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Increasing Incidence of Hospitalization for Stroke and Transient Ischemic Attack in Young Adults: A Registry-Based Study

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Background—Studies have reported increasing incidence of ischemic stroke in adults younger than 50 to 55 years. Information on temporal trends of other stroke subtypes and transient ischemic attack (TIA) is sparse. The aim of this study was to investigate temporal trends of the incidence of hospitalizations for TIA and stroke including sex- and subtype-specific trends in young adults aged 15 to 30 years.

Methods and Results—From the Danish National Patient Register, we identified all cases of first-ever stroke and TIA (age 15–30 years) in Denmark, who were hospitalized during the study period of 1994 to 2012. Incidence rates and estimated annual percentage changes (EAPCs) were estimated by using Poisson regression. During the study period, 4156 cases of first-ever hospitalization for stroke/TIA were identified. The age-standardized incidence rates of hospitalizations for stroke increased significantly (EAPC 1.83% [95% CI 1.11–2.55%]) from 11.97/100 000 person-years (PY) in 1994 to 16.77/100 000 PY in 2012. TIA hospitalizations increased from 1.93/100 000 PY in 1994 to 5.81/100 000 PY in 2012 and after 2006 more markedly in men than in women (EAPC 16.61% [95% CI 10.45–23.12%]). The incidence of hospitalizations for ischemic stroke was markedly lower among men, but increased significantly from 2006 (EAPC 14.60% [95% CI 6.22–23.63%]). The incidences of hospitalizations for intracerebral hemorrhage and subarachnoid hemorrhage remained stable during the study period.

Conclusions—The incidence rates of first-time hospitalizations for ischemic stroke and TIA in young Danish adults have increased substantially since the mid 1990s. The increase was particularly prominent in the most recent years. (*J Am Heart Assoc*. 2016;5: e003158 doi: 10.1161/JAHA.115.003158)

Key Words: epidemiology • incidence • sex-specific • stroke in young adults • transient ischemic attack

During the past decades, the incidence of stroke in developed countries has stabilized or even declined despite an aging population.[1–4] Stroke and transient ischemic attacks (TIAs) rarely occur in the young but may have a profound and long-lasting impact for the individual when they do occur. Compared with elderly individuals, stroke in the young may have greater economic impact, because it impairs the ability to work during the most productive years of life. Further, stroke in the young is associated with life-long cognitive impairment, increased risk of suicide, depression and anxiety, and increased mortality.[5,6] The consequences of TIA are less severe, but as many as 50% have from long-term cognitive impairments.[5–7]

Recent studies have reported a trend toward increasing incidence of ischemic stroke in the young.[4,8–10] Data on temporal trends of the incidence of intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and TIA remain sparse. The objectives of this study were (1) to determine the incidence rates (IRs) of hospitalizations for stroke, stroke subtypes, and TIA in young adults aged 15 to 30 years in Denmark and (2) to identify sex-specific temporal trends in IRs for hospitalizations in stroke subtypes since the 1994.

Methods

Data Sources

This study was based on the Danish National Patient Register (NPR),[11] which contains information on all hospital contacts in

Denmark since 1977 and includes all outpatient consultations since 1977 and includes all outpatient consultations since 1995. Acute in-hospital treatment and rehabilitation of patients with cerebrovascular diseases are exclusively performed at public hospitals in Denmark. From 1994 on, patient contacts were classified according to the *International Classification of Diseases, 10th Revision* (ICD-10). All inhabitants of Denmark have a unique personal identification number[12] that enables unambiguous tracing of all individuals living in Denmark through nationwide registers. Information on fatal cases was obtained from the Danish Registry of Causes of Death.[13]

Outcome

The outcome of this study was first-ever discharge diagnosis of stroke (all types) or TIA. Only inpatients and emergency department patients were considered. Stroke was further stratified according to subtype: ischemic stroke, ICH, SAH, and unspecified stroke. TIA was considered separately (Table 1). Overall stroke included all subtypes.

