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Diverging Temporal Trends in Stroke Incidence in Younger vs Older People
A Systematic Review and Meta-analysis

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IMPORTANCE Overall stroke incidence is falling in high-income countries, but data on time trends in incidence of young stroke (ie, stroke in individuals younger than 55 years) are conflicting. An age-specific divergence in incidence, with less favorable trends at younger vs older ages, might be a more consistent underlying finding across studies.

OBJECTIVE To compare temporal trends in incidence of stroke at younger vs older ages in high-income countries.

DATA SOURCES PubMed and EMBASE were searched from inception to February 2022. One additional population-based study (Oxford Vascular Study) was also included.

STUDY SELECTION Studies reporting age-specific stroke incidence in high-income countries at more than 1 time point.

DATA EXTRACTION AND SYNTHESIS For all retrieved studies, 2 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. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was followed.

MAIN OUTCOMES AND MEASURES The main outcome was age-specific divergence (<55 vs ≥55 years) in temporal trends in stroke incidence (relative temporal rate ratio [RTTR]) in studies extending to at least 2000. RTTRs were calculated for each study and pooled by random-effects meta-analysis, with stratification by administrative vs prospective population-based methodology, sex, stroke subtype (ischemic vs intracerebral hemorrhage vs subarachnoid hemorrhage) and geographical region.

RESULTS Among 50 studies in 20 countries, 26 (13 prospective population-based and 13 administrative studies) reported data allowing calculation of the RTTR for stroke incidence at younger vs older ages across 2 or more periods, the latest extending beyond 2000. Reported trends in absolute incidence of young individuals with stroke were heterogeneous, but all studies showed a less favorable 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 (ischemic, 1.62 [95% CI, 1.44-1.83]; intracerebral hemorrhage, 1.32 [95% CI, 0.91-1.92]; subarachnoid hemorrhage, 1.54 [95% CI, 1.00-2.35]); and by sex (men, 1.46 [95% CI, 1.34-1.60]; women, 1.41 [95% CI, 1.28-1.55]) but was greater in studies reporting trends solely after 2000 (1.51 [95% CI, 1.30-1.70]) vs solely before (1.18 [95% CI, 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 [95% CI, 1.55-2.27]).

CONCLUSIONS AND RELEVANCE Temporal trends in stroke incidence are diverging by age in high-income countries, with less favorable trends at younger vs older ages, highlighting the urgent need to better understand etiology and prevention of stroke at younger ages.

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Stroke incidence has declined by 42% throughout the last 4 decades in high-income countries.[1] However, there have been several reports that incidence at younger ages (age <55 years) appears to be increasing in the US 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 throughout 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 stroke in young individuals.[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 ischemic 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 (ie, stroke in individuals younger than 55 years) has been reported in some countries,[14-16] it is uncertain whether such trends might still be less favorable 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 conducted a systematic review of 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 compared with that at older ages, with stratification by study and clinical characteristics.

Key Points

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

Findings In this systematic review and meta-analysis of 50 studies, trends in incidence of young stroke (ie, stroke in individuals younger than 55 years) were heterogeneous, but a divergent trend was evident across almost all studies, with a fall in 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 etiology and prevention of stroke at younger ages.

Methods

This systematic review followed a prespecified protocol and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[17] PubMed and EMBASE were searched from inception to February 2022 and an additional population-based study by Li et al.[18] We searched for studies reporting stroke incidence in high-income countries at younger ages (usually <45, <55, or <60 years) during at least time 2 periods (full search strategy available in eTable 1 in the Supplement). We also scrutinized the reference lists of all relevant reviews and those of the eligible publications. After exclusion of duplicate studies, titles and abstracts were screened by 2 authors (C.A.S. and L.L.). For all retrieved studies, 2 authors (C.A.S. and L.L.) independently reviewed the full text against the inclusion criteria to establish their eligibility and where differences arose these were discussed with the third author (P.M.R.).

Our study inclusion and exclusion criteria are detailed in eTable 2 in the Supplement. Briefly, eligible studies could be population-based (ie, community based studies with multiple ascertainment methods) or administrative (ie, relying only on routinely collected coding data). Eligible administrative studies must have included stroke incidence data during at least 2 periods 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 (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, or stroke events combined). Studies reporting stroke hospitalization rates only (with no population denominator) were excluded.

Data were extracted and entered onto a predesigned electronic form by 1 author (C.A.S.) (eFigure 1 in the Supplement), and another author (L.L.) checked the extracted data. We contacted authors[19-21] for clarification of results in 3 published articles, of which 1 responded.[19]

No generic study quality appraisal tool incorporates the important items most relevant to reliable estimation of stroke incidence.[22] Therefore, we 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 (eMethods 1 in the Supplement)[22] and the methods used to ensure ascertainment and adjudication of minor stroke.

