries which may have influenced our generalisability. However, the most recent Global Burden of Disease study showed that stroke incidence rates in people aged <70 years increased by 14% between 1990 and 2019 in low and middle-income countries, although more detailed time trends in younger age groups were not presented.[91] Fourth, we only searched for data collected up to March 2020, as the COVID-19 pandemic is likely to have had unpredictable impacts on stoke incidence, patient behaviour, and the feasibility of reliable case-ascertainment. Fifth, there is no standardised definition of “young stroke” but we showed that the results were consistent with different cut-offs under the age of 60 years.

Continued monitoring of age-specific divergence in stroke incidence is crucial, and future studies should adhere to the gold standard reporting guidelines,[22] with analyses stratified by age, sex, ethnicity, and stroke severity. The Global Burden of Disease study[91] and the Global Outcome Assessment Life-long after stroke in young adults (GOAL) initiative[94] might provide further region-specific data. We found that age-specific divergence was least evident in Southern Europe, but data were only available from three studies.

In conclusion, in contrast to substantial falls in incidence of stroke at older ages in high-income countries, there have been convincing divergent temporal trends in stroke incidence at younger vs. older ages thus far in the 21st century. Although the focus over recent decades on prevention of vascular events at older ages in light of the ageing population has clearly been successful, there is an urgent need to better understand the causes and routes to prevention of stroke at younger ages.

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Conflict of Interest/Disclosures

The authors have no conflict of interest to disclose.

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Table 1 Characteristics of included studies reporting change in stroke incidence at younger ages

Study	Data collection	Types of events reported by age over time	Study duration continuous (c) or periodic (p)	Population[Error! Bookmark not defined.]	Number incident strokes[2]	Age range	Case finding methods
POPULATION BASED STUDIES:							
Oxfordshire studies, UK[17,25-27]	1981-2018	FES, IS, PICH, SAH , TIA	3+1yp +17y,c	92 728	3104		ABCDE(F)HIJKMN*
South London, UK[14,28-30]	1995-2015	FES IS, PICH, SAH,	16y, c	357 308	4 245	15+	ABEFJKN
Dijon, France[3,31-33]	1985-2017	FES, IS, PICH, lacunar, TIA	32y, c	156 000	5556		ABDEHKN*
Ferrara, Italy[34]	2002-2007	FES	6y, c	149 046	39	15-44	ABKN
Valle d'Aosta, Italy[35-38]	1989-2008	FES	7y, p	125 103	1 924		AB(D)E(FHKM)N
Porto, Portugal[15]	1998-2011	FES, TIA	2 x 2y, p	102212	867		(A)BDEF(HJ)KMN
Arcadia, Greece[39]	1993-2016	FES	2+1+2p	71302	1315	20+	ABEFHIKN
Belgium[40]	1984-1999	"attack rates of stroke"	4y p	137861	1 097		B
Jyvaskyla, Finland[41]	1985-1993	FES	8+1p	114 669	408	25+	AHKN
Frederiksberg, Denmark[42]	1972-1990	FES	4y, p	85 611	927		ABDHIN
Örebro, Sweden[43]	1999,2017	FES	2y,p	150291	616		ABEHIKMN
Lund, Sweden[16]	2001-2016	FES	2x1y, p	276 400	869		ABEHIJKMN
Malmo, Sweden[44]	1989-1999	FES	10y, c	250 000	3621	50-79	AEHJMN
Cincinnati, USA[4,45-48]	1993-2015	FES, TIA	5 x 1y, p	1 319 856	9733	20+	A(BD)E(H)JKN*
Texas BASICC, USA[49,50]	2000-2017	FE-IS, PICH + recurrent	18y, c	362294	4875(IS)	45+	A(B)E(H)JKN
Auckland, New Zealand[51-54]	1981-2012	FES, IS	4 x 1y p	1 119 192	5 400	15+	AB(C)DE(FHIJKMN)*
Perth, Australia[55,56]	1989-2001	FES	3x12-18m, p	143 000	647		ABCDFHJMN
Oyabe, Japan[20]	1977-1991	FES	15y c	32 859[5]	2 068	25+	ABJLN
Takashima, Japan[57]	1990-2001	FES	12 y, c	55 000	1 432		AJN
Martinique[58,59]	1998-2012	FES	13y, p	390 371	1 124		ABEJKN*
ADMINISTRATIVE BASED STUDIES:							
Scotland, UK[60]	1986-2005	Hospitalised or fatal stroke[6]	20y c	5 140 000	213 358		AKN
UK Nationwide sample[61]	1999-2008	"Read code" stroke[7]	9y, c	> 3 000 000	32 151	18+	B