Previous reports have indicated that the category unspecified stroke to a large extent (60%) consisted of ischemic stroke.[14] Therefore, we defined a new stroke subtype termed nonhemorrhagic stroke that consisted of ischemic and unspecified stroke combined, to give a more accurate picture of the incidence of ischemic stroke.

The study was approved by the Danish Data Protection Agency. The study did not include direct contact with patients and therefore patient consents and ethical approval were not required according to Danish law.

Statistical Analysis

We estimated age-specific IRs of first-time hospitalization for stroke and TIA as well as for subtypes of stroke and reported it as numbers of new cases per 100 000 person-years. The IRs were calculated annually for the study period of January 1, 1994, to December 31, 2012. The IRs were

Table 1. *International Classification of Disease, Tenth Revision* (ICD-10) Codes Included

Diagnosis	ICD-10 Codes
Stroke	
Ischemic stroke	DI63
Intracerebral hemorrhage	DI61
Unspecified stroke	DI64, DI679, DI67–DI68 (-DI674), DG46
Subarachnoid hemorrhage	DI60
Transient ischemic attack	DI45

standardized to the age distribution of the Danish population in 2012 obtained from Statistics Denmark,[15] and the approximate bootstrap method was used for calculating 95% CIs.

The temporal trends in incidence were analyzed by using Poisson regression on the age-standardized IRs. We analyzed overall stroke and subtypes of stroke for both males and females together and separately. Estimated annual percentage change (EAPC) and corresponding 95% CIs were calculated in piecewise linear models.[16] Deviations from the piecewise linear models were tested by means of restricted cubic splines.[17] A positive EAPC represents an increasing trend, and a negative EAPC relates to a decreasing trend. If the trends did not differ significantly over time during the study period, tested by a likelihood ratio test, we present a single EAPC for the entire study period. However, if the best fit of a trend for males and females together was a two-segment model, this was also applied in the sex-specific analyses. Sex-specific differences (P_{sex}) in temporal trends were tested by likelihood ratio tests comparing models with and without an interaction term between calendar year and sex.

When computing the IRs, we did not take into account stroke or TIA diagnoses recorded before 1994 and thus may have overestimated the IRs of the first-time events. To address this issue, we repeated the analyses of the trends, omitting 1994–1996 from the analyses as a sensitivity analysis. In addition, a sensitivity analysis omitting emergency department cases was performed.

The statistical software program R version 3.0.2[18] was used for all analyses, and level of significance was set to 5%.

Results

Demographics

The study covered >20 million person-years corresponding to ≈1 million persons per calendar year (Table 2). A total of 4156 incident cases of hospitalizations for stroke or TIA were identified, including 3431 cases of stroke and 725 cases of TIA.

Incidence of Hospitalizations for Stroke and TIA

The age-standardized IRs for hospitalizations for overall stroke and TIA are presented in Figure 1 and Table 2. The corresponding EAPCs are given in Table 3. The age-standardized overall stroke hospitalization IR increased significantly (EAPC 1.83% [95% CI 1.11–2.55%]) from 11.98/100 000 person-years in 1994 to 16.74/100 000 person-years in 2012. The age-standardized IR of hospitalizations for TIA increased from 1.93/100 000 person-years in 1994 to 5.81/100 000