For each study, we extracted the number of strokes, denominator population, incidence rates, and 95% CIs in a younger age group (ideally <45 and <55 years) and older age group (ideally ≥45 and ≥55 years) as well as standardized rates for each reported time period. Methods for calculating incidence rates from the data provided in individual studies are detailed in eMethods 2 in the Supplement. 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 that 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 summarized. In studies where change of TIA incidence was reported alongside changes of stroke, we also summarized the incidence change of TIA at younger ages.

Statistical Analysis

Our primary analyses were confined to studies reporting at least 1 time period after 2000. We first plotted the absolute incidence of young stroke (or ischemic 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 (≥55 years where possible) at each time point (the incidence ratio). When 2 or more studies reported from the same data set, the decision regarding which to include in the plots was based on the following hierarchy: (1) most recent time period, (2) studies reporting individuals younger than 55 years, and (3) other reported age cutoff of younger than 55 years. Plots were also produced to visually assess trends in the following prespecified subgroups: younger than 45 years, younger than 55 years, and younger than 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 minimize 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, ie, we compared the number of positive studies (increase in stroke incidence between the 2 time periods, regardless of statistical significance) with the number of negative studies (decrease in stroke incidence between the 2 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] When 2 or more studies or articles reported from the same data set, the decision regarding which to include in the vote counting and sign test used the following hierarchy: (1) most recent time period, (2) age cutoff closest to 55 years, and (3) all stroke preferred over ischemic 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 eMethods 3 in the Supplement for further details of the RTTR and the calculation of 95% CIs), thereby providing an estimate that could be meta-analyzed 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% CIs. We estimated statistical heterogeneity using Cochran *Q* test. Our primary analysis included studies reporting all stroke or ischemic stroke with an age comparison of younger than 55 years vs 55 years or older or younger than 50 vs 50 years or older, 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 eMethods 4 in the Supplement; 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 association of study duration with the RTTR, for each age group we fitted a linear regression model (ie, 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 throughout this 10-year period 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 cutoff used, region, study period, duration, and ascertainment quality in univariate and multivariate analyses. All analyses were done using SPSS statistical software version 25 (SPSS Inc) and Stata version 16.1 (StataCorp).

Results

Our search of databases and other sources (eFigure 2 in the Supplement) identified 29 221 records, with 463 potentially relevant full-text articles assessed after screening of titles and abstracts. Of these, 49 eligible published studies (eFigure 2 and eTable 3 in the Supplement)[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. The addition of our own data[18] resulted in 50 studies (**Table 1** and eTable 4 in the Supplement; 20 prospective population-based studies and 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 eTable 4 in the Supplement and study quality in eTable 5 in the Supplement. Reports differed in relation to time periods covered and age cutoffs used for young stroke.

Two studies reported data on only hemorrhagic stroke.[65,80] Among the 48 studies reporting at least some data on temporal trend in incidence of all young stroke or young ischemic stroke until at least 1990, IRRs (latest vs earliest reported time period) were calculable in 36 (eFigure 3 in the Supplement) and some other measure of the direction of any temporal trend was reported in 12 (eTables 6-8 in the Supplement). After exclud-

Table 1. Characteristics of Included Studies Reporting Change in Stroke Incidence at Younger Ages