Study	Data collection	Types of events reported by age over time	Study duration continuous (c) or periodic (p)	Population[Error! Bookmark not defined.]	Number incident strokes[2]	Age range	Case finding methods
Netherlands, Nationwide[62]	1998-2010	Stroke, IS ICH UND	13y, c		15 257	18+	KN+ death register
Extremadura, Spain[63]	2002-2014	IS HS TIA "ill-defined CVD"	13y, c	··	39 321	20+	KN
Aragon, Spain[64]	1998-2010	Only IS <55	13y, c	··	28 022		KN
Helsinki, Finland[65]	2000-2010	ICH	10y, 3m c	1 500 000	336	16-49	KN
Nationwide, Norway[66]	2010-2015	IS HS TIA Und CVA	6y, c	5 015 085	5591	0-54	KN+ death register
Studies reporting from Danish National Inpatient Register:							
1.Demant et al[67]	1997-2009	"first time stroke"	13y, c	3 662 900	167 840		KN+ death register
2.Tibaek et al[68]	1994-2012	FES, TIA, ICH, SAH, IS	19y, c	1 085 001	··	15-30	KN+ death register
3.Skajaa et al[12]	2005-2018	IS, HS ICH, UNS	14y,c	··	113 920	18+	KN+ death register
4.Yafasova et al[69]	1996-2016	"first time IS"	20y, c	4 902 421	224 617	18+	KN+ death register
Studies reporting from the Swedish Hospital Discharge Register:							
1.Gothenburg[70]	1987-2006	First hospitalisation stroke, PICH, IS	20y, c	381 701	28 154		K+ death register
2.Medin et al[71]	1989-2000	First hospitalisation stroke	2 x 3y, p	12 454 989[8]	21 107	30-65	K
3.Rosengren et al[19]	1987-2010	First hospitalisation IS	24y,c	··	391 081	18-84	K+ death register
New Jersey, USA[72]	1995-2014	Hospitalisation IS	19y, c	21 737 982	227 719	35-84	K
Studies reporting data from USA Nationwide Inpatient Sample:							
1.Towfighi et al[21]	1997-2006	Hospitalisation IS and HS	10y c	··	3 161 752	35-64	K[10]
2.Lee et al[73]	1998-2007	Hospitalisation IS	12y c	··	895 831		K
3.Ramirez et al[74,75]	2000-2010	Hospitalisation IS and TIA	11y c	··	··	25+	K
Nationwide, Canada[76]	1994-2004	Hospital admission "stroke"	10y, 3m, c	··	111 402	20+	K + mortality
Quebec, Canada[77]	1988-2002	IS and ICH	15y, c	··	113 046	15+	KN
Ontario, Canada 1[78]	2002-2013	"Stroke"	12,c	10 363 982	317 350	20+	K
Ontario, Canada 2[79]	2003-2017	"all stroke, ICH, IS"	14y, c	11300000	163574	18+	K
New South Wales, Australia[80]	2001-2009	Hospitalisation ICH	9y, c	7 300 000	11 332	20+	K + death register
Hunter Region, Australia[81]	1996-2008	change in "attack rate"	13y, c	578 486	9 796	20+	KN
Northern territory, Australia[82]	1999-2011	Hospitalised IS HS	12y c		1 962	15+	KN

Study	Data collection	Types of events reported by age over time	Study duration continuous (c) or periodic (p)	Population[Error! Bookmark not defined.]	Number incident strokes[2]	Age range	Case finding methods
Queensland, Australia[83]	2002-2015	Hospitalised IS, HS, UND	14 y, c	4778854	86208	20+	KN
South Auckland, New Zealand[84]	2005-2009	IS	5y 7m c	195,600	2 838	15-45	KN
Okinawa, Japan[85]	1988-2005	IS, PICH SAH	6y, p	55 587	627		KN
Hong Kong[86-88]	1999-2007	"new ""recurrent" stroke, IS, ICH	9y, c	..	118 414	35+	K + death register
Singapore[89]	2006-2012	Hospitalised stroke	7y, c	3 818 205	36 495	15+	(A)K