Table 2. Characteristics of Study Population 1994–2012

Calendar Year	Population Size	No. of First-Ever Stroke	Age-Standardized Incidence Rates for Stroke/100 000 Person-Years (PY)	No. of First-Ever Transient Ischemic Attack (TIA)	Age-Standardized Incidence Rates for TIA/100 000 PY
1994	1 203 942	154	11.97	25	1.93
1995	1 185 596	192	15.26	33	2.52
1996	1 165 948	165	13.44	33	2.54
1997	1 138 317	167	13.71	42	3.45
1998	1 107 762	187	15.69	47	3.97
1999	1 086 047	177	15.28	27	2.37
2000	1 070 066	152	12.90	26	2.27
2001	1 057 344	176	15.90	37	3.21
2002	1 045 331	190	17.06	29	2.42
2003	1 029 217	191	17.85	28	2.61
2004	1 018 778	194	18.08	42	3.82
2005	1 013 540	172	16.13	37	3.48
2006	1 011 326	176	16.92	36	3.23
2007	1 015 314	180	17.34	45	4.31
2008	1 030 426	187	17.86	33	3.11
2009	1 044 899	177	16.81	41	3.76
2010	1 055 245	219	20.72	51	4.79
2011	1 072 801	193	17.94	50	4.61
2012	1 085 001	182	16.77	63	5.81
Total	20 436 900	3431	—	725	—

person-years in 2012, corresponding to an even stronger positive trend (EAPC 4.12% [95% CI 2.44–5.83%]).

Temporal Changes of Stroke Subtypes

Age-standardized IRs and corresponding estimated trends of hospitalizations for ischemic stroke, unspecified stroke, non-hemorrhagic stroke (ischemic and unspecified stroke combined), SAH, and ICH are presented in Figure 2. The IR of hospitalizations for ischemic stroke doubled from 1994 to 2012 as a consequence of a small but significant increase until 2006 (EAPC 2.56% [95% CI 0.60–4.56%]) followed by a much larger increase (EAPC 11.80% [95% CI 7.40–16.38%]) in the subsequent years. The IR for hospitalizations for unspecified stroke increased significantly (EAPC 5.09% [95% CI 3.15–7.08%]) from 1994 to 2006 but was followed by a small nonsignificant negative trend (EAPC −1.82% [95% CI −5.96% to 2.49%]). The IR for hospitalizations for nonhemorrhagic stroke increased significantly (EAPC 3.92% [95% CI 2.98–4.88%]) from 1994 to 2012, whereas the IRs for hospitalizations for ICH and SAH showed only small variations and no significant trends over time.

Temporal Changes in Sex-Specific Incidence of Hospitalizations According to Stroke Subtype

Table 3 shows the overall and sex-specific EAPCs for stroke, TIA, and stroke subtypes, as well as tests for differences in sex-specific temporal trends. The age-standardized IRs and estimated trends for hospitalizations of TIA, ischemic stroke, unspecified stroke, and nonhemorrhagic stroke for men and women are given in Figure 3. Sex-specific EAPCs for men (EAPC 1.80% [95% CI 0.82–2.78%]) and women (EAPC 1.85% [95% CI 0.68–3.04%]) were similar (P_{sex}=0.94) for overall stroke. For hospitalizations for TIA, significant differences were seen between men and women (P_{sex}=0.028); in women, the IR increased slightly throughout the study period (EAPC 3.45% [95% CI 1.62–5.31%]), whereas in men, the IR appeared stable until 2006 (EAPC 0.77% [95% CI −1.84% to 3.45%]), followed by a significant increase thereafter (EAPC 16.61% [95% CI 10.45–23.12%]). In men, the IR for hospitalizations for ischemic stroke increased insignificantly until 2006 (EAPC 0.98% [95% CI −2.60% to 4.69%]), and from 2006 to 2012, it increased steeply (EAPC 14.60% [95% CI 6.22–23.63%]). A similar pattern was seen in women from 2006 to 2012 but
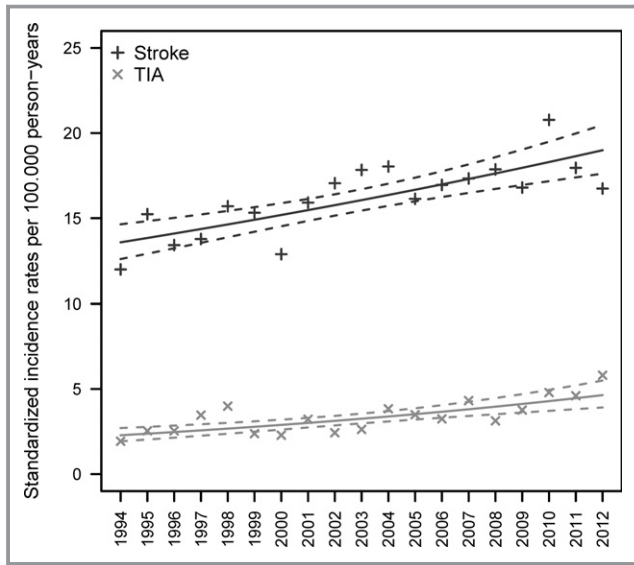
Figure 1. Age-standardized incidence rates per 100 000 person-years for hospitalizations for overall stroke (ie, all subtypes combined) and transient ischemic attack (TIA) separately. Points are the age-standardized incidence rates, whereas the solid lines are the estimated trends of the standardized incidence rates and the dashed lines represent the corresponding 95% CIs.