Source location or source and time period	Events reported by age over time	Study duration, y	Population, No.	No. of incident strokes	Study age inclusion, y	Case finding methods[a]
Population-based studies						
Oxfordshire, UK,[18,25-27] 1981-2018	FES, IS, ICH, SAH, TIA	3 + 1 (Periodic) +16 (continuous)	92 728	3104	All	ABCDE(F)HIJKMN[b]
South London, UK,[14,28-30] 1995-2015	FES, IS, ICH, SAH	16 (Continuous)	357 308	4245	≥15	ABEFJKN
Dijon, France,[3,31-33] 1985-2017	FES, IS, ICH, lacunar, TIA	32 (Continuous)	156 000	5556	All	ABDEHKN[b]
Ferrara, Italy,[34] 2002-2007	FES	6 (Continuous)	149 046	39	15-44	ABKN
Valle d'Aosta, Italy,[35-38] 1989-2008	FES	7 (Periodic)	125 103	1 924	All	AB(D)E(FHKM)N
Porto, Portugal,[15] 1998-2011	FES, TIA	2 × 2 (Periodic)	102 212	867	All	(A)BDEF(HJ)KMN
Arcadia, Greece,[39] 1993-2016	FES	2 + 1 + 2 (Periodic)	71 302	1315	≥20	ABEFHIKN
Belgium,[40] 1984-1999	Attack rates of stroke	4 (Periodic)	137 861	1097	All	B
Jyvaskyla, Finland,[41] 1985-1993	FES	8 + 1 (Periodic)	114 669	408	≥25	AHKN
Frederiksberg, Denmark,[42] 1972-1990	FES	4 (Periodic)	85 611	927	All	ABDHIN
Örebro, Sweden,[43] 1999-2017	FES	2 (Periodic)	150 291	616	All	ABEHIKMN
Lund, Sweden,[16] 2001-2016	FES	2 × 1 (Periodic)	276 400	869	All	ABEHIJKMN
Malmo, Sweden,[44] 1989-1999	FES	10 (Continuous)	250 000	3621	50-79	AEHJMN
Cincinnati, OH,[4,45-48] 1993-2015	FES, TIA	5 × 1 (Periodic)	1 319 856	9733	≥20	A(BD)E(H)JKN[b]
Texas,[49,50] 2000-2017	First-ever IS, ICH + recurrent	18 (Continuous)	362 294	4875 (IS)	≥45	A(B)E(H)JKN
Auckland, New Zealand,[51-54] 1981-2012	FES, IS	4 × 1 (Periodic)	1 119 192	5400	≥15	AB(C)DE(FHIJKMN)[b]
Perth, Australia,[55,56] 1989-2001	FES	3 × 12-18 mo (Periodic)	143 000	647	All	ABCDFHJMN
Oyabe, Japan,[20] 1977-1991	FES	15 (Continuous)	32 859	2068	≥25	ABJLN
Takashima, Japan,[57] 1990-2001	FES	12 (Continuous)	55 000	1432	All	AJN
Martinique,[58,59] 1998-2012	FES	13 (Periodic)	390 371	1124	All	ABEJKN[b]
Administrative-based studies						
Scotland, UK,[60] 1986-2005	Hospitalized or fatal stroke	20 (Continuous)	5 140 000	213 358	All	AKN
UK nationwide,[61] 1999-2008	Read code stroke	9 (Continuous)	>3 000 000	32 151	≥18	B
Netherlands nationwide,[62] 1998-2010	Stroke, IS, ICH, UND	13 (Continuous)	NR	15 257	≥18	KN+ death register
Extremadura, Spain,[63] 2002-2014	IS, HS, TIA, ill-defined CVD	13 (Continuous)	NR	39 321	≥20	KN
Aragon, Spain,[64] 1998-2010	IS	13 (Continuous)	NR	28 022	<55	KN
Helsinki, Finland,[65] 2000-2010	ICH	10 y, 3 mo (Continuous)	1 500 000	336	16-49	KN
Nationwide, Norway,[66] 2010-2015	IS, HS, TIA, UND CVD	6 (Continuous)	5 015 085	5591	0-54	KN+ death register
Studies reporting from Danish National Inpatient Register						
Demant et al,[67] 1997-2009	First time stroke	13 (Continuous)	3 662 900	167 840	≥25	KN+ death register
Tibæk et al,[68] 1994-2012	FES, TIA, ICH, SAH, IS	19 (Continuous)	1 085 001	NA	15-30	KN+ death register
Skajaa et al,[12] 2005-2018	IS, ICH, SAH	14 (Continuous)	NR	113 920	≥18	KN+ death register
Yafasova et al,[69] 1996-2016	First time IS	20 (Continuous)	4 902 421	224 617	≥18	KN+ death register
Studies reporting from the Swedish Hospital Discharge Register						
Harmsen et al,[70] 1987-2006	First hospitalization stroke, ICH, IS	20 (Continuous)	381 701	28 154	≥20	K+ death register
Medin et al,[71] 1989-2000	First hospitalization stroke	2 × 3 (Periodic)	12 454 989	21 107	30-65	K
Rosengren et al,[19] 1987-2010	First hospitalization IS	24 (Continuous)	NR	391 081	18-84	K+ death register
Swerdel et al,[72] 1995-2014	Hospitalization IS	19 (Continuous)	21 737 982	227 719	35-84	K

(continued)

Table 1. Characteristics of Included Studies Reporting Change in Stroke Incidence at Younger Ages (continued)