A=death certificates; B=family doctors (GPs); C=Rehabilitation; D=Nursing Homes; E=regular searches; F=review of radiology requests/reports; G=media attention (campaign or reporting); H=outpatient clinics/health centres; I=sudden deaths, very early deaths; J=emergency, ambulance, on call medical services; K=ICD codes; L door to door, home visits, phone calls; M=autopsy reports; N=all hospitals in region * case finding methods that were consistent for ascertainment of minor stroke for periods compared for primary outcome. IS=Ischaemic stroke; PICH=Primary intracerebral haemorrhage; SAH=subarachnoid haemorrhage; UND undetermined

Table 2 Temporal change of stroke incidence at younger ages and relative temporal changes of stroke incidence at younger vs. older ages in the 17 studies that reported data stratified by sex

Study	Age Groups	Time periods	Female IRR in (younger age group) (95%CI)	Female RTTR (younger vs older age group) (95% CI)	Male IRR (younger age group) (95%CI)	Male RTTR (younger vs older age group) (95% CI)	Relative temporal sex ratio (male vs. female) (95%CI)
Population based Studies							
Oxfordshire, UK [17,25]	0-54 vs ≥55y	2010-2018 vs 1981-1986	1.70 (1.02,2.83)	2.20 (1.31,3.76)	2.06 (1.33,3.18)	3.06 (1.93,4.85)	1.21 (0.62,2.36)
Valle d'Aosta, Italy[35,37]	0-54 vs ≥55y	2004-2008 vs 1989	0.88 (0.43,1.82)	1.22 (0.58,2.58)	1.32 (0.70,2.49)	1.58 (0.81,3.08)	1.50 (0.57,3.92)
Arcadia, Greece[39]	20-54 vs ≥55y	2015-2016 vs 1993-1995	0.73 (0.26,2.06)	0.69 (0.24,1.97)	1.27 (0.67,2.40)	1.31 (0.68,2.53)	1.73 (0.51,5.82)
Porto, Portugal[15]	0-54 vs ≥55y	2009-2011 vs 1998-2000	0.63 (0.38,1.04)	0.81 (0.48,1.37)	0.99 (0.61,1.60)	1.39 (0.83,2.33)	1.39 (0.83,2.33)
Lund, Sweden[16]	15-54 vs ≥55y	2015-2016 vs 2001-2002	0.89 (0.38,2.05)	1.19 (0.50,2.80)	0.88 (0.47,1.64)	1.34 (0.70,2.55)	1.00 (0.35,2.82)
Örebro, Sweden[43]	0-55 vs ≥55y	2017 vs 1999	0.57 (0.28,1.16)	1.37 (0.65,2.88)	0.99 (0.43,2.29)	2.06 (0.86,4.93)	1.72 (0.58,5.15)
Cincinnati, USA[47]	20-44 vs ≥45y	2015 vs 1993-1994	1.30 (0.90,1.88)	1.05 (0.72,1.53)	2.07 (1.38,3.10)	2.70 (1.79,4.11)	1.59 (0.92,2.75)
Texas, USA[49]	45-59 vs ≥60y	2017 vs 2000	1.12 (0.76,1.65)	1.62 (1.08,2.42)	1.16 (0.75,1.79)	1.73 (1.09,2.75)	1.03 (0.58,1.84)
Auckland, New Zealand[53]	16-49 vs ≥50y	2011 -2012 vs 2002-2003	2.00 (1.41,2.83)	2.79 (1.94,4.00)	1.09 (0.79,1.50)	1.40 (1.00,1.97)	0.55 (0.34,0.87)
Martinique, W-Indies[58]	0-54 vs ≥55y	2011-2012 vs 1998-1999	1.63 (1.01,2.65)	2.93 (1.75,4.91)	0.99 (0.66,1.48)	1.33 (0.86,2.07)	0.61 (0.32,1.14)
Takashima, Japan[57]	0-54 vs ≥55y	1999-2001 vs 1990-1992	0.84 (0.36,1.93)	0.76 (0.32,1.80)	1.47 (0.76,2.82)	1.81 (0.91,3.61)	1.75 (0.60,5.09)
Pooled subgroup			**1.12 (0.86,1.45)**	**1.44 (1.05,1.97)**	**1.27 (1.05,1.53)**	**1.73 (1.43,2.11)**	
Administrative based studies							
Scotland, UK[60]	0-54 vs ≥55y	2004-2005 vs 1986-1987	1.12 (1.01,1.24)	1.40 (1.25,1.55)	1.29 (1.18,1.42)	1.48 (1.34,1.64)	1.15 (1.00,1.32)
Aragon, Spain[64]	15-54 vs ≥55y	2010 vs 1998	1.04 (0.81,1.33)	1.05 (0.82,1.34)	0.99 (0.79,1.23)	1.00 (0.77,1.30)	0.95 (0.68,1.33)
Denmark[67]	25-54 vs ≥55y	2007-2009 vs 1997-2000	1.20 (1.12,1.29)	1.38 (1.28,1.49)	1.12 (1.07,1.17)	1.32 (1.25,1.39)	1.00 (0.94,1.07)
Sweden Nationwide (IS)[19]	18-54 v 55-84	2005-2010 vs 1987-1992	1.47 (1.38,1.57)	1.71 (1.60,1.83)	1.23 (1.17,1.29)	1.61 (1.53,1.69)	0.83 (0.77,0.90)
Canada[76]	20-49 vs ≥50y	2004 vs 1994	0.92 (0.86,0.99)	1.28 (1.20,1.37)	0.91 (0.85,0.97)	1.32 (1.24,1.41)	0.98 (0.90,1.08)
Ontario, Canada[78]	20-49 vs ≥50y	2013 vs 2002	0.95 (0.87,1.03)	1.48 (1.36,1.61)	1.08 (0.99,1.17)	1.58 (1.45,1.72)	1.13 (1.01,1.27)
Hong Kong [88]	35-54 vs ≥55y	2005-2007 vs 1999-2001	1.05 (1.02,1.09)	1.25 (1.23,1.27)	1.10 (1.07,1.14)	1.24 (1.22,1.26)	1.05 (1.01,1.08)
Pooled subgroup			**1.12 1.01,1.25**	**1.37 (1.24,1.52)**	**1.14 (1.06,1.22)**	**1.38 (1.25,1.52)**	