with a slightly lower, although not significantly lower (P_{sex}=0.58), increase compared with men (EAPC 9.87% [95% CI 2.16−18.15%]).

The trends for hospitalizations for unspecified stroke were similar in men (EAPC 2.63% [95% CI 0.64−4.66%]) and women (3.56% [95% CI 1.72−5.42%]) (P_{sex}=0.53). Hospitalizations for nonhemorrhagic stroke IR increased significantly throughout the entire study period in both men (EAPC 3.47% [95% CI 1.96−4.99%]) and women (EAPC 4.19% [95% CI 2.80−5.61%]). Although the IR was higher among women compared with that in men, there was no difference with regard to trend (P_{sex}=0.51).

The sensitivity analysis of 1997−2012 did not alter the main conclusions (Table 4). The main difference was that the trend for hospitalizations for SAH among women changed from near significant to significant with a faster decrease (EAPC −3.45% [95% CI −5.89% to −0.95%]) during the period compared with 1994−2012 (EAPC −1.93% [95% CI −3.89% to 0.08%]). Analysis excluding emergency department cases did not change the trends (data not shown).

Discussion

This nationwide study focuses on the youngest adults (15−30 years old) with stroke and TIA. It is, to our knowledge, one of the first studies to investigate temporal trends of incidence of stroke, including major subtypes, and TIA for this specific age group. We found increasing incidence of first-time

Table 3. Estimated Annual Percentage Change (EAPC) for Total and Sex Specific

| Type	Total					Males				Females			
	Period	EAPC	95% CI	P Value	P_{sex}*	Period	EAPC	95% CI	P Value	Period	EAPC	95% CI	P Value
Transient ischemic attack	1994–2012	4.12	2.44 to 5.83	<0.001	0.03	1994–2006	0.77	−1.84 to 3.45	0.566	1994–2012	3.45	1.62 to 5.31	<0.001
	—	—	—	—	—	2006–2012	16.61	10.45 to 23.12	<0.001	—	—	—	—
Stroke	1994–2012	1.83	1.11 to 2.55	<0.001	0.94	1994–2012	1.80	0.82 to 2.78	<0.001	1994–2012	1.85	0.68 to 3.04	0.002
Subarachnoid hemorrhage	1994–2012	−0.38	−1.62 to 0.89	0.559	0.02	1994–2012	0.91	−0.36 to 2.20	0.162	1994–2012	−1.93	−3.89 to 0.08	0.060
Intracerebral hemorrhage	1994–2012	0.22	−1.85 to 2.32	0.838	0.58	1994–2012	0.59	−1.82 to 3.07	0.632	1994–2012	−0.44	−2.94 to 2.12	0.731
Ischemic	1994–2006	2.56	0.60 to 4.56	0.010	0.58	1994–2006	0.98	−2.60 to 4.69	0.597	1994–2012	3.72	0.13 to 7.43	0.042
	2006–2012	11.80	7.40 to 16.38	<0.001		2006–2012	14.60	6.22 to 23.63	<0.001	2006–2012	9.87	2.16 to 18.15	0.011
Unspecied	1994–2006	5.09	3.15 to 7.08	<0.001	0.53	1994–2012	2.63	0.64 to 4.66	0.010	1994–2012	3.56	1.72 to 5.42	<0.001
	2006–2012	−1.82	−5.96 to 2.49	0.402		—	—	—	—	—	—	—	—
Nonhemorrhagic stroke	1994–2012	3.92	2.98 to 4.88	<0.001	0.51	1994–2012	3.47	1.96 to 4.99	<0.001	1994–2012	4.19	2.80 to 5.61	<0.001