Source location or source and time period	Events reported by age over time	Study duration, y	Population, No.	No. of incident strokes	Study age inclusion, y	Case finding methods[a]
Studies reporting data from US Nationwide Inpatient Sample						
Towfighi et al,[21] 1997-2006	Hospitalization IS and HS	10 (Continuous)	NR	3 161 752	35-64	K
Lee et al,[73] 1998-2007	Hospitalization IS	12 (Continuous)	NR	895 831	All	K
Ramirez et al,[74,75] 2000-2010	Hospitalization IS and TIA	11 (Continuous)	NR	NA	≥25	K
Canada nationwide,[76] 1994-2004	Hospital admission stroke	10 y, 3 mo (Continuous)	NR	111 402	≥20	K + mortality
Quebec, Canada,[77] 1988-2002	IS and ICH	15 (Continuous)	NR	113 046	≥15	KN
Ontario, Canada,[78] 2002-2013	Stroke	12 (Continuous)	10 363 982	317 350	≥20	K
Ontario, Canada,[79] 2003-2017	All stroke, ICH, IS	14 (Continuous)	11 300 000	163 574	≥18	K
New South Wales, Australia,[80] 2001-2009	Hospitalization ICH	9 (Continuous)	7 300 000	11 332	≥20	K + death register
Hunter Region, Australia,[81] 1996-2008	Change in attack rate	13 (Continuous)	578 486	9796	≥20	KN
Northern Territory, Australia,[82] 1999-2011	Hospitalized IS, HS	12 (Continuous)	NR	1962	≥15	KN
Queensland, Australia,[83] 2002-2015	Hospitalized IS, HS, UND	14 (Continuous)	4 778 854	86 208	≥20	KN
South Auckland, New Zealand,[84] 2005-2009	IS	5 y, 7 mo (Continuous)	195 600	2838	15-45	KN
Okinawa, Japan,[85] 1988-2005	IS, ICH, SAH	6 y (Periodic)	55 587	627	≥30	KN
Hong Kong,[86-88] 1999-2007	New or recurrent stroke, IS, ICH	9 (Continuous)	NR	118 414	≥35	K + death register
Singapore,[89] 2006-2012	Hospitalized stroke	7 (Continuous)	3 818 205	36 495	≥15	(A) K

Abbreviations: CVD, cerebrovascular disease; ICH, intracerebral hemorrhage; IS, ischemic stroke; FES, first-ever stroke; HS, hemorrhagic stroke; NA, not applicable; NR, not reported; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack; UND, undetermined.

[a] A indicates death certificates; B, family physicians; C, rehabilitation; D, nursing homes; E, regular searches; F, review of radiology requests/reports; G, media attention (campaign or reporting); H, outpatient clinics/health centers; I, sudden deaths, very early deaths; J, emergency, ambulance, on-call medical services; K, *International Classification of Diseases* codes; L, door to door, home visits, telephone calls; M, autopsy reports; N, all hospitals in region.

[b] Case finding methods that were consistent for ascertainment of minor stroke for periods compared for primary outcome.

ing 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 (eFigure 4 in the Supplement). Comparing the latest vs earliest reported incidence rate in each study (eTable 8 in the Supplement), 1 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 toward an increase in young stroke or young ischemic stroke incidence, and 10 (29%) reported at least a trend toward a decrease (sign test; $P = .02$).

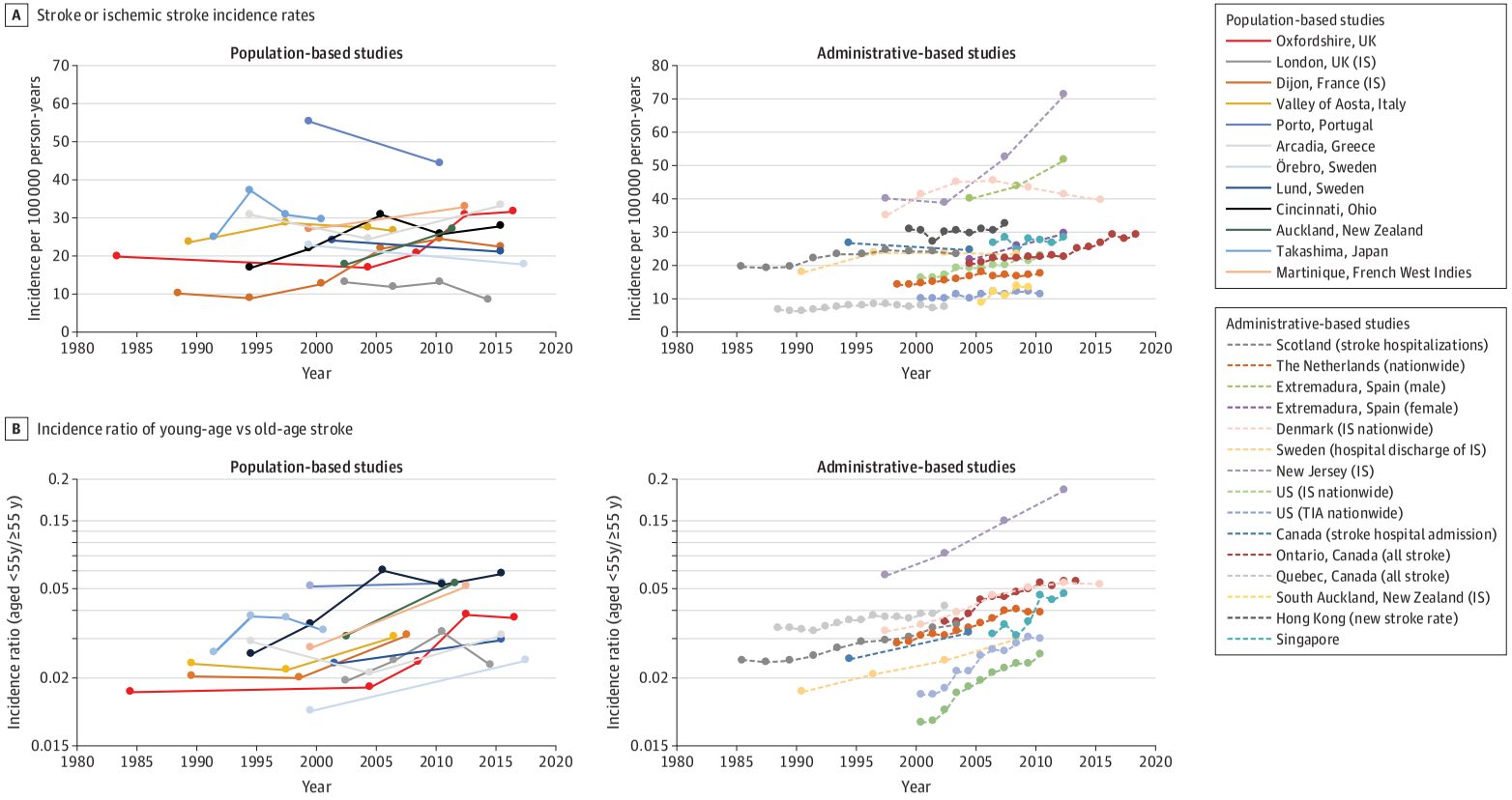
Of 36 studies that reported unique data on temporal trends in incidence of young stroke to at least 2000, 33 also reported at least some data on the temporal trend at older ages (eFigure 4 and eTable 8 in the Supplement). Of these 33 studies, 29 (88%) reported at least a trend toward decreasing incidence at older ages, and only 4 (12%) reported a trend toward increasing incidence (sign test; $P < .001$).