IRR=Incidence rate ratio; incidence during the latest vs earliest reported time period RTTR=Relative temporal rate ratio; calculated by dividing the IRR in the younger age group (where possible, <55 years) by the IRR of the older age group (where possible ≥55 years) see e-methods-3 for further details of the RTTR and the calculation of a 95%CI, IS=ischaemic stroke.

Figure legends

Figure 1 Temporal trends in population based studies and in administrative based studies in stroke incidence at younger ages (A&B) and in the ratio of incidence at younger ages/incidence at older ages (C&D)

Top: Results of individual studies reporting stroke or ischaemic stroke incidence rates at younger ages beyond the year 2000 stratified by study methodology (A. Population-based studies; B. Administrative-based studies). One study[49] reporting incident rates age 45-59 could not be plotted on the same scale. Full age specific results are reported in e-figure 5 where full details of age bands and stroke subtypes of all individual studies are provided.

Bottom: Change in the ratio of "young age" vs "old age" stroke over time within individual studies providing age specific stroke or ischaemic stroke incidence rates over time stratified by study methodology (A. Population-based studies; B. Administrative-based studies). Not all of the studies in the top figures are included in the bottom figures, as some did not report incidence rates at older ages (see e-figure 4). "young age" includes any age group <60 years, the majority reporting <55 years. IS= ischaemic stroke; TIA=transient ischaemic attack.

Figure 2. Meta-analysis of the relative stroke incidence change over time at younger vs. older ages (RTTR)

RTTR=Relative Temporal Trend Ratio, calculated by dividing the temporal Incidence Rate Ratio (IRR) within each study in the younger age group (where possible, <55 years) by the IRR of the older age group. RTTRs for each study were pooled with inverse variance weighted random effects meta-analysis to generate a pooled RTTR with 95% CI. This analysis included studies reporting all stroke/ischaemic stroke with an age comparison of <55 vs ≥55 years where possible, stratified study method (population based/administrative based data) and by recency of latest time period (2000-2010/after 2010).

Figure 3 Pooled estimates of the relative stroke incidence change over time at younger vs. older ages (RTTR) stratified according to clinical or study characteristics

*The RTTRs for each study were pooled with inverse variance weighted random effects meta-analysis to generate a pooled RTTR with 95% CI. *Limited to studies that reported data within 3 years of a decade boundary in 2 consecutive decades. ICH=intracerebral haemorrhage; SAH=subarachnoid haemorrhage; CVA=cerebrovascular disease. Details of each subgroup analysis are presented in e-figure 7*