*Test for sex-differences in EAPC.
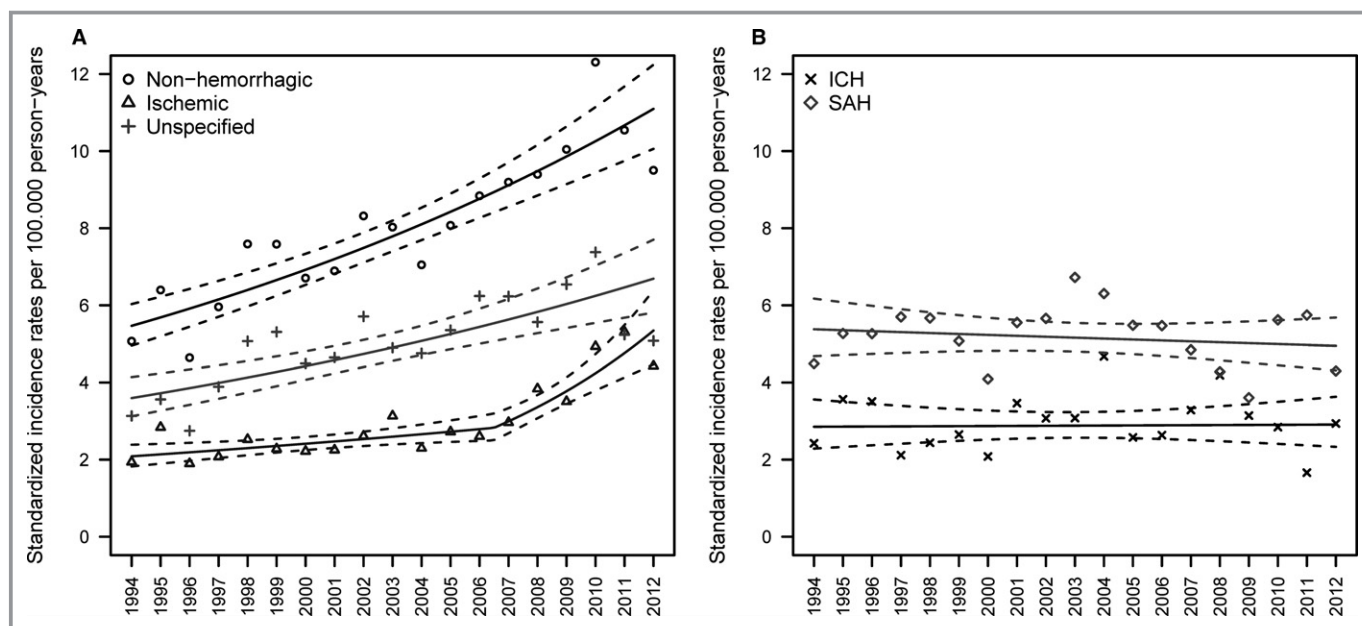
Figure 2. Age-standardized incidence rates per 100 000 person-years for hospitalizations for subtypes of stroke: (A) ischemic, unspecified, and nonhemorrhagic stroke and (B) intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), separately. Points are the age–standardized incidence rates, whereas the solid lines are the estimated trends in the standardized incidence rates and the dashed lines represent the corresponding 95% CIs.

hospitalization for both stroke and TIA among young Danish adults. Further, the IR of hospitalizations for ischemic stroke and TIA increased markedly from 2006 to 2012. The IRs of hospitalizations for hemorrhage of any type did not change. Some sex-specific differences were also detected; the IRs for hospitalizations for ischemic stroke and TIA among women appeared higher compared with those for men, while the incidence among men increased more steeply during the last part of the study period.