A total of 26 studies reported unique quantitative data on incidence of young stroke during at least 1 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 toward increased incidence in 8 studies and either stable or a trend toward a decrease in 5 (South London, UK,[14] Porto, Portugal,[15] Örebro, Sweden,[43] Lund, Sweden,[16] and Valley of Aosta, Italy[35]). However, when the incidence of stroke at older ages was taken into account, the relative incidence of stroke at younger vs older ages did increase after 2000 in all 13 studies. Results were also consistent for administrative data (Figure 1).

Twenty-six studies (eFigure 4 in the Supplement) reported incidence during at least 1 period beyond 2000 and during previous period(s) before or after 2000 or had sufficient data to allow us to derive a quantitative measure (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; $P < .001$), with a less favorable trend at younger than 55 years vs 55 years or older (ie, RTTR > 1) and was highly significant on pooled analysis (RTTR = 1.57 [95% CI, 1.42-1.74]; $P < .001$; **Figure 2**). In addition, 3 studies[55,61,63] of 4 further similar studies[55,61,63,85] 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 1.

However, there was still heterogeneity between studies in RTTR, ie, in the absolute extent to which the trend in inci-

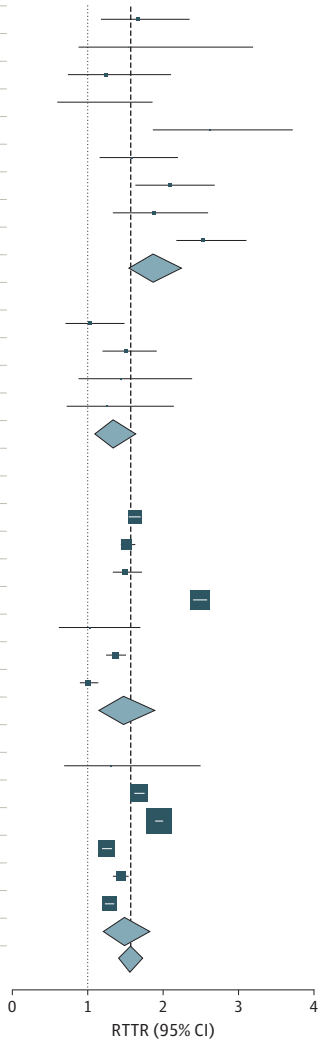
Figure 1. Temporal Trends in Population- and Administrative-Based Studies in Stroke Incidence at Younger Ages and in the Ratio of Incidence at Younger Ages/Incidence at Older Ages



A, Results of individual studies reporting stroke or ischemic stroke (IS) incidence rates at younger ages beyond 2000 stratified by study methodology (population- vs administrative-based studies). One study[49] reporting incident rates in individuals aged 45 to 59 years could not be plotted on the same scale. Full age-specific results are reported in eFigure 5 in the Supplement where full details of age bands and stroke subtypes of all individual studies are provided. B, Change in the ratio of young-age vs old-age stroke over time within individual studies providing age-specific stroke or ischemic stroke incidence rates over time stratified by study methodology (population- vs administrative-based studies). Not all of the studies in panel A are included in panel B, as some did not report incidence rates at older ages (eFigure 4 in the Supplement). Young age includes any individuals younger than 60 years, with the majority reporting younger than 55 years. TIA indicates transient ischemic attack.