Direct comparison of our results to previous studies is difficult primarily for 2 reasons. First, previously studies analyze temporal trends in a broader age range (ie, individuals up to 50 to 55 years old). The incidence of stroke increases steeply with age.[14,19] This makes it difficult to examine trends among the very young, as this group is outnumbered by individuals older than 30 years. Incidence trends in the very young thus might be concealed by the larger incidence of cerebrovascular diseases among older persons. Second, different statistical methods have been used (ie, IR ratio and annual percentage change); however, these are not directly comparable. While the IR ratio only expresses the increase or decrease, the EAPC enables us to quantify trends from 1 year to another. In this study, we focused entirely on young adult stroke and TIA, whereas temporal trends of the older part of the Danish population have been described elsewhere.[3]

The present IR for hospitalizations for ischemic stroke in the young was slightly lower than that previously reported.[8–10,20,21]

A Swedish study found that IRs of hospitalizations for ischemic stroke among adults between 18 and 44 years showed a continuous annual percentage increase of 1.3% for men and 1.6% for women during 1984–2010,[10] which were lower rates than those observed in the present study. Other studies have also reported increasing IRs, although results were given as IR ratios.[8,9,22] In addition, in individuals younger than age 30, ischemic strokes were reported more frequently in women than in men.[9,21] This was also the case in our study. However, as the hospitalization rate among men increased, the difference between men and women disappeared in the last part of the study period. Studies of TIA incidence from Greater Cincinnati and Spain reported IRs between 1.0 and 3.2/100 000 PY.[22,23] However, these studies reported temporal trends confined to the years 2006 and 1993–1994. Nevertheless, our results from 1994–2006 were similar to these findings, whereas the IRs from the last part of our study period were considerably higher. The IR of SAH has been reported to vary between 0.1 and 7.7/100 000 PY with no apparent change over time reported so far.[24–28] Our IRs were equivalent to the highest previously reported rates and also showed no apparent trend. The present results for ICH with a relative constant incidence over time are comparable to those of previous studies.[8,20]

In the past, stroke in the young was considered to be caused by rare conditions. However, recent reports argue to some extent against rare risk factors as the most common
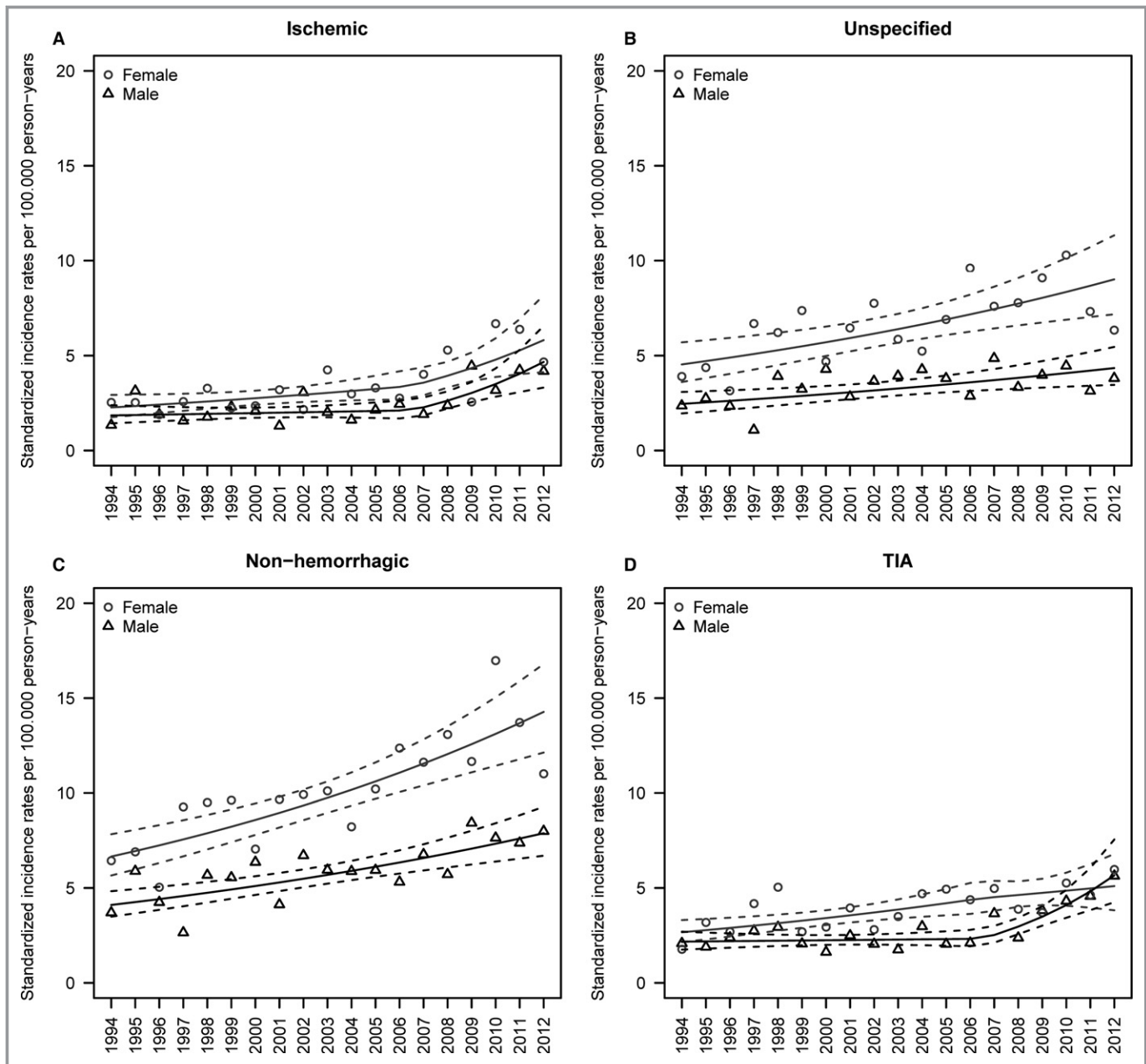
Figure 3. Age-standardized incidence rates per 100 000 person-years for men and women for hospitalizations for (A) ischemic stroke, (B) unspecified stroke, (C) nonhemorrhagic stroke, and (D) transient ischemic attack (TIA). Points are the age-standardized incidence rates, whereas the solid lines are the estimated trends in the standardized incidence rates and the dashed lines represent the corresponding 95% CIs.

causes of stroke. Instead diabetes, hypertension, smoking, low aerobic fitness, and obesity are believed to be the prominent risk factors for stroke and TIA in the young.[8,29–33] Interestingly, a family history and illicit drug abuse also seem to be important risk factors.[34] While the prevalence of most of the traditional risk factors have declined slightly during the study period,[35,36] the prevalence and incidence of diabetes have increased markedly among young adults in Denmark.[37] This is perhaps one likely explanation for the increased incidence of stroke and TIA seen in this study.

Strengths and Limitations

The use of high-quality nationwide health registries with accurate linkage enables near-complete ascertainment of all hospitalized stroke and TIA cases in a specific age group in an entire country during an 18-year period. Further, the use of a nationwide cohort enables analysis of cerebrovascular disease in young adults, which is a rare outcome. Nonetheless, the study is limited by the register-based design that includes only hospitalized cases of stroke and TIA. For stroke

Table 4. Sensitivity Analysis of the Sex-Specific Trends Omitting the Period 1994–1996