Figure 2. Meta-analysis of the Relative Stroke Incidence Change Over Time at Younger vs Older Ages

Study region	Age group, y	Time period	RTTR (95% CI)
Population-based studies			
Ascertainment of most recent period after 2010			
Texas (IS)	45-59 vs 60-74	2017 vs 2000	1.67 (1.18-2.36)
Örebro, Sweden	<55 vs ≥55	2017 vs 1999	1.68 (0.89-3.20)
Lund, Sweden	15-54 vs ≥55	2015-2016 vs 2001-2002	1.26 (0.75-2.11)
Arcadia, Greece	20-54 vs ≥55	2015-2016 vs 1993-1995	1.07 (0.61-1.86)
Oxfordshire, UK	≤54 vs ≥55	2010-2018 vs 1981-1986	2.63 (1.86-3.72)
South London, UK (IS)	15-54 vs ≥55	2012-2015 vs 2000-2003	1.60 (1.17-2.21)
Auckland, New Zealand	16-49 vs ≥50	2011 -2012 vs 2002-2003	2.10 (1.64-2.68)
Martinique, French West Indies	≤54 vs ≥55	2011-2012 vs 1998-1999	1.88 (1.35-2.61)
Cincinnati, Ohio	20-54 vs ≥55	2010 vs 1993-1994	2.62 (2.19-3.13)
Subgroup *P* for heterogeneity = .005			1.87 (1.55-2.27)
Ascertainment of most recent period started before 2010			
Porto, Portugal	≤54 vs ≥55	2009-2011 vs 1998-2000	1.03 (0.71-1.50)
Dijon, France	≤54 vs ≥55	2003-2011 vs 1985-1993	1.52 (1.19-1.93)
Valley of Aosta, Italy	≤54 vs ≥55	2004-2008 vs 1989	1.46 (0.89-2.40)
Takashima, Japan	≤54 vs ≥55	1999-2001 vs 1990-1992	1.26 (0.74-2.16)
Subgroup *P* for heterogeneity = .38			1.35 (1.13-1.62)
Administrative-based studies			
Ascertainment of most recent period after 2010			
Denmark (IS nationwide)	18-54 vs ≥55	2014-2016 vs 1996-1998	1.63 (1.55-1.72)
Ontario, Canada	20-50 vs ≥50	2013 vs 2002	1.53 (1.44-1.63)
Singapore	<50 vs ≥50	2012 vs 2006	1.52 (1.34-1.72)
New Jersey (IS)	35-55 vs 55-84	2010-2014 vs 1995-1999	2.50 (2.41-2.60)
Northern Territory, Australia	15-39 vs ≥65	2011 vs 1999	1.04 (0.63-1.71)
The Netherlands (nationwide)	18-49 vs ≥50	2010 vs 1998	1.39 (1.26-1.53)
Aragon, Spain	15-54 vs ≥55	2010 vs 1998	1.02 (0.90-1.16)
Subgroup *P* for heterogeneity <.001			1.49 (1.17-1.90)
Ascertainment of most recent period before 2010			
Hunter region, Australia	20-54 vs ≥55	2008 vs 1996	1.31 (0.69-2.49)
Sweden (IS nationwide)	18-54 vs 55-84	2005-2010 vs 1987-1992	1.69 (1.63-1.76)
US (National Inpatient Sample IS)	≤54 vs ≥55	2007 vs 1998	1.95 (1.93-1.98)
Hong Kong	35-54 vs ≥55	2005-2007 vs 1999-2001	1.26 (1.20-1.32)
Scotland, UK	≤54 vs ≥55	2004-2005 vs 1986-1987	1.45 (1.35-1.56)
Canada (nationwide)	20-50 vs ≥50	2004 vs 1994	1.30 (1.24-1.36)
Subgroup *P* for heterogeneity <.001			1.50 (1.24-1.82)
Overall *P* for heterogeneity <.001			1.57 (1.42-1.73)



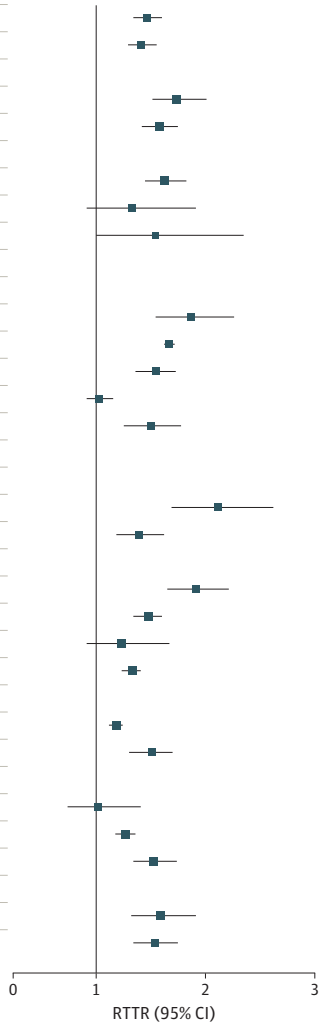
Relative temporal trend ratios (RTTRs) for each study were pooled with inverse variance–weighted random-effects meta-analysis to generate a pooled RTTR with 95% CI. This analysis included studies reporting all stroke/ischemic stroke (IS) with an age comparison of younger than 55 years vs 55 years or older where possible, stratified study method (population- vs administrative-based data) and by recency of latest time period (2000-2010 vs after 2010). RTTRs were calculated by dividing the temporal incidence rate ratio within each study in the younger age group (where possible, <55 years) by the incidence rate ratio of the older age group.

dence was less favorable at younger than 55 years vs 55 years or older (Figure 2; *P* for heterogeneity < .001). Standardizing the RTTR to a 10-year period reduced between-study differences to some extent, but heterogeneity remained (*P* for heterogeneity = .001; eFigure 6 in the Supplement). 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; 95% CI, 1.55-2.27). Having the most recent period starting after January 1, 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 [95% CI, 1.32-1.71]; *P* for heterogeneity < .001), 74% of which was explained by differences in the diagnostic codes used for stroke (eFigure 7 in the Supplement). Overall, study size, age cutoffs 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** and eFigure 7 in the Supplement), the lowest age-specific divergence in incidence was seen in 3 Southern European studies (RTTR = 1.02 [95% CI, 0.91-1.15]), and the most pronounced divergence in North American studies (RTTR = 1.87 [95% CI, 1.54-2.27]; n = 6). There was no evidence of higher RTTRs in smaller vs larger studies (Figure 3;

Figure 3. Pooled Estimates of the Relative Stroke Incidence Change Over Time at Younger vs Older Ages Stratified According to Clinical or Study Characteristics

Subgroup	Studies, No.	RTTR (95% CI)
Clinical characteristics		
Sex		
Male	18	1.46 (1.34-1.60)
Female	18	1.41 (1.28-1.55)
Age group, y		
<45 vs ≥45	18	1.74 (1.51-2.01)
<55 vs ≥55	24	1.58 (1.42-1.75)
Stroke subtype		
Ischemic	14	1.62 (1.44-1.83)
ICH	8	1.32 (0.91-1.92)
SAH	4	1.54 (1.00-2.35)
Study characteristics		
Study region		
North America	6	1.87 (1.54-2.27)
Scandinavia	4	1.67 (1.62-1.72)
Northern Europe	6	1.54 (1.36-1.73)
Southern Europe	3	1.02 (0.91-1.15)
Rest of world	7	1.49 (1.25-1.78)
Study methodology		
Population-based studies		
Consistent ascertainment of minor events	5	2.11 (1.69-2.63)
Other population-based studies	8	1.39 (1.19-1.62)
Administrative-based studies		
Presumed ischemic stroke	4	1.92 (1.65-2.22)
All strokes excluding SAH	2	1.47 (1.34-1.61)
All strokes	3	1.23 (0.91-1.67)
All strokes plus other nonacute CVD codes	4	1.32 (1.23-1.41)
Study period		
Before 2000	11	1.18 (1.12-1.24)
After 2000	13	1.51 (1.30-1.70)
Study decade[a]		
1980-1990	2	1.01 (0.73-1.40)
1990-2000	8	1.27 (1.18-1.36)
2000-2010	15	1.52 (1.33-1.74)
Size of study		
<10 000 Strokes	15	1.59 (1.32-1.91)
≥10 000 Strokes	11	1.53 (1.34-1.75)



Relative temporal trend ratios (RTTRs) for each study were pooled with inverse variance–weighted random-effects meta-analysis to generate a pooled RTTR with 95% CIs. Details of each subgroup analysis are presented in eFigure 7 in the Supplement. CVD indicates cerebrovascular disease; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

[a] Limited to studies that reported data within 3 years of a decade boundary in 2 consecutive decades.

eFigure 7 in the Supplement). Eight studies that reported time trends of stroke incidence (eTable 9 in the Supplement) 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 [95% CI, 1.43-2.11]; *P* for heterogeneity = .12) than in women (RTTR = 1.44 [95% CI, 1.05-1.97]; *P* for heterogeneity < .001). Results were unrelated to age cutoff, 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 (eTable 10 in the Supplement) and were consistent in White individuals (eTable 10 in the Supplement). Age-specific divergence was also similar for ischemic strokes (RTTR = 1.62 [95% CI, 1.44-1.83]; n = 14) and for hemorrhagic strokes (intracerebral hemorrhage: RTTR = 1.32 [95% CI, 0.91-1.92]; n = 8; subarachnoid hemorrhage: RTTR = 1.54 [95% CI, 1.00-2.35]; n = 4; Figure 3; eFigure 7 in the Supplement).