Type	Male				Female			
	Period	Estimated Annual Percentage Change (EAPC)	95% CI	P Value	Period	EAPC	95% CI	P Value
Transient ischemic attack	1997–2006	0.01	−3.92 to 4.10	0.995	1997–2012	2.47	0.31 to 4.68	0.025
	2006–2012	17.22	10.21 to 24.67	<0.001				
Stroke	1997–2012	2.10	0.88 to 3.35	<0.001	1997–2012	2.88	1.36 to 4.43	<0.001
Subarachnoid hemorrahge	1997–2012	1.03	−0.69 to 2.79	0.241	1997–2012	−3.45	−5.89 to −0.95	0.007
Intracerebral hemorrhage	1997–2012	1.10	−2.31 to 4.62	0.533	1997–2012	0.37	−2.82 to 3.66	0.824
Ischemic stroke	1997–2006	2.34	−2.38 to 7.30	0.337	1997–2012	5.94	2.92 to 9.05	<0.001
	2006–2012	13.69	5.80 to 22.17	<0.001				
Unspecified stroke	1997–2006	4.24	−0.44 to 9.15	0.076	1997–2006	3.23	−0.44 to 7.04	0.085
	2006–2012	−2.51	−10.10 to 5.73	0.540	2006–2012	−0.08	−6.20 to 6.43	0.979
Nonhemorrhagic stroke	1997–2012	3.77	1.87 to 5.71	<0.001	1997–2012	3.38	1.73 to 5.05	<0.001

diagnoses in NPR, misclassification may have occurred in up to 20% of the patients[38]; however, other studies report that ischemic stroke in particular may be underestimated.[14] Although validation of stroke diagnoses in NPR has led to varying conclusions, we find it less likely that the underestimation should have changed during the study period. Therefore, although our data may underreport IRs, this would most likely not affect temporal trends. The quality of neuroimaging improved significantly, leading to detection of smaller brain lesions during the study period. Further, imaging became more widespread and available in the Danish hospitals. Together, these issues would potentially flaw our results by leading to more accurate diagnosis of stroke subtypes, which in turn would alter the "true" IRs for, in particular, unspecified stroke and ischemic stroke. Thus, improved imaging quality would in theory lead to increased detection of ischemic stroke incidence and, to some extent, explain the decrease of registered unspecified stroke seen in this study as well as in previous studies.[3] Nevertheless, we do not believe that this change in case ascertainment influenced our results to a large extent, because even though subtypes were not determined on imaging in the 1990s, the patients were still diagnosed as having "unspecified" stroke. In an attempt to adjust for neuroimaging availability, we constructed the category of nonhemorrhagic stroke (ischemic and unspecified collapsed into 1 category). We found that hospitalization of patients with nonhemorrhagic stroke increased at a constant rate throughout the study period, indicating that admissions of nonhemorrhagic stroke increased regardless of changes in diagnostic practice. In addition, a study of the older part of the Danish population showed increased rate of hospitalization for ischemic stroke.[3] This suggests that the increase of incidence over time found in this study represents a real increase in incidence. For TIA, the improved detection of smaller ischemic lesions may have caused a decrease in incidence and a corresponding increase in ischemic stroke, because some patients may have had visible lesions on imaging, regardless of clinical TIA symptoms. Nonetheless, we saw an increased incidence of hospitalizations for TIA over time despite these improvements. We therefore believe that the changes in diagnostic routines did not have a major impact on our findings. Finally, it must be noted that we found increased incidences only for ischemic type and not for SAH and ICH. This indicates that the increases for ischemic stroke and TIA are not caused by a general increase in hospitalization for stroke but represent a real increase in incidence.

Summary/Conclusion

We found increased rates of hospital admissions for stroke and TIA. This was particularly prominent in the later period of the study. Ischemic stroke and TIA showed similar patterns, with steep increases among men from 2006 to 2012. In contrast, the hospitalization rates for SAH and ICH appeared stable. These results may suggest that the increase in both TIA and ischemic stroke is caused by risk factors, which should be explored in future research.

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interpretation of the data; and preparation, review, or approval of the manuscript.

Disclosures

None.

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