With regard to studies covering different time periods, we compared results for studies spanning adjacent decades (Figure 3; eFigure 7 and eTable 11 in the Supplement). The pooled RTTR was greater for comparison of incidence trends during 2000 to 2010 than those during 1990 to 2000, with consistent results within 6 of 7 population-based studies that spanned these decades (eTable 11 in the Supplement).

Table 2. Temporal Change of Stroke Incidence at Younger Ages and Relative Temporal Changes of Stroke Incidence at Younger vs Older Ages in the Studies That Reported Data Stratified by Sex

Source location	Age group, y	Time period	Female (95% CI)		Male (95% CI)		Relative temporal sex ratio [male vs female] (95% CI)
			IRR (younger age group)[a]	RTTR (younger vs older age group)[b]	IRR (younger age group)[a]	RTTR (younger vs older age group)[b]	
Population-based studies							
Oxfordshire, UK [18,25]	0-54 vs ≥55	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 ≥55	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 ≥55	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 ≥55	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 ≥55	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 ≥55	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, OH[47]	20-44 vs ≥45	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[49]	45-59 vs ≥60	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 ≥50	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, West Indies[58]	0-54 vs ≥55	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 ≥55	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	NA	NA	1.12 (0.86-1.45)	1.44 (1.05-1.97)	1.27 (1.05-1.53)	1.73 (1.43-2.11)	NA
Administrative-based studies							
Scotland, United Kingdom[60]	0-54 vs ≥55	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 ≥55	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 ≥55	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 vs 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 ≥50	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 ≥50	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 ≥55	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	NA	NA	1.12 (1.01-1.25)	1.37 (1.24-1.52)	1.14 (1.06-1.22)	1.38 (1.25-1.52)	NA

Abbreviations: IRR, incidence rate ratio; IS, ischemic stroke; NA, not applicable; RTTR, relative temporal rate ratio.

[a] The IRR is the incidence during the latest vs earliest reported time period.

[b] The RTTR is 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). eMethods 3 in the Supplement provides further details of the RTTR and the calculation of 95% CIs.

Discussion

We showed that age-specific divergence in stroke incidence was present to some extent in almost 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 favorable 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 undertreated at younger ages, owing at least partly to the widespread use treatment thresholds based on model-based predictors of vascular risk, such that a large proportion of young patients with stroke, especially women, have predicted premorbid vascular risks below the current treatment threshold.[18] However, although we showed that traditional vascular risk factors were highly prevalent and poorly controlled among young patients with stroke compared with the age-matched underlying population in the present population,[18] they did not appear to explain the increase of stroke incidence, particularly as incidence of myocardial infarction at younger ages is continuing to fall.[18]

The impact of other emerging vascular risk factors, such as air pollution, appear to be age-specific,[90] and long working hours are more strongly associated with risk of stroke than myocardial infarction.[91] 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 association of possible increases in exposure to environmental estrogen 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 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 artifact? 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 2 age groups and would not therefore fully adjust for the aging 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 owing 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 behavior 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 minimized underascertainment 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.[18]

In relation to other potential biases, the relative increase in magnetic resonance brain imaging use over time in TIA/stroke referrals has been similar at younger vs older ages in our own study and where it has been reported elsewhere.[4,18,49] Moreover, the similar increase in incidence of TIA and stroke at younger ages does not suggest diagnostic drift from TIA to stroke owing to increased use of magnetic resonance imaging. Furthermore, we found similar age-specific divergence for ischemic and hemorrhagic strokes, with the latter being less likely influenced by the use of magnetic resonance imaging. In relation to patient behavior, we did not find any temporal change in initial perception or behavior after stroke symptom onset in younger patients in Oxfordshire, UK.[18]

Limitations

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 favorable 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 (eMethods 3 in the Supplement). 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 association. 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 generalizability. However, the most recent Global Burden of Disease study showed that stroke incidence rates in people younger than 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 behavior, and the feasibility of reliable case ascertainment. Fifth, there is no standardized definition of young stroke, but we showed that the results were consistent with different cutoffs in individuals younger than 60 years.

Continued monitoring of age-specific divergence in stroke incidence is crucial, and future studies should adhere to the criterion standard reporting guidelines,[22] with analyses stratified by age, sex, ethnicity, and stroke severity. The Global Burden of Disease study[94] and the Global Outcome Assessment Life-long After Stroke in Young Adults initiative[95] might provide further region-specific data. We found that age-specific divergence was least evident in Southern Europe, but data were only available from 3 studies.

Conclusions

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 aging 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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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
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